FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PADAC) MEETING

Tuesday, January 12, 2016

8:06 a.m. to 4:56 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jennifer Shepherd, RPh

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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Maryland Department of Health and Mental Hygiene

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Global Development Leader, Pain and Core Therapeutics and Distinguished Scholar

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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. KRAMER: I think we're going to go ahead and get started. Good morning. I would like to first remind everyone to silence your cell phones, smartphones, and other devices that you have if you've not already done so. That would be very helpful. I'd also like to identify the FDA press contact in the back raising his hand, Eric Pahon. Thank you. If you have any questions, Eric is the person to talk to.

My name is Judith Kramer, and I'm the acting chairperson of the Psychopharmacologic Drugs Advisory Committee. I'd like to call this meeting to order and start by going around the table and having everyone introduce themselves. Let's start at the right.

DR. CONLEY: Good morning. I'm Rob Conley. I am the industry representative today. I'm distinguished scholar in neuroscience at Eli Lilly

and an adjunct professor of psychiatry in pharmacy science at the University of Maryland.

DR. BICKEL: Hi. I'm Warren Bickel. I'm director of the Addiction Recovery Research Center at the Virginia Carilion Research Institute of Virginia Tech.

DR. DODD: I'm Lori Dodd. I'm a biostatistician at the National Institutes of Health at NIAID, the infectious and allergy institute, and I'm primarily focused on clinical trials.

DR. TROENDLE: I am James Troendle. I'm a statistician at the National Heart, Lung, and Blood Institute.

MR. YESENKO: Michael Yesenko, patient representative.

DR. HIGGINS: Jennifer Higgins, consumer representative.

DR. PRESTON: Kenzie Preston. I'm the chief of the clinical pharmacology and therapeutics research branch at the National Institute on Drug Abuse Intramural Research Program.

DR. McNICHOLAS: Laura McNicholas, University of Pennsylvania.

DR. GRIEGER: Tom Grieger, psychiatrist working for the state of Maryland and also adjunct professor at Uniformed Services University.

DR. PICKAR: Dave Pickar, former chief of experimental therapeutics, intramural research, NIMH, and adjunct professor at Hopkins and Uniformed Services.

DR. KRAMER: As I said, I'm Judith Kramer. I'm professor emerita at Duke University.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. IONESCU: Dawn Ionescu, psychiatrist at Massachusetts General Hospital.

DR. NARENDRAN: Raj Narendran, psychiatrist, University of Pittsburgh.

DR. KRAMER: If we could hold just a moment. Kathleen Carroll is ill but is able to join us by phone. So we're going to have Kathleen introduce herself so we can recognize her voice before Adam introduces himself.

Kathleen?

DR. CARROLL: Hi. This is Kathleen Carroll, professor of psychiatry, Yale University School of Medicine -- not my real voice.

DR. KRAMER: The connection was a little spotty there. I don't know if anyone could work on that. It sounded like Kathleen's voice broke up a couple times.

Okay. Go ahead, Adam.

DR. GORDON: Good morning. Adam Gordon, professor of medicine, clinical and translational sciences, health services researcher; University of Pittsburgh, VA Pittsburgh Healthcare System.

DR. KOTZ: Margaret Kotz. I'm professor of psychiatry and anesthesiology at Case Western Medical School and director of Addiction Recovery Services at University Hospitals in Cleveland.

DR. LEHRFELD: Kim Lehrfeld, FDA, Division of Risk Management, and I'm team leader.

DR. PETULLO: David Petullo, FDA, Office of Biostatistics.

DR. WINCHELL: Celia Winchell. I'm the

medical team leader for addiction drug products at FDA.

DR. HERTZ: Sharon Hertz. I'm director of the Division of Anesthesia, Analgesia, and Addiction Products.

DR. ROCA: I'm Rigo Roca. I'm deputy division director in the Division of Anesthesia, Analgesia, and Addiction Products.

DR. KRAMER: Thank you very much. I'm going to read a statement that I hope you all will listen to and pay attention to.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the 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 the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now, I'll now pass it to Lieutenant-Commander Jennifer Shepherd at my left, who will read the Conflict of Interest Statement.

Actually, I think Kathleen Brady just joined us. Kathleen, do you want to introduce yourself and give your institution?

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

DR. KRAMER: Thank you. Glad you come make it.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of Federal Advisory Committee Act of 1972. With the exception of 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 federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees and federal regular employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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 New Drug Application 204442, Probuphine, buprenorphine hydrochloride and ethylene vinyl acetate, subdermal implant, submitted by Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals for the proposed indication of maintenance treatment of opioid dependence.

This is a particular matters meeting during which specific matters related to Titan Pharmaceuticals new drug application 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 may have made concerning the product at issue.

With respect to FDA's invited industry representative, we would 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 would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with Titan Pharmaceuticals and Braeburn Pharmaceuticals. Thank you very much.

Dr. Kramer?

DR. KRAMER: We will now proceed with Dr. Winchell's introductory remarks.

FDA Opening Remarks - Celia Winchell

DR. WINCHELL: Good morning. Dr. Kramer, members of the Psychopharmacologic Drugs Advisory Committee, and invited guests, thank you for your participation in this important meeting. Today, we will ask for your assistance in our evaluation of Titan and Braeburn's application to market Probuphine, an implantable formulation of buprenorphine, as a treatment for opioid dependence

in a population of patients who've been successfully and stably treated on transmucosal buprenorphine at moderate to low doses.

Buprenorphine was originally approved in 1981 as an injectable analgesic. It is a partial agonist at the mu receptor, unlike most opioid analgesics, which are full agonists. Agonist maintenance therapy of opioid dependence is a well-established paradigm.

In the several decades since methadone maintenance treatment was introduced, epidemiological studies have established that participation in methadone treatment reduces mortality in HIV seroconversion. However, to control the risks of diversion and accidental overdose, methadone treatment is limited by law to specially registered opioid treatment programs or OTPs. Patients must report to the OTP daily for supervised medication administration until they're sufficiently stable to begin to earn take-home doses according to a specific schedule.

Buprenorphine was developed as a treatment

for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone that would be less attractive for diversion and abuse, and as such, it could be made available in physicians' offices rather than being limited to supervised dosing in the OTP setting.

Unfortunately, in the decades since the introduction of sublingual buprenorphine for the treatment of opioid dependence, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in a number of cases of accidental poisonings of small children. Therefore, a depot injection or an implantable product, which would be difficult to divert or abuse and would be less likely to be accidentally ingested by small children, offers potential advantages.

Probuphine was developed to provide these advantages as well as to provide enhanced adherence

to treatment and to offer some convenience to patients in terms of the need for office visits and filling of prescriptions. The division agrees with the sponsor that an implantable formulation of buprenorphine has the potential to meet an important public health need.

When Titan first submitted this application in 2012, the clinical trials explored the efficacy of Probuphine for patients newly entering treatment for opioid addiction. We found that the results of the study, taken together with the comparative pharmacokinetic study findings, pointed to the conclusion that the plasma buprenorphine level associated with Probuphine was simply too low to be effective in that population.

We recommended that Titan study a higher dose. However, Titan and their marketing partner Braeburn elected instead to explore whether Probuphine would be effective in maintaining stability in patients who have been successfully treated with sublingual buprenorphine and have been tapered down to moderate-to-low doses, meaning

doses that the plasma level of buprenorphine produced by Probuphine can reasonably match.

It was a challenge to determine the appropriate design of this study. Typically in addiction treatment studies, fully stable patients are not enrolled in trials in which they're withdrawn from a medication that's working for them. This formulation does offer some convenience to the patient, and we understood there was a demand and interest from patients, and they may be willing to participate. But a placebo-controlled trial didn't seem appropriate because it would place patients at risk of relapse that might be difficult to reverse.

On the other hand, an active controlled trial presented challenges for analysis. You might expect that a passive compliance formulation that ensures medication adherence could be shown to be superior to a medication that must be taken daily, but it could be difficult to show superiority in non-relapse rate in stable patients. This is a population in which non-relapse over a matter of

months is more or less expected.

So this led us to conclude that a trial of the type called noninferiority trial would be the most appropriate. Active control noninferiority trials are intended to show that the new treatment is not inferior to an unacceptable extent; that is that any difference between the two treatments is small enough to allow a conclusion that the new drug can be expected to be effective.

Now historically, the division has been reluctant to agree to noninferiority designs for trials of drugs to treat opioid dependence because there really has not been good information about the expected response rate. This is because trials have been quite heterogenous with respect to the study designs, the populations, the treatments, the treatment settings, the way response was defined. But in this situation with Probuphine, we felt it was appropriate for us to be flexible, and we really did see the potential public health benefit of an implantable formulation like this in addressing this growing problem of misuse, abuse,

an accidental exposure.

We encouraged the sponsor to seek out sources of information about the expected rate of non-relapse in stable, successfully treated patients who continue on buprenorphine over a six-month period to support this study, which they did. But because of the remaining uncertainties about conducting a study like this -- a noninferiority trial in this clinical setting -- because we could not anticipate all of the potential factors that could influence outcome in this particular study, we did let the sponsor know we couldn't just say up front that having the study meet its proposed endpoints would be enough evidence to support a finding of efficacy; and that it would be a matter for review; and that we're going to look quantitatively and qualitatively at the analysis and clinical meaningfulness of the findings.

There are many different ways that one could choose to define a successful patient in a trial like this. We did agree to one because there has

to be a single, agreed-upon analysis for statistical reasons. But we believe that reasonable people could hold many different opinions about what constitutes success, and that's one of the things we want to discuss today.

Certain aspects of the quality of the trial, which are important in any setting, are particularly important in noninferiority trials. Some issues in study conduct can make treatment arms look more similar. In a superiority trial, poor study conduct tends to reduce the between-treatment differences, which introduces a bias toward the null, meaning the study's more likely to fail. But in a noninferiority trial, anything that reduces the ability to detect a difference between the treatments actually biases the study for success.

So, some aspects of study conduct that might make it harder to show a difference would be enrollment of patients who didn't quite meet entry criteria, missing data, and use of rescue medication. And we did see some of these issues in

the study, and we'll ask you to discuss how they affect interpretation.

We'll be asking you to consider whether the applicant has succeeded in identifying a population for whom Probuphine is effective, and this would involve discussing whether the submitted study provides evidence of efficacy for treatment with Probuphine in the study population. And if so, we'll ask you to comment on what factors define a patient who would be a candidate for this treatment and to discuss the impact that factors such as use of rescue or missing results from urine samples could have on expressing a responder-based outcome.

The topic of rescue medication deserves particular comment. The study criteria called for enrollment of patients who were considered clinically stable and on a sublingual dose of no more than 8 milligrams a day for at least the last 90 days before entering the trial.

Rescue use during the trial was expected to be a rare occurrence if it happened at all. But as it turns out, it wasn't at all uncommon for

patients to need extra doses during the trial. Of particular note is that none of the patients who needed rescue during the trial had required extra doses of medication in the six months prior to the trial.

Of course, clinically it isn't necessarily a concern if patients require an occasional dose adjustment in order to maintain stability, but the problem is that Probuphine isn't titratable. The main public health benefit of Probuphine is that the medication isn't in the medicine cabinet or the kitchen cupboard where it's vulnerable to being stolen, or given away, or risk of accidentally poisoning a household contact to the patient.

If nearly 20 percent of Probuphine patients require supplemental sublingual buprenorphine from time to time, we'll ask you to discuss how clinicians should address this. Would every patient have a prescription for as-needed buprenorphine in the medicine cabinet or the kitchen cupboard? Maybe it doesn't really matter if it's a new bottle every month, as a patient on

sublingual buprenorphine would have, or one bottle sitting there for six months. The risks could be similar.

If there must be a supply of sublingual buprenorphine in the home, does the product provide the purported benefit with respect to diversion, abuse, and accidental pediatric exposure? And what if the patient actually needs to take the rescue medication? At what point does that patient not adequately treated on Probuphine be managed with a different medication? We'll ask for your thoughts on this topic.

From a safety standpoint, 370 patients have been treated with this product. Most of them only have one six-month treatment cycle in what could potentially be a lifelong treatment. We did not identify systemic risks that differed from currently available sublingual buprenorphine products. But we do have some concerns about the risks associated with the insertion and removal procedures and potential complications such as device migration, expulsion, and extrusion.

A product that was similar in format and the procedures necessary for insertion and removal is Norplant implantable contraceptive. Norplant has been associated with some procedural complications, even though Norplant procedures are performed by surgically trained physicians. Complicated removals may require imaging equipment and surgical exploration. And physicians who are currently involved in providing buprenorphine treatment of addiction have not commonly had surgical training.

To address this, the applicant has proposed a risk evaluation and mitigation strategy, a REMS, consisting of a training and certification program for healthcare professionals who will prescribe Probuphine and for the healthcare providers who will insert or remove Probuphine.

Additionally, the REMS will restrict distribution to REMS certified prescribers, and we'll be asking the committee to discuss whether the proposed REMS is adequate to address the risks of potential complications associated with improper insertion on removal, as well as abuse, misuse, and

accidental overdose if an implant protrudes from or completely comes out of the skin.

Your deliberations and recommendations will play an important role in our decision-making process, and I'd like to thank you for taking time from your other extensive responsibilities to participate in this process.

DR. KRAMER: Thank you, Dr. Winchell.

We'll now go on with the sponsor presentations. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they 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, the 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 this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Applicant Presentation - Behshad Sheldon

MS. SHELDON: Good morning. Thank you, Madam Chair. Thank you to the committee and FDA members for devoting your time today for this discussion. I'm Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals. I've worked in the development and commercialization of medicines in chronic diseases for over 20 years, including glucophage for diabetes, Plavix for heart disease, and Abilify for serious mental health disorders.

Braeburn is a neuropharmaceutical company dedicated to developing long-acting treatments for

patients suffering from addiction, pain, and serious mental health disorders. While long-acting treatments can be helpful in almost any chronic disease, they can be essential in the areas we are focused on due to the significant personal and public health impact of adherence issues.

People with opioid dependence represent an underserved population that is growing rapidly as the epidemic of opioid abuse progresses. From public perception of the disease as a moral failing, to the limits on how many patients can be treated by an individual physician and insurance coverage limitations on medicines that work, to the paucity of research and development of new treatment options, nothing seems easy in the addiction medicine field.

We have had our challenges as well. This is the second submission, as Dr. Winchell mentioned, of Probuphine and addresses the two key issues that FDA identifies in the original submission: the demonstration of clinical benefit in a specific population and the validation of the training

program for insertion and removal procedures.

FDA suggested we could either increase the dose delivered by Probuphine or examine the potential benefits of Probuphine in a stable population requiring lower doses of buprenorphine. As it made clinical sense to treat patients with a 6-month implant only once they've responded well to buprenorphine and have progressed in their treatment, we chose the target population dose who are already stabilized. Patients requiring 8 milligrams Subutex equivalent or less were selected because, again as Dr. Winchell mentioned, the plasma concentrations delivered by 4 implants approximate those delivered by lower doses of sublingual daily buprenorphine.

Importantly, the objective of the study was not to show that Probuphine is equivalent to a particular dose of sublingual buprenorphine but to demonstrate that patients on as low as 2 milligram and as high as 8 milligram of sublingual daily buprenorphine can be safely and effectively transferred to 4 Probuphine implants.

But we did not forget about the need for higher doses in some patients. In order to address the needs of patients who are initiating treatment or require higher doses of buprenorphine, we licensed two additional depot injection products. So our suite of investigational products now include highly titratable weekly and monthly injectable buprenorphine products in addition to the 6-month buprenorphine implant. We hope to be able to offer treatment options that help personalize dose and frequency depending on the patient's stage of treatment.

We stand here with great humility towards all of you who have devoted your careers to people with opioid dependence, whether in the treatment community or in public service, hoping to bring forward the first of our products, Probuphine, to help make a dent in this devastating disease.

Today's discussion on Probuphine will focus on a specific investigation on patients who are already stable on buprenorphine at doses of 8 milligrams or less. Each Probuphine implant

contains 80 milligrams of buprenorphine, 4 implants inserted subdermally in the upper arm in a simple office procedure, and deliver continuous blood levels of buprenorphine for 6 months. The implants have been studied in trials involving 647 subjects over the past 12 years, and Probuphine was granted priority review by FDA in 2012 due to its potential to reduce the risks of diversion, misuse, and accidental pediatric exposure.

With guidance from FDA and global addiction experts, we designed an innovative, double-blind, double-dummy trial to demonstrate that clinically stable buprenorphine patients can be safely and effectively transitioned to Probuphine and maintain stability over time. This methodologically rigorous trial demonstrated unequivocally the efficacy of long-term use of buprenorphine in stable patients. The data further demonstrated the clinical benefit of Probuphine in the target population, those stable on 8 milligrams or less.

We certainly anticipated that the study would demonstrate noninferiority and were

pleasantly surprised that the study results met criteria for superiority even though the moderately size study was not prospectively powered to detect superiority. Why we are not seeking a claim for superiority, we do look forward to the committee's comments on these data.

We are very grateful for the close collaboration with FDA and our advisors in addiction medicine that have brought us to this point and for the opportunity to present and discuss this new treatment option with the committee. Following this introduction, Dr. Frank Young, Braeburn's executive vice president of regulatory and medical and former commissioner at FDA, will describe the growing public health need for effective and safe treatments in opioid addiction.

Then Dr. Michelle Lofwall, associate professor of psychiatry at Kentucky University, will describe the unmet needs in this underserved population of stable patients who face challenges of adherence, drug, supply, and stigmatization that

are only worsened by the need for daily dosing.

Dr. Sonnie Kim, Braeburn's vice president of clinical development and medical affairs, will present the results from the efficacy study that show by every parameter Probuphine is at least as efficacious as sublingual buprenorphine and that stable patients can be transitioned effectively to Probuphine.

Then Dr. Steve Chavoustie, volunteer assistant professor of OB/GYN at University of Miami Miller School of Medicine, will show Probuphine has a safety profile similar to that of sublingual dosage forms and that the current training and certification for implant insertion/removal assures the safety of these procedures.

I will then return to describe the risk management program that provides patient education and assures that only trained and certified healthcare professionals are able to obtain Probuphine.

Dr. Michael Frost, medical director at

Eagleville Hospital, a 300-bed inpatient addiction treatment facility, and president of Frost Medical Group, a state accredited outpatient addiction treatment center, will then show that the benefit-risk profile of Probuphine is highly favorable for the management of stable patients in need of buprenorphine maintenance treatment.

I'd now like to welcome Dr. Frank Young

Applicant Presentation - Frank Young

DR. YOUNG: Thank you, Behshad.

My name is Frank Young. I've devoted 60 years to health care in various positions as an academic scientist, dean of a medical school, chairman of an executive hospital committee, government official in the public health service, and a member of the executive committee of the World Health Organization. In these roles, I've lived through important public health crises.

Our nation's abuse of opioids has reached epidemic proportions. 4.3 million Americans abuse opioids each year, and 2.4 million of these Americans are dependent on opioids. Unfortunately,

only a small percentage of Americans dependent on opioids receive treatment. This has dire consequences.

Over 26,000 Americans died from opioid related overdoses in 2014, and the problem is getting worse. The CDC recently reported that from 2013 to 2014, there was a 9 percent increase in deaths from prescription opioids and a 26 percent increase in deaths from heroin overdose. The rate of heroin deaths has tripled since 2010.

Let's take a look at age as one example of the breadth of this addiction. Here are the sudden, unexpected deaths from prescription opioids by age. When I look at this slide, I don't see data. I see instead gaping holes in the fabric of our families, our communities, following the deaths of our children, our spouses, and our parents.

I'm here today because I've committed the remaining of my life to do something about this crisis, which is worse than anything that I have seen before in the time that I have been either in public service or in the private sector dealing

with health. This is a growing call to action at all levels of government on a bipartisan basis, including the president, members of Congress, governors, and local law enforcement. We can see the magnitude of opioid addiction in the way it has emerged in the 2016 presidential race. Nevertheless, if this call to action is not translated into policy and implemented at all levels, it is for naught.

As I've seen before in public health crises like AIDS, where I helped speed the access to investigational drugs, we make progress when we reach a point of genuine urgency. Complex public health challenges do not have simple solutions. But step by step, translating words into action, we can resolve this crisis the way I've succeeded and seen us succeed in tackling others.

I hope that Probuphine will prove to be an important addition to the therapeutic resources patients, doctors, and communities have at their disposal, and I believe Probuphine could play a part in helping to address the opioid abuse

epidemic.

I'm now pleased to introduce Dr. Michelle Lofwall to present her information.

Applicant Presentation - Michelle Lofwall

DR. LOFWALL: Thank you, Dr. Young. I'm Dr. Michelle Lofwall. I'm a physician board certified in psychiatry and addiction medicine, and I'm an associate professor of behavioral science in psychiatry at the University of Kentucky in the Center on Drug and Alcohol Research.

I have an active outpatient addiction treatment clinic where I treat many adults with opiate dependence and teach residents and other health professionals about substance use disorders. I also conduct research aimed at improving the treatment of opiate addiction and was the principal investigator for study 814. I have received consulting, honoraria for my time. I do not have any financial interest in the company or the outcome of this meeting.

Kentucky is often considered the epicenter of the prescription opiate epidemic, although

heroin use has also increased substantially in the last several years. As in most other states, we're often faced with more people who need and want treatment than there is treatment available, and we routinely are turning people away.

Some patients have to wait a very long time to initiate treatment, and the hurdles are much higher for these patients than for patients with other medical disorders. There are often not enough providers, and many providers have wait lists due to patient limits. Reimbursement is low, and some insurances create significant barriers to care. There are also few medication options in contrast to other chronic conditions like schizophrenia or diabetes, and no long-acting formulations.

Medication diversion is also an important issue. In a NIDA funded study, I researched the relationship between buprenorphine diversion and treatment access among adults abusing prescription opioids who were out of treatment in Appalachia, and results showed that those who tried

unsuccessfully to enter buprenorphine treatment were 7 times more likely to use diverted buprenorphine at follow-up than those who did not try to access treatment.

This is consistent with other studies reporting that people often use diverted buprenorphine for self-treatment of opiate addiction. This does not justify diversion. This suggests that finding novel medications that minimize diversion and expanding treatment access matched to patients' needs may be one of the most effective public health strategies.

Patients have different needs and challenges during opiate dependence treatment. Many have been addicted a long time and have significant psychosocial problems or comorbid untreated psychiatric and medical disorders.

There are also challenges with the criminal justice system. It's not uncommon for providers to be placed in a position with the courts -- for instance, family or drug courts -- whereby the courts are requiring that the patients come off of

their buprenorphine treatment. This can extend to jails as well. I've had experiences when patients have been jailed, and the jails refused to allow the patient to take their medication that I prescribed.

Other patients have fewer comorbidities, and many start treatment already holding jobs and having the support of their family and friends who don't use drugs, so their care can be less complicated. These are patients who often become stable quite quickly.

The literature does not have a clear definition of stability, but there are commonly understood general characteristics of stable patients. Stable patients are doing well in treatment, although stable does not mean perfect. They have a low rate of positive urine tests and have abstinence from illicit opioids for longer durations of time.

Stable patients are regularly attending their clinic visits. They're adherent to their treatment plan, and they have much improved

psychosocial function. They tend to have consistent doses of buprenorphine, which may be lower than their initial maintenance dose. However, dose adjustments still remain possible, especially when insurance changes formulations. This is not uncommon.

Treatment is dynamic and dose adjustments can occur for a variety of reasons. This is not synonymous with treatment failure or treatment rescue. About 40 percent of my patients at the clinic are stable on 8 milligrams per day or less. My stable patients need treatments tailored to suit their needs and challenges, which often are more practical.

One challenge is adherence. They worry, what if somehow I lose my medication or someone takes it? And if a patient doesn't take their medication for several days and then uses a full opioid agonist, this can be fatal. Opiate dependence is a very unforgiving disorder.

Another challenge is retaining confidentiality and avoiding being stigmatized. As

a patient, they worry, what if someone finds out that I have opiate dependence, like my employer, and I lose my job? This is a realistic concern, so our clinic often opens at 5:30 in the morning so that our stable patients can come for appointments before their work day begins, so they do not need a work excused absence.

Other challenges are logistical. For some patients, the logistical challenges are paramount and getting to the physician's office is a real burden. For instance, IO patients who are the primary breadwinner of their family, they have spouses and children who depend upon them to work full time. They're often working more than 40 hours a week. We also serve a rural population, and they live over an hour away from the clinic, and they want to be able to come less than monthly.

Other patients have jobs that require them to travel out of state, and this is good because we encourage work and becoming tax-paying productive citizens. But they worry that they're going to run out of their medication while on a last-minute

business trip, and then slip into withdrawal. They worry about the best place to pack their medicine when traveling. Do they keep it in their jacket and risk it falling out, or do they pack it in the suitcase and risk theft or lost baggage? Reducing these concerns that are real and stressful may allow for further improvement in recovery.

Stable patients work hard to be in treatment. Not everyone can do this, but there certainly is a population that can and is doing this currently. It makes sense that our most successful patients want more. They want more convenience and confidential treatment, and they want medication that works reliably to keep them well for which they can control and not worry that it will be taken away.

Providers and the public clearly want treatment that's less likely to be diverted, misused, and result in unintentional pediatric exposures. With implantable buprenorphine, these wants can be met. Other aspects of the treatment can still be delivered tailored to each stable

patient's needs. But the doctor and patient will no longer have to worry about the fate of the prescription for daily ingestion, whether it will rightly remain with the patient and be taken as prescribed. Thank you.

Applicant Presentation – Sonnie Kim

DR. KIM: Good morning. I'm Sonnie Kim, vice president of clinical development and medical affairs at Braeburn. Study PRO814 demonstrated that Probuphine delivers substantial clinical benefit in patients who have been clinically stable on a maintenance dose of 8 milligrams or less of sublingual buprenorphine. This double-blind, double-dummy study demonstrated that Probuphine is at least as efficacious as sublingual buprenorphine and that patients can successfully transition to Probuphine for maintenance treatment.

Additionally, patients on Probuphine had higher response rates than patients on sublingual buprenorphine even though the rates of response was high for the sublingual group. 814 was the seventh clinical study for Probuphine. The seven studies

included one PK study and one comparative bioavailability study.

In addition, there were two phase 3, randomized placebo-controlled studies and two open-label extension studies. These studies were conducted in patients who are new entrants to buprenorphine treatment. The focus of today's presentation is study 814, which looked at Probuphine in patients who are already stable on sublingual buprenorphine.

The definition of this population was critical for the design of the study. Stable patients were defined as being on buprenorphine treatment for at least 6 months on a dose of 8 milligrams or less for the 90 days prior to enrollment. They had to have no evidence of illicit opioid use in the 90 days prior to randomization and be free from symptoms of withdrawal.

In addition, treating physicians had to attest to the clinical stability of their patients based on their own clinical judgment, considering

the following list of characteristics identified by addiction experts: stable living environment; participation in a structured activity or job; consistent participation in cognitive therapy or peer support; compliant with clinic visits; no reported desire or need to use illicit opioids for the past 90 days; or no hospitalizations, ER visits, or crisis interventions in the past 90 days.

Given the needs of these patients, it would be unethical to conduct a placebo-controlled study in this population. Literature shows that when stable patients are removed from maintenance treatment, the vast majority will relapse. Since these were stabilized patients, it was essential to provide an active control. To compare the two treatment arms, the study used a double-blind, noninferiority study design with a double-dummy and an active control.

As described in the briefing document, we were in agreement with the agency in the 20 percent noninferiority margin based on data from the

literature and external addiction experts. In addiction treatment, this an innovative approach applied to a population not usually included in randomized clinical trials. Therefore, the development of a noninferiority margin required input and involvement of addiction experts in addition to review of any relevant literature.

These analyses determined an appropriate effect size of sublingual buprenorphine versus placebo in stable patients to be approximately 75 percent, while the FDA guidance documents on noninferiority design allows for preserving 50 percent of effect size in which the margin would have been 37.5 percentage points. In agreement with the agency, we chose a conservative margin of 20 percentage points that preserves greater than 70 percent of the effect size.

The results of the study showed that Probuphine met the criteria for noninferiority with the lower bound of the confidence interval well above the margin and also met criteria for superiority in this double-blind, double-dummy

design.

Patients were enrolled and randomized to either 4 Probuphine implants plus placebo sublingual tablets or sublingual buprenorphine tablets plus 4 placebo implants. The dose of sublingual buprenorphine was based on patients' baseline dose of buprenorphine prior to enrollment in the trial, which had to be 8 milligrams or less.

The study duration was 6 months with monthly visits during which patients underwent all assessments, including urine toxicology. Patients also had 4 random urine samples during the course of the study for a total of 10 urine samples. Urine toxicology results were analyzed using a highly sensitive quantitative method of liquid chromatography, tandem mass spectrometry, which can detect concentrations as low as 50 nanograms per mL for opiates, 6 times more sensitive than the standard immunoassay methodology.

The increased sensitivity extends the duration of detection of possible opioid use. Urine samples were tested for all available opioid

analytes and their metabolites. This method was used as screening to determine eligibility for entry into the study.

Baseline characteristics were similar in both groups with a mean age of around 40. Fifty-eight and 60 percent were males in Probuphine and sublingual buprenorphine group, respectively. The majority were Caucasians. Approximately 80 percent of the subjects had at least a high school degree. Additionally, most subjects had a job or participated in a structured activity.

The majority used prescription opioids as their primary opioid of abuse with a mean time since first abuse of opioid being 11 years. Mean time since first diagnosis was 6 years. The mean duration of buprenorphine treatment was 3.5 and 3.4 years for Probuphine and sublingual buprenorphine, respectively. The distribution of buprenorphine dose ranged from 2 milligrams to 8 milligrams per day with 70 to 75 percent on 8 milligrams at enrollment. The study enrollment period was very short and had a high rate of

completion.

A total of 21 sites participated in the study, and enrollment was completed in 4 months, demonstrating a very high level of patient interest. Of the 211 patients screened, 177 were randomized to either Probuphine or sublingual buprenorphine. 176 subjects, 87 in Probuphine and 89 in sublingual buprenorphine arms, were included in the safety data set defined as all subjects who received any study medication. 173 subjects, 84 in Probuphine and 89 in the sublingual buprenorphine arms, were included in the intent-to-treat data set defined in the statistical analysis plan as randomized subjects who provided at least one post-baseline assessment.

The ITT data set did not include 3 subjects due to being lost to follow-up after day 1 and not providing any study assessments. Of the 11 subjects who did not complete the study, 7 were lost to follow-up, 1 was incarcerated, 2 withdrew consent, and 1 had an adverse event leading to discontinuation. Completion rates were high and

similar across treatment arms, 93 percent in Probuphine and 94 percent in sublingual buprenorphine.

The primary efficacy analysis was the difference of responder rates between Probuphine and sublingual buprenorphine. The definition of a responder was determined to be at least 4 out of the 6 months with no evidence of illicit opioid use by both urine toxicology and self-reported use. Each month was determined to be either positive or negative for illicit opioid use based on scheduled urine toxicology results, self-reported use, and if it occurred in that month, random urine toxicology collection. With this responder definition, the primary efficacy analysis demonstrated that Probuphine met criteria for noninferiority as well as meeting criteria for superiority.

This is an illustration of the prespecified 20 percent, noninferiority margin. In order to achieve noninferiority, the lower bound of the confidence interval needs to be to the right of negative 0.2. All of these examples meet criteria

for noninferiority.

The red example meets noninferiority criteria but has a point estimate to the left of the zero, favoring the comparator, meaning that the investigational drug did not perform as well as the comparator. The yellow example meets noninferiority criteria and has a point estimate that is no different from the comparator.

The green example meets noninferiority criteria and has a point estimate that is numerically greater than the comparator but does not achieve superiority because the lower bound is crossing zero. In order to achieve superiority, the point estimate and the lower bound of the confidence interval need to be to the right of the zero.

The primary analysis results for Probuphine meet both noninferiority criteria and superiority criteria because the point estimate and the lower bound of the confidence interval are right to the zero. The primary efficacy results in this study demonstrated proportion of responders to be

96.4 percent in Probuphine group and 87.6 percent in sublingual buprenorphine. The difference was statistically significant in favor of Probuphine with a chi square p-value of 0.034 demonstrating superiority for Probuphine.

While responders needed to have no evidence of illicit opioid use for 4 out of the 6 months in the study, a secondary endpoint looked at cumulative evidence of no opioid use throughout the 6 months. The cumulative proportion of subjects without evidence of illicit opioid use for each month of the study favored Probuphine, reaching statistical significance at month 3 and all subsequent months.

At month 6, 86 percent of Probuphine patients had no evidence of illicit opioid use for the entire duration of the study compared to 72 percent of the sublingual buprenorphine patients. Similarly, the time to first use of illicit opioid was significantly longer for Probuphine.

The separation is apparent by month 3 with a

statistical significance difference in time to illicit opioid use in favor of Probuphine with a hazard ratio of 0.49, a 51 percent relative risk reduction in the risk of first illicit opioid use versus sublingual buprenorphine with a log rank p-value of 0.037.

If we look at the actual rate of use, there were 31 total events in Probuphine and 64 events in the sublingual buprenorphine groups. The rate of illicit opioid use was significantly more in the sublingual buprenorphine group versus Probuphine, with a hazard ratio of 0.52 and a p-value of 0.003. Therefore, cumulative evidence of no opioid use in 6 months, time to first illicit opioid use, and the number of recurrent uses all corroborate the results of primary endpoint and contribute to the totality of evidence for Probuphine's benefit.

Objective and subjective measures of withdrawal remain stable on both treatment arms. The Clinician Opioid Withdrawal Scale, COWS, captures clinicians' assessments of objective signs of withdrawal. It demonstrated that patients

remained stable and did not experience symptoms of withdrawal in transfer to Probuphine, and in fact maintained the same results before and after transition to Probuphine, showing that patients had no clinical symptomatology associated with the change. Similarly, patient-reported Subjective Opioid Withdraw Scale also remained stable throughout the study with no apparent differences between the treatment arms.

Consistent with these results, patients also showed low scores under need and desire to use illicit opioids on both arms, demonstrating that patients remain stable throughout the trial in both groups with no increases in need or desire to use opioids.

Several sensitivity analyses demonstrated the robustness of the clinical efficacy results. The primary endpoint was 4 out of 6 months with no evidence of illicit opioid use. Sensitivity analyses looking at 5 out of 6 months free of illicit opioid use and all 6 months free of opioid use support the outcomes of the primary efficacy

endpoint. These more stringent definitions of response demonstrate favorable point estimates and confidence interval for Probuphine.

Additional sensitivity analyses examined the impact of the three subjects who were not included in the ITT data set because they had no efficacy data. Prior to the development of the statistical analysis plan, the protocol defined the ITT population to include all randomized subjects who received at least one study dose. Our statistical analysis plan, finalized approximately 6 months prior to unblinding of the study, defined the ITT population as those randomized, received treatment, and provided at least one post-baseline assessment.

The division considers the earlier definition from the protocol to be applicable. Therefore, we also conducted the primary analysis with the three subjects not included in the SAP defined ITT population. Using primary imputation methods, this analysis was consistent with the primary prespecified ITT data set with the point estimate and confidence interval favoring

Probuphine.

Imputing the three subjects with no efficacy data as non-responders so yielded a result that meets noninferiority criteria, though no longer meeting superiority criteria. Thus, even the most conservative approach of imputing patients with no data as non-responders still supports the positive results for the primary endpoint. This is truly conservative because these were stable patients, and there is an anecdotal report that 1 of the 3 subjects was likely to be a responder.

Additional sensitivity analyses examined the impact of missing urine toxicology data. In studies of opioid dependence, missing urine toxicology values have been handled in various ways. In clinically unstable patients, these missing values are generally imputed as positive for illicit opioid use. However, in clinically stable populations, it would be expected that most of the missing values would be similar to non-missing values.

For the sublingual buprenorphine arm, the

missing values were imputed consistent with this expectation, i.e., the proportion of positive urine samples for each subject was computed for each treatment group, and then the average of these proportions across subjects in this group was computed as group specific, probability of positive urine toxicology.

However, to be conservative, a penalty was applied to the missing urine values in the Probuphine arm by using an additional 20 percent penalty. In this group, the maximum estimates of the two group-specific probability of positive urine, multiplied by 1.2, was used as a basis for imputation. Therefore, this method of classifying patients with missing values as non-responders or responders in the primary analysis implements a penalty in the Probuphine group relative to sublingual buprenorphine.

Only 3 percent in both treatment arms had missing urine samples. The number of random and scheduled samples that were missing were similar in both groups. Each urine toxicology test comprises

22 urine toxicology panel items, and approximately 1.5 percent of the nearly 40,000 total panel items were not reported. These panel items affected 7 percent of the Probuphine urine samples and 4 percent of the sublingual buprenorphine urine samples.

Although missing data were minimal, sensitivity analyses were conducted to assess the impact of these missing data. Multiple analyses assess the impact of different approaches of imputing missing data. Sensitivity analyses using conservative approaches of imputing all missing urine toxicology results as positive for the ITT data set, and the same analysis with the inclusion of the three subjects without any post-baseline data, demonstrate that the point estimates favor Probuphine.

Additionally, imputing missing samples and missing panel items as positive also show that the point estimate favoring Probuphine with the lower bound of the confidence interval are well within the margin at negative 6.2 percentage points.

These results support the robustness of the primary result.

Supplemental use was another factor assessed for its potential impact on the primary endpoint. Even stable patients are expected to have periods when they require temporary dose adjustments. The study allowed investigators to provide supplemental buprenorphine as needed by their clinical judgment. Patients were told that the dose of buprenorphine they were receiving was expected to be adequate, but any additional supplemental treatments were allowed in addition to supplemental counseling and supplemental pharmacologic treatment.

Rates of use of supplemental buprenorphine were low and similar in both arms, 13 subjects in sublingual buprenorphine and 15 subjects in Probuphine. It's important to note that 5 of the subjects, one-third of the total in the Probuphine group, only required one dispensing episode. All 13 subjects in the sublingual buprenorphine arm who used supplemental buprenorphine had two or more dispensing episodes. There was one subject who was

an outlier in the Probuphine group with 21 total episodes.

This slide illustrates that although supplemental buprenorphine were used in both treatment groups, the majority of the subjects, overall 84 percent, did not require any supplemental buprenorphine. A closer review of the subjects with supplemental buprenorphine use shows that the use was similar in both groups with no specific pattern to the timing of use.

Clinical outcomes for the 28 subjects that received supplemental buprenorphine demonstrate that all subjects were responders except for one in the sublingual buprenorphine group. Eighty-seven percent were free of illicit opioid use throughout the 6 months in the Probuphine group compared to 69 percent in the sublingual buprenorphine group. Buprenorphine dose prior to study entry were similar in both groups, and very few had missing urine samples or even missing panel items.

These outcomes mirror clinical practice and dose modulation is not equivalent to lack of

response to treatment. Therefore, these subjects should not be characterized as non-responders. However, a conservative approach was used to analyze subjects who took supplementals, and we imputed patients who took supplementals as non-responders. This analysis is consistent with all the other sensitivity analyses. The point estimate favors Probuphine compared to sublingual buprenorphine with a lower limit of confidence interval well within the margin of negative 8.6 percentage points.

Study PRO814 met the primary endpoint demonstrating noninferiority of Probuphine relative to sublingual buprenorphine. The confidence interval was well above the prespecified noninferiority margin and in fact met criteria for superiority with a p-value of 0.034. Additionally, the major secondary endpoint analyses strongly support the primary finding and contribute to the totality of evidence, showing the benefit of Probuphine. Further, all sensitivity analyses demonstrated the robustness of these results.

I will now introduce Dr. Steve Chavoustie, who will present the Probuphine insertion and removal procedure and Probuphine safety.

Applicant Presentation - Steven Chavoustie

DR. CHAVOUSTIE: Thank you, Sonnie, and good morning, everyone. My name is Steve Chavoustie. I am a principal investigator with the Segal Institute for clinical research. I am board certified in obstetrics and gynecology and have extensive experience implanting and removing contraceptive implants.

I have received honoraria for my time. I do not have any financial interest in the company or the outcome of this meeting. I was a sub-investigator in the phase 2 PK study, all phase 3 studies, and served as an advisor to help develop the Probuphine applicator, surgical procedures, and training program.

During the clinical development program of Probuphine, subdermal implant, development, equipment procedures evolved. Norplant was approved in 1990. The 6 silastic Norplant implants

were inserted using a trochar and were removed by a technique developed by the Population Council referred to as the standard technique.

The technique involved pulling the implant out by its end using a hemostat from an incision at the base. Since fibrosis forms around the implants, removing them utilizing the standard technique was difficult and time consuming. A new removal technique referred to as the U-technique was published by Dr. Praptohardjo in 1993 to enhance the removal procedure and deal with the fibrotic implants. It was considered more convenient and preferable to clinicians and to the patients. Subsequently, several other implantable medications, including Implanon, Vantas, and Supprelin were approved.

In response to lessons learned from the Norplant experience and from Probuphine's first double-blind study 805 and its extension study 807, we modified the equipment, procedures, and training related to the implant insertion and removal. Let's start by talking about the equipment and

procedure modifications.

In studies 805 and 807, we used a blunt-tipped applicator and a 5 to 10-millimeter incision for implant insertions -- so about your fingernail breadth -- and the standard removal technique for Norplant. For studies 806, 811, and 814, we modified the procedures to use a sharp, bevel-tipped cannula and a 3-millimeter incision for implant insertions and utilized the modified U-technique for removal.

This technique involves grasping the implant in the middle using a modified vasectomy clamp and removing it through a midline incision parallel to the implant tracks. The modified vasectomy clamp, or X-clamp, has a 2.5 millimeter opening to grasp the implant atraumatically.

The training program also evolved. For studies 805 and 807, we provided implanting physicians with an instructional DVD, written instructions for self-guided training. If needed, our implant medical monitor provided additional training at the study sites.

In studies 806, 814, and 811, we introduced the Competency Based Training program consisting of a training manual, an instructional video, and an half-day interactive classroom session involving reviewing the brachium of the arm, managing complications such as fibrosis, protrusions, extrusions, bleeding, and infections. Participants from various medical specialties received hands-on training where they practiced implant insertion and removal techniques using a meat simulation model. The master trainers observed each trainee carefully during this session to confirm that they had achieved competency. We did not stop evolving the training program at the end of the 814 clinical trial either.

This is a Probuphine training classroom setup at the National Center for Human Factors in Healthcare within MedStar Health. MedStar was engaged to design and execute a thorough and robust human factors study. They validated all steps involved with the procedures and associated training components to equip users with the

knowledge and skills to safely complete both the insertion and removal procedures while minimizing risk of harm to patients.

The final training program is designed to have a 5 to 1 ratio of trainees to master trainers to allow for more intensive observation and education. The training includes three primary components. First is the implant procedure training, which includes a slide presentation and live demonstration of the procedures on a meat-simulated human arm presented by a master trainer.

Next, as shown in this photograph, is in the insertion and removal live practicum. This is where trainees practice the insertion and removal procedures using the meat model. The meat model is preimplanted with a deep implant, a normal implant, a fractured implant, and an implant designed to represent fibrosis, the adhered one.

To simulate this, Super Glue was injected around that implant to create the fibrosis. Actually, it's technically more difficult to remove

that implant than it is in the human arm. This gives the trainees practical experience dealing with difficult removals. The trainers are available to guide participants through each step and answer any questions they may have.

Finally, there's a certification exam. Trainees must both successfully answer a series of knowledge-based questions and demonstrate proficiency of 21 critical tasks for insertion and 18 critical tasks for removal. I've shown you how we have enhanced the equipment procedures and training during the development program. Let's now review an actual insertion and removal procedure.

The first step in Probuphine insertion is to set up a location that is appropriate for performing a sterile procedure and assuring aseptic technique is practiced throughout the procedure. Identify the proper insertion site, preferably on the non-dominant arm about 8 to 10 centimeters above the medial epicondyle of the humerus, and then prep the skin.

The skin prep is a two-step process. First,

we wipe the skin off with alcohol to remove any debris, or surface dirt, or any oils, and then we mark the site with a single marker. Then the second part of the prep involves using ChloraPrep triple sticks in three sequential swipes.

Inject local anesthetic under each marked track and make a 3-millimeter incision. Insert the beveled cannula along the first track. Important. By maintaining less than a 20-degree angle and tenting the skin, you insert subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper below the subdermal plane.

Load the applicator and insert the implants under each marked track into the subdermal plane. Apply Steri-Strips to close the incision. Palpate the implant to confirm proper location and apply a pressure dressing. Instruct the patient on proper wound care and remind them to notify their doctor immediately if they see any signs or symptoms of infection, including pain, swelling, redness, fever, drainage or pus or incisional opening.

The insertion process takes about 10 to

15 minutes. After a treatment duration of 6 months, the implants will be removed. The removal process is also a minor office-based procedure utilizing aseptic technique throughout. Begin by locating all of the implants by palpation and mark each one before prepping the skin. Inject local anesthetic beneath the implants; this way they lift the implants towards the skin.

You make a 7- to 10-millimeter incision length-wise between the second and third implant. You gently grasp the middle of the implant with a modified vasectomy clamp, thus utilizing the U-technique. You dissect the fibrous tissue around the implant, lift and remove the implant through the incision, and ensure that all 4 implants have been removed in their entirety. Once the 4 implants have been removed, suture the incision, apply an adhesive bandage, and a pressure dressing wrap. Emphasize proper wound care to the patient as we have previously discussed.

The implant removal is typically completed in 20 minutes. It is important to stress that all

4 implants need to be palpated before beginning the procedure. If they are not, refer the patient for implant localization by ultrasound.

I'll now present and overview of implanting physicians in the clinical development program. Within the clinical studies, the implanting physicians came from a variety of backgrounds, including surgery and subspecialties, family medicine, internal medicine, obstetrics and gynecology, anesthesiology, and psychiatry.

The safety database consists of 7 Probuphine clinical studies. The primary safety evaluation is based on pooled data from the three double-blind studies 805, 806, and 814. This is unlike the discussion of clinical efficacy, which was focused on the results of study 814.

I will first discuss buprenorphine, which is contained in multiple FDA-approved transmucosal formulations and briefly its safety data as an implantable formulation. We will then focus on the safety profile of the implant itself and the insertion and removal procedures.

370 patients were exposed to Probuphine during the clinical development program; 151 subjects were exposed for 6 months or longer and 85 subjects were exposed for 12 months or more. Additionally, in a recent case, a study [sic] returned to the clinical investigator's site approximately 7 years after the insertion procedure and had the implants removed without difficulty.

The safety database for the procedure includes subjects who received placebo implants. An additional 198 subjects received placebo implants in the controlled clinical trials for a total of 568 subjects who were exposed to either Probuphine or placebo implants.

Here is an overview of subjects who reported adverse events during the double-blind studies. You will note that rates of adverse events declined from the earliest study, 805, to the most recent study, 814. The next row shows rates of adverse events leading to study discontinuation. Serious adverse event rates were similar between study arms across the 3 double-blind studies.

There was one death in the sublingual buprenorphine group during the development program. This death occurred in a sublingual buprenorphine control arm 806. The subject was a 29-year-old woman who suffered a fatal heroin overdose 3 days after she voluntarily withdrew from the study.

Looking more closely at the most recent study, 814, there are several events of interest to consider. A 2-year-old child of a subject in the sublingual buprenorphine group was admitted to the ICU after consuming an unknown number of sublingual buprenorphine tablets that were accidentally dropped and scattered on the floor. She was discharged home from the hospital the following day in stable condition.

In addition, 2 subjects in the sublingual buprenorphine group entered rehab facilities due to relapse. These subjects remained in and completed the study. Also in study 814, 2 subjects had incidents related to alleged theft. One subject in the sublingual buprenorphine group reported that a relative stole her study medication. A second

subject reported that her study medication was stolen from her vehicle.

Non-implant site adverse events were similar between treatment groups. These are the events that occurred in greater than 5 percent of subjects in the pooled, double-blind studies. The most frequent adverse events were headache, insomnia, nasal pharyngitis, upper respiratory infection, nausea, anxiety, and back pain. While a few events were more frequent on Probuphine, the overall rate of adverse events was the same in both groups, 64.7 percent.

What is unique about Probuphine is the safety related to the implant and the associated procedures. The implant site adverse events decreased substantially when we compare the first double-blind study, 805, the yellow column, with the last study, 814, the blue. These changes correlate with the refinement of the equipment, procedures and training.

By the time we got to the study 814, implant site related events are much less frequent. We

combined all implant site adverse event terms that could indicate infection. The overall infection rates across all 7 clinical studies was 4 percent. The infection rate in PRO814 was 3.4 percent. Only 6 subjects discontinued from the clinical studies due to implant site adverse events. All of these discontinuation events occurred in study 805 and its extension label study 807 when we were using the original technique and the standard technique for removal. There were no implant site adverse events that led to discontinuation from studies 806 or 814.

The overall safety profile for Probuphine in the clinical development program was comparable to approved forms of buprenorphine for the treatment of opioid dependence and approved types of subdermal implants. No unexpected adverse events, based on the known safety profile of buprenorphine, were identified.

The implant site adverse events that occurred were minor and manageable. Moreover, implant site adverse event rates declined during

the development program after the equipment and the insertion and removal procedures were refined and the training program enhanced. Thank you.

Application Presentation - Behshad Sheldon

MS. SHELDON: Thank you, Dr. Chavoustie.

Probuphine risk management program is a comprehensive approach to ensuring the safety of patients, which we designed in collaboration with our advisors, both in addiction medicine and in implementation procedures. Because Probuphine administration requires a procedure not common to addiction medicine, we agree with FDA that a risk evaluation and mitigation strategy, or REMS, is required.

We've designed a REMS in keeping with guidance also from the DEA and SAMHSA because the REMS must comply with the applicable laws relating to controlled substances as well as to those relating to office-based prescribing of buprenorphine. As we've reached agreement with the FDA's Division of Risk Management on the proposed REMS, we are providing this overview of the REMS on

behalf of FDA as well.

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the improper insertion/removal of Probuphine and also the risk of accidental exposure, misuse or abuse if an implant comes out or protrudes from the skin. This is done by educating providers, informing patients about the risk of complications, and distributing Probuphine only to trained and certified healthcare providers.

Dr. Chavoustie's already explained the educational program, the 4-hour competency-based training program that we will be using to ensure that the procedure is managed if Probuphine is approved and is on the market. We'll provide these REMS training programs at sites throughout the nation so that all interested healthcare providers will have an opportunity to be certified as a prescriber or an implanter.

The program incorporates what we've learned from the human factor study and includes a didactic

lecture, live demonstration using the pork model, and a practicum using the same pork model will provide us practice and necessary skills. Then, participants who intend to be certified as implanters need to correctly perform 21 critical tasks for insertion and 18 critical tasks for removal as part of the procedural competency assessment.

So who do we think will likely participate or want to participate in this training and certification program? Current buprenorphine prescribers represent a variety of disciplines. The largest two groups are primary care physicians and psychiatrists. These groups represent 44 percent and 23 percent of prescribers, and 49 percent and 24 percent of prescriptions. Other prescribers include specialists in emergency medicine, pain management, anesthesiology, OB/GYN, surgery, and others who also provide addiction treatment.

Based on surveys to date, we expect that the majority of potential Probuphine prescribers plan

to fill a dual role of both prescriber and implanter. But we also recognize that some potential Probuphine prescribers are likely to have limited experience performing sterile surgical procedures and may need the assistance of other colleagues for their patients.

Based on the human factory study, we expect that providers who've completed a medical residency or fellowship in a procedural specialty, or who do procedures more regularly, are most likely to be able to pass the procedural competency assessment to be certified to be able to be implanters.

We initially proposed to FDA that the participation even in the REMS training program for implanters be limited to healthcare providers who have procedural backgrounds or specialties. However, we subsequently agreed with FDA's Division of Risk Management that providers who are able to pass the rigorous procedural competency assessment, regardless of their backgrounds or specialties, should be able to implant and remove safely. This is particularly important for psychiatrists who are

critical to the adoption of any new medicine but who may not have prior procedural experience.

Braeburn will not exclude non-proceduralists from seeking to be certified to perform insertion and removal procedures. Rather, we strongly recommend that providers seeking to be certified have proficiency in aseptic technique in suturing and removal of foreign bodies prior to participating in the training program.

We expect that psychiatrists will appropriately self-select based on their own prior clinical experiences. Some psychiatrists may be able to demonstrate procedural competency and perform the dual role of prescriber and implanter. In the human factors study, for example, we saw that several psychiatry residents who had pretty recent training did extremely well in learning the procedure and passing the competency test.

The psychiatrists who determine they're unable to implant or unable to pass the procedural competency test will have two options. Those who are practicing in a multi-specialty environment

where an implanter can come to the psychiatrist to provide the procedure will do so in the psychiatrist's office. Those psychiatrists with a solo practice or who otherwise do not have the correct facility for the implantation will be able to refer out to an implanter who's either DATA-2000 waived or practices at an OTP.

Although our proposed REMS program distinguishes between healthcare providers who prescribe versus implant, all healthcare providers must participate in the live training program. As a conditional certification, both prescribers and implanters must attest that they will counsel patients on the potential risk of Probuphine, complete the didactic and live practicum training, pass the Probuphine REMS knowledge test, and document the completed Probuphine insertion/removal in the patient log.

Prescribers have an additional obligation of ensuring that the insertion/removal procedures are only performed under the supervision of a healthcare provider who's certified to implant

Probuphine unless they refer the patient out to a certified implanter. In addition, implanters must pass the procedural Competency Assessment Test and ensure that the facility where the procedure will be conducted has the appropriate equipment to safely perform the procedure.

Certified healthcare providers will receive a series of take-home materials and the insertion/removal checklist, which highlights key components to ensure effective insertion and removal of Probuphine is intended for use at every procedure. Healthcare providers will also receive the instructions for use booklet, the slides from the training program, the package insert, medication guide, the patient counseling tool, and insertion/removal log that they'll also need to use for every procedure.

The second main component of achieving the REMS goal relates to patient education. The REMS program is designed to ensure that patients are aware of the general risks associated with insertion and removal of Probuphine and that

serious risk can occur if Probuphine implant is expelled. The REMS program is also designed to ensure that patients have adequate guidance about wound care and preventing further complications and accidental exposures in the unlikely event of an expulsion.

Both prescribers and implanters will be required to provide live counseling to patients. Implanters will use the medication guide prior to performing the insertion procedure. In addition to the medication guide, prescribers will also use the patient counseling tool, which confirms awareness of all potential risks and could be signed by both patient and provider.

The Probuphine website will provide an overview of the REMS program and requirements as well as the training slides, the medication guide, and patient counseling tool. The website will include adverse event reporting information. It will also include a locator tool that will enable prescribers to search for nearby certified implanters.

The final component to achieve Probuphine REMS goals is a closed distribution system. Probuphine will only be distributed directly to providers through a specialty distributor hub under a buy and bill model. Only certified prescribers will be eligible to order Probuphine, and the hub will verify that the prescribing physician is either DATA-2000 waived or practices at an OTP; that the prescribing physician is REMS certified, and that there is a certified provider who will insert and remove Probuphine.

Healthcare providers will be required to store Probuphine in accordance with the Controlled Substances Act. Following the removal procedure, providers will be required to dispose the Probuphine implants as pharmaceutical, biohazardous waste. Thus, under this system, there is no mechanism for obtaining Probuphine through a prescription that patients fill at a retail pharmacy. Probuphine is never in the hands of patients.

The Probuphine REMS also includes ongoing

assessments to ensure that the program is working as well as intended. The FDA is still reviewing the assessment plans, so the summary presented here represents Braeburn's current proposal. We'll record and report the aggregate number of certified prescribers and implanters. We will review evaluations of the REMS program didactic and live practicum training submitted by program participants and make quality improvements as needed.

We'll monitor and evaluate the closed distribution system by tracking orders that are filled by the specialty hub, by reviewing orders that are rejected by the verification hub, including identifying reasons for rejection and investigating any suspicious orders. We'll investigate any improper shipments of Probuphine as determined through semi-annual audits of all shipped orders.

Finally, we'll investigate any irregularities and third-party reports suggesting that there's been any kinds of diversion of

Probuphine and collaborate with any licensing boards or law enforcement as necessary.

In addition to the elements of the REMS that we've already discussed, we will also provide additional support for healthcare providers. Upon request, insertion/removal toolkits will be available. These will include all materials necessary for the insertion/removal process except for lidocaine. Additionally, upon request, Braeburn's clinical educators will be available for the first insertion/removal procedures subject to compliance with HIPAA regulations. Probuphine master trainers will be available for consultations, and clinicians may attend additional training programs at any time.

The Probuphine risk management program is a comprehensive system to assure the safe use of Probuphine and of the procedure. It includes patient and provider education, mandatory training and certification for prescribers and implanters, and a closed distribution system that limits distribution to only certified providers. We are

committed to assuring the safe use of Probuphine and will continue to monitor the effectiveness of this program and to improve all aspects of the program based on healthcare provider feedback.

I'd now like to welcome Dr. Frost to discuss the benefit-risk conclusions.

Applicant Presentation - Michael Frost

DR. FROST: Thank you. I'm Dr. Michael Frost. I'm a physician, board certified in both internal medicine and addiction medicine. I'm the medical director at Eagleville Hospital, which is a 300-bed inpatient addiction treatment facility outside of Philadelphia. I also serve as president of Frost Medical Group, which is a state accredited outpatient addiction treatment center.

I've received consulting honoraria for my time, but I do not have any financial interest in the company or the outcome of the meeting. I had the opportunity to act both as a principal investigator in the 814 study as well as an implanter, and I have experience with both insertion and removal of Probuphine.

We've provided substantial evidence that Probuphine is effective for clinically stable patients. These are patients that are maintained at 8 milligrams or less of buprenorphine and have been taking the same dose for at least six months. I treat patients like this every day in my practice. They are engaged in their treatment and demonstrate a commitment to their long-term wellness.

Study 814 compared Probuphine to sublingual buprenorphine in clinically stable patients maintained on doses of 8 milligrams or less. This first of its kind study demonstrated that Probuphine is not inferior to sublingual buprenorphine. 96.4 percent of subjects treated with Probuphine and 87.6 percent of patients treated with sublingual buprenorphine had at least 4 out of 6 months with no evidence of illicit opioid use. Strikingly, 85.7 percent of subjects in the Probuphine group showed absolutely no evidence of illicit opioid use.

In the 814 study, there were two instances

of sublingual tablet theft and one instance of accidental pediatric exposure to the sublingual buprenorphine tablets. Probuphine reduces these real-world occurrences that patients receiving sublingual buprenorphine currently face.

Probuphine contributes to reducing the number of buprenorphine tablets available from misuse, diversion, or accidental exposure. In the 814 study, patients in the Probuphine arm received only a total of 1,288 buprenorphine tablets. By contrast, patients in the sublingual buprenorphine arm received a total of 16,667 tablets. Moreover, these equivalent outcomes were obtained with 76 percent less medication overall.

The reduction in pill burden coupled with Probuphine's extended release characteristics and closed distribution system will help to reduce the risks associated with sublingual buprenorphine.

Probuphine can reduce the anxiety that many of my patients feel about medication supply, dosing, and medication loss or theft. It can also ease the fear of accidental exposure of a child or

other member in their household. Probuphine is more convenient for patients by offering increased discretion compared with monthly trips to the pharmacy or the daily burden of sublingual self-administration that can pull them away from their family and work for up to 20 minutes or more per day. Probuphine allows the patients the freedom to work and play without the stress of managing their medication supply.

As a provider, I welcome the flexibility that Probuphine offers me and my patients. I will be able to spend more time addressing factors related to my patients' recovery and less time on issues surrounding medication adherence or availability. Perhaps most importantly, several of my patients told me that treatment with an implant would make them feel much less self-conscious about their addiction and much more like normal people. This is really about giving peace of mind to patients and providers.

Buprenorphine has been well characterized, and Probuphine's general safety profile is

comparable to the profiles of various transmucosal formulations. There were no unexpected adverse events and no deaths from Probuphine during the clinical development program. The adverse events related to the implantation and removal procedures were not serious and did not result in patients withdrawing from the study.

While some patients experienced mild, localized and transient bleeding, pain, swelling, or fibrosis and scarring from implantation and removal, these are minor risks and are common to all surgical procedures. While procedure related events are key risks to consider for Probuphine, the clinical safety data and the validated training program show that these risks can be managed effectively.

Finally, while Probuphine is designed and expected to be sufficient to maintain clinical stability among patients treated with 8 milligrams or less of sublingual buprenorphine, the waxing and waning nature of opioid dependence may require periodic intensification of treatment. None of the

patients I cared for in the 814 study required or requested supplemental buprenorphine, but in clinical practice, psychosocial stressors or biologic changes may necessitate adjustment of pharmacologic or psychological therapies.

Dose increase may be indicated not as rescue therapy but as physician-directed temporary dose adjustments. This occurs in the management of all chronic diseases. It is analogous to a patient with diabetes on a long-acting insulin, requiring the intermittent addition of a shorter-acting insulin to better maintain stable blood glucose levels.

The episodic use of physician-directed supplemental buprenorphine in a patient who maintains clinical stability on Probuphine should still be considered a treatment success. For doctors and patients alike, Probuphine can take away the uncertainty about ensuring consistent delivery of medication.

We know that buprenorphine works well when it's taken, but sublingual daily dosing creates

opportunities, inadvertent or not, to miss doses. The six-month dosing of Probuphine has the potential to reduce those opportunities while offering convenience and much greater discretion compared with daily dosing. Just as sublingual buprenorphine allowed patients to move away from the stigma of daily clinic visits, an implantable formulation goes even further to provide patients greater freedom and security.

Opioid addiction is a chronic, relapsing brain disease, and clinicians need more treatment options. Effective treatments that are less susceptible to diversion and abuse benefit patients, clinicians, and our society. As an addiction treatment provider, I need more treatment options, and my patients certainly deserve the same range of long-acting therapies that are available to patients with other chronic illnesses. No medication alone is going to solve the opioid epidemic, but Probuphine has a valuable role to play in a disease that claims so many lives. Thank you.

Clarifying Questions to Applicant

DR. KRAMER: Thank you very much. We're a little bit behind schedule, so I'd like to explain to everyone, and the committee in particular, what we're going to do. We are going to preserve 15 minutes as was on the original schedule just to receive clarifying questions for the sponsor. These are things you don't understand that you really couldn't get from both the packet and the presentations that you need to have before we proceed with the meeting. After that, we will take a 10-minute break, so the FDA presentation will start 10 minutes later than on the schedule.

What we'd like to do is if you have a question, put your name tag vertical and also try to get Jennifer Shepherd's eyes so that she can write you on a list, and we'll go through the list. And try to be very succinct with your questions.

MS. SHELDON: Could I just have -- sorry -- the last slide back up? I wanted to introduce the other folks who are available to answer questions, if that's okay.

DR. KRAMER: I think people have that in their packet.

Dr. Bickel?

DR. BICKEL: I have three questions. I was wondering if there was any qualitative analysis of the statements that led to supplemental dosing between the two groups and whether they were of similar or dissimilar statements. I am interested to know if patients are advised, if they are lost to follow-up technically from the study, what are they supposed to do with the medication that is in their arm? Are they given instructions about that?

Lastly, I want to know if they were to extract the rods themselves, could they get the medication out of it. How would they extract it? Is that possible?

MS. SHELDON: So we'll start with the last one first. It is unlikely that patients will take rods out of their arms. And I'll have both Dr. Chavoustie and Dr. Torrington discuss the surgical skills necessary to do that, but also the risk-benefit of getting what ultimately will be the

equivalent of 10 pills that could be available on the market. It is possible to extract buprenorphine, but let me I guess maybe start with Dr. Torrington.

DR. TORRINGTON: Hi. Matthew Torrington. I'm a family medicine doctor with a specialty in addiction medicine. I've received honoraria for my time, but I have no financial interest in the outcome of this meeting or in the company.

Yes. So it is possible to extract some buprenorphine from the implants with either alcohol or with like a long-term saturation method. But the estimates are that they get a very small amount of buprenorphine from them. There's about 80 milligrams total I think in the dose of 4 rods. So considering how available buprenorphine seems to be on the street from our patients, it just seems very unlikely considering these patients are incredibly resourceful and efficient in what they do. So it is possible, but it seems somewhat unlikely for us.

MS. SHELDON: You also asked about the

patients who were lost to follow-up. All patients are told during the procedure that they need to return after 6 months for the implants to be removed, and that we really don't know how much longer after that the medication will continue to work.

That did happen with one of our patients who was incarcerated for the duration of the study. We made actually -- he was out for a little bit of time, and we were really hoping to get some assessments from him. We made actually every attempt to even access him while he was incarcerated to be able to get data back, but were unsuccessful. He did return after the study was completed to have his implants removed and reported that while he was incarcerated, he did not use, and ultimately tapered off buprenorphine.

DR. BICKEL: My question actually was, are patients given instructions if they were to leave the ability to go through what would be the standard procedure for the extraction of the rods, what they should do, like if they move to another

part of the country or something.

MS. SHELDON: In the REMS program, the website will actually have locators. And so they'll be able to click on their zip code or their area and be able to find a different implanting physician to help them with the removal process.

DR. BICKEL: And my first question was about qualitative statements.

MS. SHELDON: On the supplemental use?

DR. BICKEL: Yes.

MS. SHELDON: We have narratives on all 28 patients who received supplementals. There were a variety of reasons given. The outlier patient actually who received 21 -- slide up, please. I'll give you just one example. This was the patient who received 21 episodes, actually asked to come back for weekly psychosocial counseling as well as incremental doses of buprenorphine.

This patient was experiencing situational anxiety and depression, had some life stressors going on, and ended up actually doing quite well from an overall perspective of not having any

positive urine toxicology and completing the study successfully.

There seemed to be some practice differences in how clinicians deal with supplemental use. Some clinicians have told us and as you saw in the briefing book, 21 out of the 28 patients who received supplementals came from two sites. And what we've heard from clinicians is some of them believe buprenorphine has other benefits beyond treating opioid dependence.

So if somebody has some symptoms relating to anxiety or depression, they don't mind increasing the dose a bit in order to manage that. Other clinicians would use specific medications that are for those diseases. They would given them an anxiety medication or an SSRI instead. We think that that's part of why we see some variation across practices.

DR. KRAMER: Okay. We're going to go on because we have a lot of people that have questions. Dawn Ionescu?

DR. IONESCU: Hi. Just a very quick

question. I'm Dawn Ionescu. For study 807, there were two patients that had some implant site AEs that hemorrhaged, infection. And it was not related to the procedure. I'm just curious. What was it related to?

MS. SHELDON: Dr. Chavoustie?

DR. CHAVOUSTIE: We can put that slide up. That's actually -- slide up. One of the subjects, as I recall -- and I'd have to maybe after the session pull that slide for 807. But there is a subject that had an infection that was a cellulitis that was in the contralateral arm to the implant. And that was from self-injecting, and it got infected. It had nothing to do with implant.

Any increase amount of hemorrhage or bleeding during that 805-807 trial is -- remember, I mentioned about the incision was 5 to 10 millimeters for putting these implants in, which was much too large. It's now 3 millimeters. So that's why you'll see that the rate of bleeding has markedly -- almost nil in the 814 trial.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: I have a couple questions. I know you guys didn't do PET studies to look at the receptor occupancy. Now, pharmacokinetically, you say like 50 percent based on trough levels and 30 percent, 16-milligram dosage equivalent, based on area under the curve. So where do you think -- what percentage receptors are you occupying? Have you done any kind of simulations to estimate PK/PD data?

MS. SHELDON: So I'd like to ask Dr. Sharon Walsh to come and address your question directly. But it's important to remember that this was a clinical trial. Essentially, not trying to equate doses, but answering the empirical question with clinical data, showing that you could transfer patients effectively who've been stabilized on 8 milligrams or less.

DR. NARENDRAN: But that range, it seems to be quite important to know if you're closer to 4 or you're closer to 8. You know what I mean? And then that also relates to the amount of sublingual dosing they're getting.

DR. WALSH: Good morning, everybody. My name is Sharon Walsh, and I'm from the University of Kentucky. And I will receive consulting fees for time today, but I have no financial interest in the company or the outcome of this study.

Slide up, please. This slide illustrates data from a study that was published by Dr. Mark Greenwald, in which he examined the receptor occupancy from mu opioid receptors following maintenance on buprenorphine across a range of doses that cover largely the clinical range. And you can see that at a dose of 2 milligrams, there's about 41 percent receptor occupancy, and at 16 milligrams, this is increased to nearly 92 percent.

Next slide. In a subsequent study that Dr. Greenwald and colleagues published this past year, they examined the imaging data along with pharmacokinetic data and clinical outcomes to try and get exactly at the question that you're asking. And what they estimated was that there was a dose needed of about 4 milligrams of sublingual

buprenorphine or about 50 percent occupancy for adequate withdrawal suppression, a much higher dose needed for blockade.

Based upon FDA's clinical pharmacology team and their assessment of the Probuphine product, it is expected that the concentration of buprenorphine would be -- I'm going to estimate somewhere around the 6-milligram dose for the coverage for the range from 8 or lower seems to be appropriate and practicable.

In the next slide -- slide up, please -- you can see the outcomes for the responder rates by the doses that the patients were on at the time that they came into treatment. In the upper part of the panel, you're looking at those individuals who are stabilized on 8 milligrams before starting, and in the lower part, you're looking at those who were on less than 8 milligrams. And there were patients who were on 2, 4, and 6 milligrams.

What you can see is that if the concern is that there's inadequate plasma concentration, that those people who were on 8 milligrams when exposed

to Probuphine, they had a 98 percent response rate really supporting the efficacy of this plasma delivery concentration in this group of patients.

DR. NARENDRAN: My second question kind of relates to this. The 814 trial, it seems like these weren't -- I mean, 70 percent of them were using prescription opiates. Less than 15 or 20 percent were using really heroin. And I assume that most of these people are inhaled users and were using IV heroin, because you have a low fraction of IV heroin.

So is this fair to say that this is a more clinically less ill sample compared to the previous trials? And could that relate to why your implant side effects are lower? Because I would assume for your IV drug user, you're probably going to have more complications with infections still and fibrosis.

MS. SHELDON: We did have some IV drug users, and we can get you the exact numbers after the break. Certainly, the fact that these patients were clinically stable, that tested to be

clinically stable by their clinicians and had not been abusing for at least -- that they were abstinent for the last 3 months and had been in treatment for 6 months would suggest that they were, in overall, better health and certainly clinically stable.

DR. WALSH: If I can just add one thing to that. They were on their stable dose for 6 months, but the average time in treatment was actually 3 and a half years. So these patients had probably been doing pretty well. And we don't really know -- obviously, they were having difficulty before they had initially entered treatment --

DR. NARENDRAN: Sure, sublingual.

DR. WALSH: -- so they had a long period of treatment before they came into the study.

DR. NARENDRAN: Thank you.

DR. KRAMER: If committee members could try to be really concise and limit your questions to things you think the sponsor could provide quickly, we could have longer discussion during -- we have plenty of time this afternoon in our discussion

period, and we can call them back up if we need be; because we're not going to get through everyone at the rate we're going.

Lori Dodd is next.

DR. DODD: Yes. I have a simple question related to the three early terminations in the Probuphine arm. Can you tell me what happened to those three?

MS. SHELDON: We don't know what happened to two of them. Well, we know where one patient ended up. He left and went to Key West and did not return.

DR. DODD: I'm sorry. This was prior to any treatment, receipt of any treatment?

MS. SHELDON: After receiving the implant --

DR. DODD: After the implant received.

MS. SHELDON: -- after the implant was -- yes. And then one was the one that I described that went to jail for the duration, and we have no information on the third patient.

DR. DODD: But all three did receive

implants --

MS. SHELDON: They did.

DR. DODD: -- and then went missing. Okay. Thank you.

DR. KRAMER: To the sponsor, your terminology to call that group intent to treat, including people that -- and excluding people who received drug is not standard and very confusing. So I think that's an important question. I hope everyone heard that. Three people who received the implant were not included in the analysis.

Dr. Higgins?

DR. HIGGINS: I'm particularly interested in the correlation, if any, between those who are older adults and the Probuphine. I know it's probably hard to do this analysis because you have fewer people who are older, but I'm wondering if there were any correlations between the Probuphine and any adverse effects, rescue medication used, wound control, and any missing urine samples.

MS. SHELDON: The average age, as you noted, was below 40, and we did not have many older

subjects in our trial. But overall, we have not seen an impact on any demographics, including age, in terms of safety or efficacy for Probuphine.

DR. KRAMER: Dr. Grieger?

DR. GRIEGER: Just a quick question. Comparing slides CE-54, in which 15 of the Probuphine individuals received some supplemental sublingual buprenorphine with slide CB-106, where it says 1288 pills -- I presume those are actually the sublingual --

MS. SHELDON: They were the supplemental.

DR. GRIEGER: -- sublingual version.

MS. SHELDON: Yes.

DR. GRIEGER: What was the distribution? It would seem like some of those individuals are receiving hundreds of pills, and others maybe a handful. Is that correct?

MS. SHELDON: Exactly correct. There was quite a variation as low as 1 single 2-milligram pill and as high as 210 pills. So there was the variation of dispensing episodes, and each dispensing episode really depended on the

clinician's judgment. We wanted to make sure we were not restrictive at all, artificially, in directing supplemental use so that this could mimic would could happen in the real world. So we're very liberal, giving no guidance whatsoever.

Slide up, please. So you can see the range of number of 2-milligram doses that were given.

DR. GRIEGER: Okay. Thank you. With a concern for potential diversion in the real world, in a clinical world, would you consider implant withdrawal at some point if someone's asking for hundreds of supplementals?

MS. SHELDON: Certainly, we would think that that would be based on the clinical judgment and the relationship between the clinician and their patient. From our perspective, if a patient does not appear to be doing well on Probuphine after one set of implants, it is a decision that would be logical to reconsider.

DR. KRAMER: David Pickar?

DR. PICKAR: Yes. A quick pharmacology question. It plays off of what Rajesh was talking

about. In the lower dose range, it acts as an agonist, the classic buprenorphine, mixed agonist/antagonist. The dose range that will be delivered by this implant would be in the agonist category but not the antagonist category. Is that correct?

Do I understand that right? It does not act as an antagonist, as opposed to the mix, naloxone buprenorphine, which is Suboxone and so forth, which is very commonly given. Do I understand this right, that in the blood levels you're getting here, it would seem to be in a 50 percent occupancy of the mu receptor, and it would be considered pharmacologically as an agonist, not an antagonist? Is that correct?

DR. WALSH: So let me try to clarify. Buprenorphine is only considered a mixed agonist/antagonist because it has agonist properties at one receptor and antagonist properties at another receptor, which is -- as the kappa antagonist. People frequently refer to it as a mixed agonist/antagonist and think of it as

having antagonist properties at higher doses. But that's actually because it's a partial agonist.

So as a partial agonist, you're familiar I'm sure with the ceiling effect. But what happens at higher doses is that it can behave like an antagonist in someone who's opioid dependent because it can precipitate withdrawal, just as if you had someone, say, on methadone, and they received an injection of naloxone, and they went into withdrawal.

We know that if you have someone on methadone, and you give them buprenorphine because it has lower efficacy, it will essentially knock the methadone off the receptor, and it can also precipitate withdrawal. And we know that that's a dose-related phenomena. It depends on what people have had.

So I think what I think you're really asking about is blockade and the idea that you get cross-tolerance or blockade with antagonist-like features. Is that --

DR. PICKAR: The real question behind it --

DR. WALSH: Yes.

DR. PICKAR: -- is the agonist properties. Is that additive to mu agonists properties of heroin of exogenous opiates? And in that case, does it make you more sensitive to overdose. That's where I was going with it. Because it's not going to be an antagonist.

DR. WALSH: Right.

DR. PICKAR: And a comment. In an addiction population, an individual on oral sublingual dose are certainly clever enough to stop their medicine for a day if they want to expand into other opiates.

DR. WALSH: Yes.

DR. PICKAR: It just is. I'm sorry, but it is.

DR. WALSH: Yes.

DR. PICKAR: Here, you don't have the option. So if you want to experiment in exogenous opiates, you're going to add it to what you have. So the question is a little simple. Is its agonist properties at the mu receptor additive to exogenous

mu receptor agonists from an overdose point of view?

DR. WALSH: Yes.

DR. PICKAR: I'm just -- error of safety at this point.

DR. WALSH: Thank you. Yes. It's not additive. Maintenance on buprenorphine, even at lower doses, will produce some protection against overdose. That's one of the reasons that it's effective. Will it produce as much blockade against an illicitly used drug as 32 milligrams? The answer is no to that. We know that it's a dose-dependent phenomena, and that the higher the dose is, the better blockade.

We actually have some data that illustrate this. Is it possible to see the Comer data? While they're finding that -- and if they don't, we can do it after the break. But what we know that is -- even at doses that we think are -- slide up, please -- higher than the Probuphine dose -- so these are data from Sandy Comer's lab that show people who are maintained on buprenorphine at 8 and

then 16 milligrams. And we generally think of 16 milligrams and higher as a blocking dose.

In this case, these individuals are in a laboratory setting, and they're maintained on buprenorphine, and then they're being given the opportunity to take heroin. And they're being asked in the left panel how much do you like the drug if they choose to take the heroin, and on the right side, you're looking at the actual heroin-taking behavior in a self-administration procedure.

What you can see is that at 8 milligrams, you don't see good blockade for taking heroin at these doses, and that by doubling the dose of buprenorphine to 16 milligrams, you see some reduction, but it's not a complete reduction.

Next slide. In this slide, this is a study that we did a number of years ago, basically doing the same thing, looking at the efficacy of methadone, which we have a lot more clinical experience with. And in this study, we maintained people on doses of methadone, and then also gave them opportunity to take heroin in the laboratory.

In this case, patients were maintained on 50, 100, and 150 milligrams per day of methadone. And if you are a methadone treatment provider, you know that these are substantially high doses. And the surprising finding about this study is that we also think that methadone produces the same kind of cross-tolerance or blockade.

In this study, even at 100 milligrams, which is much higher than the average dose, we don't see complete blockade of heroin on top of the methadone. And in fact, we needed to go to a dose of nearly 150, which very few patients are on, to see nearly complete blockades. So we know that methadone and buprenorphine are both efficacious, but they don't actually need to have complete opioid blockade in order to be so.

DR. PICKAR: Physiologically -- you're showing behavior. But in terms of respirations and so forth, when you put heroin on top of the lower dose of buprenorphine, do you get any enhancement of respiratory depression?

DR. WALSH: It would depend on the dose of

heroin. If you were -- you're going to get some blockade where you're not going to get additive effects because receptors are already occupied. It's a competitive receptor phenomenon. So if you push the dose high enough, you're going to start to see additive effects. It's kind of the same situation where you've got somebody, say, on a high dose of buprenorphine and maintenance, and then they need analgesia. You want to be able to surmount that in order to get an analgesic response.

DR. PICKAR: At doses that don't blockade, you get an added physiologic effect --

DR. WALSH: No.

DR. PICKAR: -- okay. That's the question.

DR. WALSH: No.

DR. KRAMER: Okay. I think we're going to have to interrupt our questions. We will come back to all the people that had -- we have your names down. We will return to the clarifying questions after the FDA presentation. We will have a 10-minute break now. We're going to return at

10:25, quick break. We're going to start exactly at 10:25.

(Whereupon, at 10:17 a.m., a recess was taken.)

DR. KRAMER: Okay. We're already past our scheduled time, so if everyone could take their seats.

Is FDA ready to start their presentations? We will come back to the people who have questions for the sponsor. And for the sponsor, the clarifying questions are really important, and we will come back with the additional ones and give you a chance to answer, after the FDA.

FDA Presentation - Rachel Skeete

DR. SKEETE: Good morning, everyone. My name is Rachel Skeete, and I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. I'm the primary clinical reviewer for the Probuphine new drug application resubmission, and today, I along with Dr. James Travis -- he's a statistical reviewer -- will be presenting on the efficacy and safety findings for

Probuphine for a subpopulation of patients with opioid addiction.

Specifically, we'll be presenting these findings for Probuphine for the maintenance/treatment of opioid dependence in patients who are considered clinically stable by their treating healthcare provider.

During this talk, we'll be providing background information on buprenorphine in the transmucosal forms currently used for treatment of opioid dependence, the Probuphine drug product, and a summary of the regulatory history leading up to the present new drug application submission being discussed today.

The efficacy discussion will focus on the results of the PRO814 trial, the single trial conducted in patients deemed clinically stable, and on low to moderate doses, up to 8 milligrams, of a transmucosal buprenorphine product. Dr. Travis will discuss these findings. Finally, the discussion of safety will focus on the safety of the individual indwelling rods and the procedures

to insert the rods and remove them at the end of a treatment cycle.

Probuphine is an implantable formulation of buprenorphine. And as we discussed so far today, the drug substance buprenorphine is a partial mu opioid receptor agonist. Currently, there are transmucosals specifically, both sublingual and buccal formulations, that are approved for the treatment of opioid dependence.

These transmucosal forms can be used for new entrants to treatment. And when used for new entrants to treatment, the typical maintenance dose is 16 milligrams. And this is Subutex tablet equivalents, and that's as a single ingredient. When used in the combined buprenorphine naloxone forms, the dose is 16/4 and as a Suboxone tablet equivalent.

Buprenorphine has dose-dependent activity. It takes only small amounts to stave off withdrawal symptoms. These are doses approximately in the range of 2 to 4 milligrams. To achieve blockade however, higher doses, approximately 16 milligrams

and above, are typically needed.

Compared to full agonists, buprenorphine safety and tolerability profile is notable for withdrawal syndrome that is delayed and reduced in intensity as well as a so-called ceiling effect, in that there's a plateau of the agonist effect such as respiratory depression.

As mentioned, transmucosal forms of buprenorphine are available for the treatment of opioid dependence. This summarizes the landscape of the transmucosal products. These include Suboxone and Subutex tablet formulations, which were approved in 2002 and were the first products approved. They are no longer marketed, but generic forms are available.

The sublingual film was approved in 2010, and later a supplement for a buccal administration was approved for the film last year. More recently Zubsolv sublingual tablet was approved in 2013, and Bunavail buccal film was approved the following year in 2014.

So over the course of the evaluation of

Probuphine for clinically stable patients on low to moderate doses of transmucosal buprenorphine product, additional products have come on the market in recent years. Across the products, there are differences in the bioavailability and buprenorphine plasma exposures at particular doses. Both of these points are important for providing guidance on appropriate administration procedures for Probuphine.

This table provides an overview of the corresponding doses for the transmucosal buprenorphine containing products. There is a lot of detail on this slide, but there are two main points that I'd like to highlight from this slide. The first is that the doses of Zubsolv and Bunavail are lower than the doses for the Suboxone products, as you can see.

Zubsolv and Bunavail are more bioavailable, so only lower doses are necessary to achieve comparable plasma exposure levels to the Suboxone products. Another important take-home from this slide is that although the corresponding doses for

Suboxone tablets, including the generic equivalents and Suboxone film, are nominally the same for each strength, Suboxone sublingual films are more bioavailable, particularly the two highest doses -- that's the 8-milligram/2-milligram, and the 12-milligram/3-milligram doses -- and they provide higher buprenorphine exposures than their tablet counterparts at the same dose.

Again, the array of transmucosal products and the differences in bioavailability would have bearing on any guidance on transitioning stable patients on a transmucosal product to the fixed dose Probuphine product.

Now that we have some background on the available transmucosal products and as the potential role of Probuphine in the addiction treatment is being considered via transfer from these types of products, the drug-use patterns for these products bear mention. Members of the drug utilization analysis staff within the Office of Surveillance and Epidemiology provided 2014 drug utilization data, which is an update to the drug

utilization data provided in FDA's background documentation.

In 2014, 1.3 million patients received dispensed prescriptions of transmucosal buprenorphine containing products from U.S. outpatient retail pharmacies, which is a modest increase from the 2012 data, while the total number of prescriptions, 10.6 million, remained relatively stable.

As was the case in 2012, prescribers whose specialty is identified as general practice, family practice, or osteopathic medicine wrote for the largest number of buprenorphine prescriptions. This was followed by prescribers whose specialty is defined as psychiatry and internal medicine to round out the top three groups of prescribers.

With the background on the transmucosal forms in mind, we'll shift to discussing Probuphine, the implantable form and the purpose for our discussion today. The applicant has already described their product in their presentation, so I won't repeat the full

discussion. Here, I'll only highlight a few points pertinent to our discussion today.

The first is in regard to terminology. During the presentation, you'll hear me refer to the individual Probuphine implants, that's 1 of 4, as either rods or as implants. The other points I'll mention have to do with the applicant's indication and proposed dosage and administration procedures as they relate to what was studied in the PRO814 trial, which supports this resubmission.

The applicant's proposed indication is for the maintenance treatment of opioid dependence and should be used as part of a complete treatment program to include counseling and psychosocial support. This indication would indicate that all-comers, including new entrants to treatment, would be appropriate for Probuphine. However, only a subpopulation of patients, specifically patients who are considered clinically stable by their treating healthcare provider, was studied in the PRO814 trial. The proposed indication should, thus, reflect the population that was eligible for

study intended to establish efficacy.

Similarly, the applicant's proposed dosage and administration directions include instruction that Probuphine is appropriate for patients who are opioid tolerant and on a dose of 8 milligrams or less of a sublingual Subutex or Suboxone equivalent. Although these subjects were on a maintenance dose of 8 milligrams or less of a Subutex or Suboxone equivalent -- and I'll stress that this should be specifically a tablet equivalent -- the patients in this trial are considered clinically stable and having been on the dose alone was not supposed to be sufficient for entry into the trials, or trial. As with the indication, the dosage and administration instructions should more closely reflect the population studied.

The final point I'll make here is that in the clinical development program, there hasn't been experience with insertion or removal of Probuphine rods or implants beyond two administration sites. There are also no data examining the efficacy and

safety of reinsertion into a previously-used site.

The applicant proposes that there are 4 administration sites, 2 sites per arm. So at this point in the drug product's development, there are a maximum of only 4 treatment cycles for this product, which is intended to be used for chronic relapsing condition. In some cases, even fewer site would be available if there are complications requiring early removal of the implants and reinsertion into the other arm during a single treatment cycle.

I've been describing this present application as a resubmission. The initial submission of Probuphine, of the NDA, was in October of 2012. The application was an is a 505(b)(2) application, meaning in this case that it relies in part on agency safety and efficacy findings for Subutex and Suboxone sublingual buprenorphine tablets.

When the Probuphine application was initially submitted, it was intended for maintenance treatment of opioid dependence in

all-comers, including new entrants to treatment. To use this product, a patient would first receive sublingual buprenorphine with the intent of reaching a target dose of 12 to 16 milligrams per day for at least 3 days.

After reaching a target dose, patients would undergo an initial insertion of 4 rods. At the time, there was an option for the fifth rod when certain criteria, based on amount of rescue use, were met. There are no longer plans to maintain this option for a fifth rod.

To support this initial application, there were 2 main trials conducted. These studies, identified as PRO805 and PRO806, were two nearly identical safety and efficacy trials. The clinical development program also included two 6-month extension trials, PRO807 and PRO811, which were the extensions to 805 and 806, respectively; a pharmacokinetic study; and a comparative bioavailability study comparing Probuphine to 16 milligrams of sublingual buprenorphine.

The 6-month PRO805 and PRO806 trials

enrolled new entrants to treatment who initially received 4 Probuphine or 4 placebo rods As I mentioned previously, there formerly was an option for a fifth rod that was planned for the original development program.

Rescue or supplemental buprenorphine use was permitted and used in a treatment failure definition. Subjects were withdrawn from the trial if they met protocol-specified rescue buprenorphine-based withdrawal criteria. Although it was used to define treatment failure, supplemental use wasn't taken into account for determining treatment response.

The efficacy evaluation was based on urine toxicology and self-report. Urine toxicology was collected 3 times per week. The reason for this frequency in urine testing was that the window of detection for many opioids is up to 3 days, so that the frequent testing helps to avoid urine samples being classified as negative simply because use of an illicit opioid was outside of the detection window for a particular urine sample.

Urine toxicology findings were taken along with self-report of illicit opioid use occurring around the time the urine samples were collected, to adjudicate a urine sample as being positive or negative. If either the urine toxicology or self-report was positive, the sample was considered positive.

Investigators were blinded to urine toxicology findings during the trial. And because the goal was to evaluate individual treatment response, a response profile was used for the analysis. In this case, the cumulative distribution function, or CDF, of the percent of opioid-negative urines was evaluated to assess treatment response. Missing urines were considered positive for the purposes of the analysis, and once withdrawn from the study, patients' urine samples were considered positive from the point of discontinuation on.

These are the results of the trials based on the cumulative distribution function. On the left of the slide is the graphical representation of the

findings for each trial showing the CDF curves. On the right is a tabular summary. Let's first look at the graphs starting with the PRO805 graph.

On the X-axis is the proportion of negative urine samples. On the Y-axis is the proportion of patients. The solid curve is the Probuphine arm. The dashed curve is placebo. If you look at the 0.3 mark, which is a little bit difficult to see, on the X-axis, this refers to 30 percent or more urine samples negative for opioids. Now, looking at the proportion of subjects meeting this threshold, between 40 and 50 percent of Probuphine patients had 30 percent or more opioid-negative samples, while a little under 30 percent of placebo patients had 30 percent or more.

For both trials, we had hoped to see more of a separation of the curves and a higher number of patients on the right-hand side of the X-axis, representing higher proportions of patients achieving abstinence or near abstinence. However, what we saw instead was the curves approaching zero towards the right of the X-axis, where abstinence

and near abstinence were represented and higher proportions of patients represented towards the left and the middle of the X-axis, where the changes in drug-use behavior were less conclusive, particularly in study 5.

The tabular summary on the right shows the same findings. There were no abstinent patients and few near abstinent patients. The placebo rates in study 6 are markedly lower compared with study 5 and probably represent a higher dropout rate as a result of stricter criteria for receiving supplemental medication imposed for the trial.

We also looked at subject-level analyses for these earlier trials. Again, we were interested in individual response. You'll see more presentations similar to this of the data for study for PRO814, and I'll spend a few moments orienting you to this data presentation strategy.

These are subject-level urine toxicology data for study 5. Each subject is represented as a point along the Y-axis. There was 2 to 1 randomization in the trial, so the Probuphine data

points are twice as many. When you follow a line across, you see all of that patient's urine toxicology results over the 24-week period of the study. A blue dot is a negative urine sample, red is positive, and a plus sign is missing.

As an example, the first placebo patient on the bottom had one opioid negative urine sample, then 2 positive samples, and then was discontinued. From that point on, all the rest of the urine samples are missing and are represented by a plus sign, and would be considered positive from then on.

Ideally on these graphs, you would see a lot of blue, especially on the Probuphine side. But instead, you see a lot of red representing submission of opioid-positive urine samples throughout the treatment period. Drug-use behavior based on urine toxicology and self-report data was used to evaluate efficacy, and that's what you're seeing here.

We found this subject-level urine toxicology results to be similar for study 6. And here in the

Probuphine arm, compared with study 5, there's arguably more evidence of opioid use. So in review of the original application submitted in October 2012, the review identified concerns with efficacy. Buprenorphine exposure with Probuphine is about 0.9 ng per ml, which is enough to manage withdrawal symptoms, whereas about 3 ng per ml is needed for blockade, raising concerns that on Probuphine, a subject could potentially avoid experiencing withdrawal symptoms but still continue to experience euphoric effects of illicit opioids.

There were also concerns about the comprehensiveness of the evaluation of implant safety at that time. An advisory committee meeting was also held in March of 2013 that addressed safety concerns with the procedures for insertion and removal, efficacy, and the REMS, and included experts in addiction medicine, obstetrics and gynecology, risk management, and statistics.

Although the majority of the committee voted that efficacy had been demonstrated, that safety had been adequately characterized, and the

risk-benefit ratio favored approval, the comments during the discussion and the breakdown of votes revealed considerable ambivalence about the application.

Based on review of the totality of information supporting the application, the application was not approved, and the application received a complete response in April of 2013. The major deficiency in the application was that it was unclear to us that the clinical benefit of the seemingly minor changes in drug-taking behavior had been established.

Because Probuphine provides lower buprenorphine exposures and a target maintenance dose for new entrants to treatment, it appeared that the dose was too low. To address these issues, the applicant was advised to conduct an opioid blockade study and/or study higher doses of Probuphine. There were also concerns about the safety with insertion and removal procedures, and the applicant was advised to conduct a human factors evaluation to validate the training

program.

In November of that same year, we met with the applicant after the complete response to action to discuss next steps. The applicant proposed limiting the indication for Probuphine patients stabilized on a dose of no more than 8 milligrams of sublingual buprenorphine. Comparative by availability data had shown that Probuphine provides plasma buprenorphine exposures in the range covered by 8 milligrams or less of sublingual buprenorphine. The applicant aimed to find a population for whom Probuphine might be appropriate, in lieu of studying higher doses or demonstrating opioid blocking properties.

This represented a novel indication, a new population never previously studied, as well as the need for a novel study design in an area where clinical trial design already is continuing evolving. There is also no singular established definition for clinical stability, which could present a number of challenges in making an efficacy determination.

In the case of Probuphine, we took into consideration the potential public health benefit of this product, which may reduce misuse, abuse, and accidental pediatric exposure in the face of a growing public health crisis surrounding opioid abuse and addiction, and recognized that some flexibility was warranted. Additionally, Probuphine offers the potential for improved patient adherence to the prescribed dose.

We were willing to consider the limited indication, but another trial in this new population and for the new indication would be needed to establish efficacy. Afterward, there were a series of post-meeting communications to discuss the study design for PRO814. The trial intended to support limited indication.

During these communications, the applicant was informed that meeting the primary endpoint would not automatically lead to a finding of efficacy, particularly given all the uncertainties and given some of the latitude that would be needed to take in permitting such an evaluation.

In August of last year, the applicant resubmitted the Probuphine NDA, and the PRO814 trial is intended to provide evidence of efficacy for the limited indication. The applicant provided details of the study design in their presentation, so I'll only summarized a few key points. Again, this was a phase 3, multicentered, double-blind, double-dummy active control, with the active control being sublingual buprenorphine, efficacy and safety trial that took place in 21 U.S. sites.

The study enrolled adults with a diagnosis of opioid dependence who were considered stable by their healthcare provider and were confirmed by three criteria, including that they were on sublingual buprenorphine for at least 24 weeks.

Although this was intended to be for the 24 consecutive weeks prior to study entry, it appears to have been interpreted as a cumulative lifetime duration or lifetime total used. At screening, subjects were asked, "In your lifetime, how long have you been treated with buprenorphine and how many times have you entered buprenorphine

treatment?"

They were also supposed to be on a dose of sublingual buprenorphine of no more than 8 milligrams a day for the last 90 days. This was envisioned to be a buprenorphine sublingual tablet equivalent, but as we saw earlier, there are other transmucosal forms available for treatment of opioid addiction. And some subjects were on these other transmucosal forms where they may have been a bit of a mismatch between their pretrial and on-study buprenorphine exposures. Eligible subjects also submitted no opioid positive urine samples in the past 90 days.

The treating healthcare providers completed and signed a clinical stability checklist attesting to their patients' clinical stability and indicating the clinical stability criteria on which they were judging their patients to be stable.

The Clinical Stability Checklist is reproduced here, and the questions are excerpted on the next slide for better readability. Treating healthcare providers were asked to check off items

for their patients related to self-reported illicit opioid use in the past 3 months, their living situation' withdrawal symptoms; participation in recommended psychosocial support groups; compliance with clinic visits requirements; desire or need to use illicit opioids; hospitalizations, ER visits, or crisis interventions; and other indicators.

During the trial, subjects either received 4 Probuphine rods or sublingual buprenorphine along with the placebo for the comparator treatment for this double-dummy trial. Subjects could also receive supplemental buprenorphine, which I also will be referring to as rescue for short at times. But use was expected to be rare, and it was written into the protocol that patients were to be told that while additional counseling and other pharmacological interventions were available.

The then current dose of buprenorphine was expected to be adequate to maintain stability and that they were not expected to need supplemental sublingual buprenorphine. Because use of supplemental was expected to be sporadic, if at

all, supplemental use was not factored into the response definition.

Urine toxicology and self-report were assessed for their efficacy evaluation. There were 6 scheduled monthly urine toxicology visits at which time self-report of illicit opioid use was assessed. And there were 4 random urine toxicology visits, where only the urine sample was collected. The scheduled and random urine toxicology visits combined for a total of 10 samples for the trial.

Recall that in the previous trials, urine samples were collected 3 times a week, and in addiction, trials, urine samples are commonly collected 1 to 3 times a week. So this represents a small number of urine samples for a trial and for one of 6 months duration. But because this was a stable population, less frequency seemed to be more consistent with clinical practice. However, likewise, because this was a stable population and the sampling was infrequent, the applicant was informed that there shouldn't be very many missed urine samples.

As you will see, there weren't many missed visits for urine samples, but there were a number of analytic issues with submitted urine samples.

The efficacy analysis employed a responder definition. A subject was considered a responder if they had no more than 2 months with evidence of illicit opioid use either by urine toxicology or self-report. The efficacy analysis was intended to establish noninferiority rather than superiority.

Although it's conceivable that a product that offers so-called passive compliance could potentially be demonstrated to be superior, it also seemed reasonable to permit a noninferiority analysis. This strategy for analysis was informed by the literature, which is limited and a small survey of addiction specialists.

The key questions in the physician survey that were used by the applicant to inform the proposed noninferiority analysis were how often do you expect the average stable patient in your practice to test positive for opioids over a 6-month period? The responses were converted to

opioid-negative urines, and on average, the specialists endorsed that their clinically stable patients would be opioid negative more than 90 percent of the time.

They were asked if these patients were to continue on the same dose, what would be the overall average percentage of opioid-negative urine toxicology results they would anticipate in 6 months. These responses were reported as the amount of opioid-negative urines anticipated over the next 6 months, and the responders endorsed only if they're a bit less.

Next, they were asked if their patients' buprenorphine treatment were to be stopped, what would be the average percentage of relapse in these patients over a 6-month period. This question serves as a proxy for understanding the placebo response in these patients, and on average, respondents believed that approximately 70 percent of these patients would relapse if their buprenorphine treatment were to be stopped.

Finally, the specialists were asked to

assume that urine toxicology is measure monthly for 6 months. In that context, they were asked what they considered to be the maximum reasonable change in a stable patient's urine toxicology status for the patient to continue to be considered stable, and they were given 4 choices: no change, 1 out of 6 urine-positive urine toxicologies, 2 out of 6, or 3 or more out of 6.

These were converted to percentages to report the results. On average, the specialists thought that 14 percent was a reasonable change, which as a percentage is closest to 1 out of 6 positive urine toxicology results over that period.

In sum, with buprenorphine, the specialists on average considered that their clinically stable patients would submit an opioid-positive urine sample 1 or fewer times in the first 6 months and 1 or fewer times in the subsequent 6 months if they continued on buprenorphine. If they were to have one additional positive urine during a 6-month period, the respondents on average thought that those patients could still be considered stable in

that setting.

Given these findings, a responder was defined as no more than 2 months with evidence of illicit opioid use. I'll again emphasize that a certain amount of flexibility was applied in this case. The typical conditions needed for a noninferiority study and for defining a responder were not present in this situation. What information could be garnered was used in designing this trial, again with the understanding that careful review of the findings would be undertaken because of the many uncertainties with a trial design such as this one.

The population studied in PRO814, as was discussed briefly previously, was a predominantly male, almost exclusively white, non-Hispanic, non-Latino group. They were about 40 years of age and reported prescription opioids as their primary opioid of abuse.

In contrast, the population of new entrants to treatment studied in the earlier trials, PRO805 and PRO806 for the original application, more

commonly identified heroin as their primary opioid of abuse. On average, subjects had been on buprenorphine for 2 years consecutively before entering the study, and there were a total of 28 patients with a buprenorphine treatment episode prior to entry of less than 24 weeks.

I'll point out here that these data may not fully represent the length of the treatment episode prior to entry. Recall that patients were asked how long they were on buprenorphine treatment in their lifetime. So these data are a rough approximation indirectly estimated from other sources of data available in this submission, for example, from the concomitant medications history collected during screening.

The specific length of the treatment episode prior to entry does not appear to have been captured directly by asking a question of either the patients and/or the providers. And in fact, for these same patients, their reported lifetime buprenorphine history was on average 34 months, nearly 3 years, and the shortest duration was

6 months for one patient, with the longest lifetime duration being almost 10 years.

The highest lifetime dose for patients was 14 milligrams on average for both groups. The highest lifetime individual doses reported on average were 8 milligrams, 16 milligrams, and 24 or more. At study entry, the majority of subjects were on the 8-milligram dose.

On the clinical stability checklist, the healthcare providers were to check all the items that applied to their patients. These are the proportions of subjects for who a particular item was checked off. For many of the items, healthcare providers universally endorsed them for their patients. Only participation in a structured activity or job, consistent participation in a recommended cognitive behavioral therapy program or support program, and hospitalizations, ER visits, or crisis interventions were not unanimously endorsed. But they still represent relatively high proportions of the patients. The applicant did note that it is possible that hospitalizations, ER

visits, or crisis intervention item may have been underreported because of an artifact of the form that was used.

Now, I will discuss the results of the efficacy analyses for the trial, and I'll now turn the discussion over to Dr. Travis, the statistical reviewer, to discuss the results of the efficacy findings.

FDA Presentation - James Travis

DR. TRAVIS: Good morning. My name is James Travis, and I'm the statistical reviewer for this application. We'll begin this session of the presentation by giving an overview of the study design, as this was a noninferiority study, so I will begin by discussing the concept of noninferiority and how it relates to this study. I will also discuss the applicant's definition of a responder and how they incorporated missing data in their analysis.

Following the discussion of the study design, I will discuss the efficacy results. There were several factors, including the choice of

analysis population, missing data, and the use of rescue medication, which were not adequately explored in the primary analysis of the planned sensitivity analyses. The effect of these factors on the efficacy analysis will be explored in this presentation.

Now, on to the study design. The current trial enrolled patients who were stabilized on 8 milligrams or less of buprenorphine. It was thought that if these patients discontinued buprenorphine treatment, a significant number would relapse. Consequently, the agency agreed that conducting a placebo-controlled study in this population would be unethical.

Conducting a superiority study of Probuphine compared to sublingual buprenorphine would be infeasible because patients in this population were expected to be clinically stable with a low chance of relapse. In order to see superiority of Probuphine compared to sublingual buprenorphine, patients stabilized on sublingual buprenorphine would need to deteriorate to a greater degree than

patients receiving Probuphine. So it was agreed that a double-dummy noninferiority design would be utilized, where patients would be randomized to either remain on sublingual buprenorphine and receive sham implants or receive Probuphine and be switched to sham sublingual tablets.

In this slide, I will present the rationale given by the applicant in determining their noninferiority margin. The applicant stated in their protocol that they believe a margin that preserves at least 70 percent of the effect of the active control would be considered clinically acceptable. As there were no historical placebo controlled studies directly comparing the active control sublingual buprenorphine to placebo in this population, the applicant estimated the placebo response rate using a survey of addiction specialists.

The addiction specialists expected a median of 75 percent of subjects would relapse if their stable dose were to be discontinued, and so it was assumed that 25 percent of the patients would

maintain clinical stability if they discontinued.

Using this estimate, the applicant then assumed that the difference in responder rates, which is also referred to as the effect size, for sublingual buprenorphine when compared to placebo is 75 percent. A margin of 20 percent was then selected, which the applicant assumed would preserve slightly more than 70 percent of the assumed effect size.

Noninferiority can be concluded if the lower bound of the 95 percent confidence interval of the difference in response rates between Probuphine and sublingual buprenorphine is greater than minus 20 percent.

Now, moving on to the applicant's definition of a responder. A responder was defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid usage. Evidence of illicit opioid use was defined as either a positive urine test or a self-report of illicit opioid use. A total of 10 urine tests were to be conducted in the study, 6 during the subject's monthly site

visits and 4 randomly scheduled. The applicant specified that no more than one random test be conducted per month.

Subjects were also asked to report any illicit opioid usage only during the monthly site visits and not during the random visits. It is important to note that the applicant's definition of a responder did not consider use of supplemental sublingual buprenorphine.

The applicant described the following procedure for imputing the illicit opioid usage status when there were no urine samples provided for a particular month. The assumed proportion of positives was determine by taking the average of the intra-subject positive rate for that treatment arm. The analysis was made more conservative by increasing the positive rate by 20 percent over the higher of the two rates for the Probuphine treatment arm.

A final important aspect of the clinical trial was the choice of the analysis population. The applicant stated that they intended to use a

modified intent-to-treat population, or mITT, for their primary analysis. However, they provided two different definitions for this population.

The first definition, which was provided in the study protocol, included all randomized subjects who received any study medication. The second definition excluded subjects who failed to provide any post-baseline efficacy data. This definition was utilized by the applicant in their primary analysis.

Now moving on to the efficacy results. Presented on this slide are the results of the applicant's primary analysis. The lower bound of the 95 percent confidence interval is greater than minus 20 percent, or minus 0.2, so noninferiority to sublingual buprenorphine was concluded. Further, when the applicant tested for superiority, the p-value was 0.03, and superiority of Probuphine to sublingual buprenorphine was also concluded. However, there were several deficiencies with this analysis, which I will now discuss further.

First, I will discuss the issue with the

selection of the analysis population. A total of 4 subjects who were randomized into the study were excluded from the analysis population. One subject randomized to sublingual buprenorphine did not receive study drug, and I believe it is appropriate to exclude this subject from the analysis population.

Three subjects randomized to Probuphine received study medication but did not provide any efficacy data. Two were lost to follow-up and one was incarcerated. These subjects were excluded from the applicant's primary analysis population, which I do not believe is appropriate.

On the next slide, I will present my analysis where these subjects were included and considered to be non-responders. The first listing in this table is the applicant's original primary analysis, which was previously shown. The second listing shows the results of the analysis when the 3 excluded subjects were included as non-responders.

We see that the p-value for superiority is

greater than .05 for this analysis, meaning that we cannot conclude superiority. However, the low bound of the confidence interval is still greater than minus 20 percent, and so Probuphine would still be considered to be non-inferior to sublingual buprenorphine.

In addition to the selection of the analysis population, we noted 4 deficiencies with the applicant's missing data procedure for their primary analysis. First, missing data was only imputed if all samples were missing for a particular month. For example, if a random sample was scheduled and missed in a particular month, and if the regular sample was negative, no imputation was performed.

Second, illicit opioid usage was assumed to be equally likely for missing and observed data. The plausibility of this assumption was explored in various sensitivity analyses, which I will present.

Third, as designed, the applicant's missing data imputation scheme has a small probability of classifying a subject, who provided absolutely no

efficacy data in the study as a responder. For example, in the primary analysis for the imputation, it used a positive rate of approximately 13 percent, which gives a 97 percent probability that someone who provided absolutely no efficacy data would be classified as a non-responder, which we do not think is realistic.

Finally, there are a number of issues with inconclusive samples that the applicant made no attempt to explore in their original efficacy analyses. We will discuss these issues on the next slide.

The first and largest issue was interference with the analysis of the norfentanyl content in the urine. The applicant states that this problem can occur when there are other compounds that could have interfered with the chromatography of the lab's methods. The applicant said that it was not possible at this time to rule out tampering with the sample in order to conceal use.

There were also issues with the sites providing urine specimens to the lab after the

applicant's defined creatinine acceptability cut-off. Approximately half of these samples were also provided after the defined stability cut-offs for the majority of the opioids.

Overall, we see that there were approximately twice as many positive tests for the sublingual buprenorphine treatment arm than for the Probuphine treatment arm. There were however many more issues with missing data for subjects in the Probuphine arm.

This figure shows the results of the urine toxicology assessments conducted during the study with the subjects receiving Probuphine on the left and the subjects receiving sublingual buprenorphine on the right. Each row in the figure represents the results for a single subject.

The green crosses represent the negative tests, the orange squares represent positive tests, and blue circles represent either missed visits or tests where the results were incomplete. The black open squares indicate the subjects who did not provide all 10 urine specimens. Subjects above the

black line provided at least 3 positive urine toxicology specimens during the trial. As you can see, there were a greater number of responders in the sublingual buprenorphine arm who provided 1 or 2 positive urines.

There were several subjects in the study who repeatedly provided urine specimens that could not be completely analyzed. This appears to be due to the issues with the analysis of norfentanyl.

This table shows a summary of the percentage of the subjects in each treatment arm who experienced each type of issue. Just over half the subjects in both arms completed the study and provided 10 negative urine samples. The proportion of subjects who provided positive urine tests was high in the sublingual buprenorphine arm than the Probuphine arm, while the proportion of subjects with missing data is higher in the Probuphine arm than the sublingual buprenorphine arm.

In order to evaluate the extent of the effect of missing data on the conclusion of the study, two further analyses were conducted. For

the first analysis, all occasions where a sample was missed were classified as positive. The non-responder definition used for this analysis was the same as for the primary analysis, i.e., the subjects were classified as a non-responder if there was evidence of illicit opioid usage or missing data for at least 3 of the 6 months in the study.

The second analysis was to explore the effects of incomplete and missing urine samples on the conclusion. In this analysis, any subject with a missed or inconclusive sample was assumed to be positive. The responder definition was again unchanged. We see that the lower bound of the 95 percent confidence interval is greater than minus 20 percent for both these analyses, and so noninferiority can be concluded for both.

It was anticipated that since the patients who were to be enrolled in this study were stabilized on a low dose of buprenorphine, that the current dose of buprenorphine should be adequate to maintain stability and hence, there should not be a

need for any additional supplemental buprenorphine. However, supplemental buprenorphine was required by approximately 15 to 18 percent of the subjects in the study, with a similar proportion in both arms requiring supplemental doses.

Though the proportion of subjects requiring rescue in the two arms was fairly similar, the quantity of rescue medication tablets used was considerably higher for the subjects in the Probuphine arm with subjects receiving approximately 70 percent more tablets on average than the subjects in the sublingual buprenorphine arm.

The supplemental buprenorphine was dispensed as a 2-milligram tablet. To distinguish rescue medication from study drug and maintain blinding, a different brand of sublingual buprenorphine tablet was used. The blue circles represent when the supplemental buprenorphine was dispensed to the patient. The duration of use represented by the blue lines was calculated by assuming that the patient used a single additional 2-milligram tablet

per day unless otherwise specified.

As you can see, there were a number of subjects who received supplemental medication for the majority of the study. Though the majority of these subjects appear to be adequately managed, the level of rescue used may indicate that the dose of buprenorphine delivered by Probuphine, a non-titratable product, is insufficient for these subjects, so we explored a different definition of responders considering use of rescue.

In this slide, we present the results of the sensitivity analyses we conducted to explore the impact of supplemental buprenorphine on the responder rate. These analyses correspond to those previously presented to explore the effect of missing data but with any subjects who required any supplemental buprenorphine classified as non-responders.

For both these analyses, the response rate is considerably smaller than that seen with the previous analyses. In both cases, the lower bound of the 95 percent confidence interval is greater

than minus 20 percent, and hence, noninferiority can still be concluded.

This figure corresponds to the first analysis where all subjects with missing urine samples are assumed to be positive. Subjects above the black line provided at least 3 positive or missing samples. And this figure corresponds to the second analysis, where all subjects with missing or inconclusive urine tests are assumed to be positive.

According to the applicant, one of the main advantages of Probuphine is that it has the potential to reduce the opportunity for diversion and the risk of accidental exposure to buprenorphine compared to the currently available treatment options. However, if patients require additional sublingual buprenorphine in order to remain stable, these advantages are eliminated. Consequently, the impact of patients randomized to receive Probuphine requiring additional sublingual buprenorphine may be more significant than for those continuing to receive sublingual

buprenorphine.

To examine this, I conducted two additional analyses to explore the impact on the responder rates. Probuphine patients requiring rescue were considered non-responders. The first analysis shows the response rates if all subjects who received rescue are considered to be non-responders. We see that Probuphine would no longer be considered non-inferior to sublingual buprenorphine, and in fact, sublingual buprenorphine would also be considered to be superior to Probuphine.

The first analysis considered any subjects who required supplemental medication to be a non-responder. This may be overly harsh, as there are also a number of subjects who required only a limited number of doses for a short period of time. However, hence, a second analysis was conducted where the definition of responder was considered to be no more than 2 occasions where rescue medication is dispensed or months with evidence of illicit opioid usage.

We see that under this less strict definition, Probuphine would be considered to be non-inferior to sublingual buprenorphine. Missed samples were considered to be positive in both analyses.

Finally, here is the conclusion of the efficacy analysis. Here is a summary of the analyses we have presented. In addition, the final three lines show the responder rates when no positive or missing urines are allowed with varying levels of rescue use permitted. In these analyses, we have explored the impact of several factors, including the choice of the analysis population, the handling of missing data, and the impact of rescue medication on the response rate for Probuphine.

From a regulatory perspective, in order to establish the efficacy of a drug, it is important to examine a range of plausible assumptions and consider the worst case scenarios. However, the analyses considered in these explorations may not be clinically useful or even realistic.

Now, we will return to Dr. Skeete, who will summarize the clinical implications of the efficacy findings.

FDA Presentation - Rachel Skeete

DR. SKEETE: Thank you, Dr. Travis.

As you saw from the discussion of the efficacy results, we identified a number of challenges in interpreting the efficacy data. This in turn presented challenges for defining an appropriate population for Probuphine and determining the most appropriate way to present these results.

The applicant defined the ITT or intent-to-treat population as randomized subjects who are randomized and receive study medication, and provided post-baseline efficacy data. Based on this definition, 3 patients in the Probuphine arm, who received study medication but didn't return during the treatment period, were admitted from the applicant's analysis. These included 2 patients who were lost to follow-up and 1 incarcerated patient.

However, in a patient population deemed stable by their treating healthcare providers, discontinuations for these reasons in patients who just underwent procedures to insert Probuphine was seen to have implications for judging treatment response.

Some urine toxicology samples were missing because subjects did not attend visits to provide urine samples. In other cases, the subjects submitted the sample, but there were problems analyzing the samples. Of the total samples collected, samples that were missed or not properly analyzed occurred more frequently in the Probuphine arm than sublingual buprenorphine arm. Of the samples submitted and analyzed, a higher proportion of positive samples were see in the sublingual buprenorphine arm. The urine toxicology data, along with self-report, were used to define a responder.

Although supplemental buprenorphine use was anticipated to be sporadic among stable patients, some patients required sublingual buprenorphine

throughout the entire treatment period. None of the patients who required supplemental sublingual buprenorphine during the trial had received rescue in the 6 months prior to entry to the study. Although the transmucosal forms of buprenorphine used to treat opioid addiction allow for dose titration, Probuphine is a non-titratable, fixed-dose product that does not offer the same paradigm for dose adjustment.

Baseline characteristics of the study population for pre-trial treatment duration and transmucosal form used were also examined. A treatment effect based on buprenorphine treatment duration immediately pre-trial was not demonstrated. But as you'll recall, these data, however, were a rough approximation and were not the most reliable.

The transmucosal form that Probuphine has been compared to is the sublingual buprenorphine tablet. However, there are other transmucosal forms on the market, and some, like the sublingual film, offer higher levels of buprenorphine exposure

at the same nominal dose of the tablet. But as with the pre-trial treatment duration, a treatment effect was not demonstrated based on transmucosal formulation use, specifically film use, pre-trial.

Dr. Travis presented a number of different analyses, which are shown here taking into account the interpretation issues that were identified. The analyses explored the effect of the chosen analysis population, the choice of responder definition, methods for handling missing data, and rescue use. Noninferiority was established for Probuphine in each and every case.

There are many approaches that would be considered reasonable for presenting these data, and we are seeking input from the committee about the representation that would be most appropriate and most useful for clinicians. I'll discuss our reasoning as it relates to each of these factors based on our review of the data.

For the analysis population, the first column, we believe the correct population should include the 3 patients admitted by the applicant,

as we are inclined to assume that being completely lost to follow-up or being incarcerated are not positive outcomes in this case.

The second column looks at the responder definition. The responder definition allowed subjects to have up to 2 months with evidence of illicit opioid use. Said another way, a subject could submit 4 positive samples out of a total of 10. That would be 2 monthly samples and 2 random samples in the same 2 months and still be considered a responder.

We're not convinced that allowing 2 months of opioid use is justified in a population that wasn't using opioids before, so we think that the analysis in which there are any positive months indicates treatment failure and might come closest to representing the effective treatment.

The original assumptions we had about missing urine samples may also need to be reconsidered. We anticipated that the overwhelming majority of patients would submit opioid-negative samples and that an imputation strategy that

doesn't assume missing samples are positive would be appropriate. The fact that 20 percent of the patients actually provided a positive sample suggests our original assumptions were incorrect. So we'd be inclined to use a missing-equals-positive approach.

There were a number of samples where the patient presented for the visit submitted a sample, but because of issues with the specimen, they weren't properly analyzed. We might be willing to believe that samples that were provided but not analyzed correctly are negative if the parts that were analyzed are negative.

For the examination of the extent and pattern or rescue use, we examined a few permutations, included all permitted, non permitted, and up to 2 uses permitted. We think there is probably some minimal amount of rescue that could be attributed to extraordinary circumstances, but needing rescue all along seems to indicate that Probuphine, which provides only a fixed dose, doesn't provide adequate treatment for

that particular patient. Although it may seem overly strict, we're inclined toward the strategy that allows no more than 2 rescue occasions for Probuphine but allows dosage estimate for sublingual buprenorphine, the product of the two that can actually be titrated.

Taking all of those conditions into consideration, we're inclined to think that the analysis that best represents the efficacy findings is the analysis that defines the analysis population as all patients who are randomized and receive study drug; allows no opioid-positive months; imputes a missing sample because of a missed visit as positive and an incompletely analyzed sample as negative if those portions of the sample that were analyzed were negative; and allows for up to 2 uses of rescue for the fixed-dose product and all use of the rescue for sublingual buprenorphine, the product that permits titration.

The resulting responder rates are then 69 percent for Probuphine and 64 percent for

sublingual buprenorphine, and noninferiority is established.

In summarizing the efficacy review and findings, this was an overview of some of the conclusions that we've come to regarding how to best represent these findings. Again, we acknowledge that there are multiple reasonable approaches that can be taken to present these data. And along those lines, we suggested one option that we consider to be reasonable.

We'll be asking the committee to weigh in on the various approaches to presenting these results and to provide feedback on what you consider to be an appropriate representations, or representations, based on your expertise in this area. This concludes the efficacy portion of our discussion.

Now, on to the discussion of safety. The applicant summarized the overall safety database in their presentation. It's a safety database, which includes safety exposures from three phase 3 control trials, the most recent being PRO814, the trial under discussion, 2 open-label extension

studies, and 2 clinical pharmacology studies.

The development program includes exposures to Probuphine, to placebo implants, and to sublingual buprenorphine. Across these studies, safety assessments included assessment of treatment-emergent adverse events, implant site examinations, clinical laboratory assessments, urine toxicology screens, EKG evaluations, and vital signs.

The framework we used for the review of safety was to look at systemic safety related to the drug substance, buprenorphine, safety of the implants themselves, and the procedural safety related to insertion and removal of the product. The safety profile for buprenorphine is fairly well-characterized, so we directed our review to identifying any new or atypical systemic findings for the drug substance with these new patient exposures provided by the Probuphine safety database and to systemic findings that may be related to buprenorphine in its new formulation.

The review did not identify novel safety

signals that emerge related to buprenorphine's systemic safety on review of Probuphine safety data. Accordingly, the safety related to this novel implantable formulation was emphasized, including the safety experience as it relates to the rod insertion and removal procedures and the indwelling rods; foreign bodies, which are intended to remain in place for 6 months; and key findings from the human factors evaluation.

As mentioned, there are similarities between the outpatient procedures for insertion and removal of Probuphine and the procedures for the implantable contraceptives, particularly Norplant. So we asked our obstetrics and gynecology physician colleagues in the Division of Bone, Reproductive, and Urologic Products, DBRUP for short, who have specific experience with the implantable contraceptives and with surgical procedures in general to consultatively review the procedural safety data included in the submission and to provide a clinical perspective based on their expertise in this area. This summary of procedural

safety is based extensively on DBRUP's consultative review.

Procedural safety data from the phase 3 studies were evaluated. These included the three phase 3 control studies, 805, 806, and 814, and extension studies 807 and 811, which are the 805 and 806 extensions, respectively.

This table summarizes the number of subjects who underwent at least one insertion procedure during a particular trial. Some subjects required more than one insertion procedure when there were complications requiring removal of the initial set of rods and insertion of new rods to continue a treatment cycle. Still others had a fifth rod placed in the studies prior to the most recent trial and underwent another insertion procedure for the dose increase.

The cumulative exposure across the trials was 654; that is there were 654 patients who underwent an initial insertion procedure. Probuphine and placebo implants are examined together because the same procedure is required for

insertion and removal.

There were a similar number of removals, but there were also some patients who were lost to follow-up, and the rods were never removed. So to place these numbers in context, the scope of the procedural safety database for the implantable contraceptives is provided.

Norplant, the implantable contraceptive where 6 rods were inserted for up to 5 years, is the one most similar to Probuphine. For Norplant, the clinical development program included 849 removals prior to approval. For Jadelle, the 2-rod contraceptive, there were 1100 removals prior to approval. There were 849 for Implanon, the single-rod contraceptive, and 296 for Nexplanon, the next-generation implant.

The applicant described these procedures in their presentation. During the previous review cycle, there had been concerns about the use of the U-technique for removal, which is not commonly used in the U.S. DBRUP found evidence supporting the use of this method for Norplant removal. There was

an additional modification to the procedure for Probuphine in that a longer incision is used 7 to 10 millimeters separate from the original incision, versus 4 millimeters for making suturing necessary for closure in the case of Probuphine.

Compared to the implantable contraceptives in general, Probuphine requires a new incision to continue treatment. In contrast, for contraceptive implants, a single incision can be used for the rods that are to be removed and for the insertion of the new rods. When rods are removed at the end of a treatment cycle, the new rods are commonly inserted through the same incision in the opposite direction from the rod or rods that are being removed.

I'll now discuss the implant related safety findings. The numbers and proportions of patients who had an implant site adverse event are represented here by study. Adverse events that occurred in at least 5 percent of all patients who underwent insertion and removal procedures in a study are listed. Note that these are all the

implant site adverse events that occurred and included the full spectrum of events from non-serious adverse events, like erythema and pain, that are not unexpected, to the more important procedural complications.

Because improvements were made to the device and the training and certification program during the clinical development program, we sought to compare safety findings before and after these changes were introduced, and that's represented by that red line.

So more than half the patients in study 805, which pre-dates the equipment and training and certification improvements, had an adverse event. In 811, the extension to 806, there were no patients with an implant site adverse event that was reported by at least 5 percent of the patients. In the last study completed, PRO814, 18 percent of patients reported at least one event, and pain was the only adverse event reported by more than 5 percent of patients. This is a notable decrease in events, suggesting that the improvements in the

device, the procedures, and training program may have contributed to an improved procedural safety profile for Probuphine.

On the previous slide, you saw a summary of the incidence of all implant site adverse events that occurred. Here's a more focused summary demonstrating the key procedure related adverse events as identified by our DBRUP colleagues. These events include implant expulsions, implant site infection, wound complications, complication of removal or requiring multiple attempts, and bleeding, including implant site hemorrhage or hematoma and incision site bleeding.

In comparing the safety findings before and after implementation of improvements to the device and a training program, the results for studies 805 and 807, which pre-date these changes, are demarcated to distinguish them from the other studies, which occurred after the changes. So when comparing the earlier and the later studies, fewer key procedure-related adverse events were reported following the changes. For example, removal

complications were reported in about 9 percent of patients in study 805 and in no subjects in 806, the subsequent control trial after 805.

Despite these improvements, it must be noted that in the Probuphine development program, rates of bleeding, complicated removals, and implant site infection were higher than rates seen in implantable contraceptive development programs.

The applicant described the human factors evaluation that was performed in an effort to validate the training program. Our DBRUP colleagues assisted us with the review of the human factors study, lending our proceduralists' perspective to the interpretation of the findings.

A number of caveats identified by DBRUP, particularly as it relates to the live practicum portion, should be noted. A live practicum of procedures use a pork tenderloin as a simulated human arm. Although the pork tenderloin may be a suitable model for demonstrating technical proficiency for the insertion procedures, it is not suitable for predicting whether certain events like

infection and bleeding can be mitigated by training.

Also, the removal procedures and potential complications do not lend themselves to modeling. The pork tenderloin, or an artificial arm for that matter, can't provide an adequate representation of the scarring that would develop after a foreign body has been indwelling for 6 months.

Additionally, situations that may arise when performing the procedures on a patient, such as a patient moving or having pain that may require more anesthesia cannot be simulated. For this evaluation, only clinicians from specialties that involve performing procedures or surgery participate in a simulation component, so the results may not be generalizable to clinicians from non-surgical specialties.

Overall, the subtasks and critical subtasks for the live practicum appeared appropriate. Most of the 15 proceduralists, which included 8 physicians and 7 mid-level practitioners, could adequately perform the tasks required to mitigate

the risk of infection, bleeding, and fibrous scar formation around implants.

Notwithstanding this overall finding, review of the narratives of the task failures reveal important issues related to procedural safety. The applicant appeared to equate receipt of knowledge with ability to perform a task. It was an assumption that once a provider recognizes a task failure, they would be able to perform the task the next time around. However, the study provides no data to support this notion. There were also 3 task failures related to mitigating infection. This is noteworthy, as infection related AEs in the Probuphine clinical development program have already been seen at higher rates than those for implantable contraceptives.

Not all participants could remove all the implants, even in the practice session, and postmarketing data for implantable contraceptives have revealed that some implants are never localized or removed. Consideration should just be given to how these situations are to be managed in

a real-world setting.

Finally, 10 percent of the clinicians inserted the rods beyond a desired depth; that is more than 5 to 7 millimeters, but less than 10. Although an insertion depth that is still less than 10 millimeters is unlikely to result in injury, the findings suggest that the training program tasks related to insertion depth may need to be reinforced.

Probuphine will have a REMS. The applicant described their proposed risk evaluation and mitigation strategy. Briefly, the goals are to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the improper insertion and removal of Probuphine. It is also intended to mitigate the risk of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin. And this is through prescriber and patient education.

The proposed elements include a training and certification program for healthcare professionals who insert or remove the product in a restricted

distribution system. Because of the improvements in the safety profile with the implementation of the training program and other improvements, we consider the proposed strategy to be reasonable. We will ask the committee to consider the appropriateness of the REMS for addressing the attended risks in clinical practice.

In closing, efficacy data from this evaluation of Probuphine compared with sublingual buprenorphine in clinically stable patients showed that noninferiority was established. However, as described in the presentation, there were a number of issues that presented challenges in interpreting and presenting the data on which we are seeking advisory committee input.

More than a few episodes of supplemental use were unanticipated in this population, however, we saw some patients received rescue throughout the entire treatment period, and none of these patients who received rescue during a trial had received it in 6 months prior to entry into the trial. This has implications for clinical practice with this

non-titratable fixed-dose product and implications for the touted public health benefit of decreased abuse, misuse, and pediatric accidental overdose if transmucosal buprenorphine use is still required.

Urine toxicology results were used for the evaluation of efficacy. There were missed visits for urine samples and improperly analyzed samples among the already small number of samples that were collected over the course of the trial. Additionally, on review of the data, the responder definition that incorporates the urine toxicology findings may be too permissive, patients who are submitting opioid-negative samples prior to entry. So allowing 2 months with evidence of illicit opioid use may be too permissive.

Defining the appropriate population for Probuphine also presented a challenge considering the use of rescue, both the amount and pattern of use, in light of the fixed dosing, and when incorporating both the urine toxicology findings and the supplemental use. The appropriate population for analysis was also a matter to

carefully consider in interpreting these data.

Finally, Probuphine requires an outpatient surgical procedure for both insertion and removal. A training and certification program is in place for Probuphine, including training on removals, the more challenging of the two procedures. Training on removals and complicated removals cannot be fully modeled, however.

Probuphine will have a REMS, and the training and certification program are part of the REMS whose objectives are to mitigate procedural complications and the risk of abuse, misuse, and pediatric accidental exposure.

This concludes the FDA presentation of our review of the Probuphine efficacy and safety data in a clinically stable population on 8 milligrams of less of sublingual buprenorphine. With that, I'd like to thank all those from the Center for Drug Evaluation and Research and the Center for Devices and Radiologic Health who contribute to the efficacy and safety review for this application. And I'd like to thank the committee members for

your attention and for the opportunity to present this information and gain your perspective on the efficacy and safety data submitted in this resubmission application. Thank you.

Clarifying Questions to FDA

DR. KRAMER: Thank you very much. We are recalibrating time-wise and are thinking that we should try to adjourn for lunch by 12 and be back here at 12:45 for the open public hearing. So that makes it, again, very challenging.

I'm going to start by just a very simple question for the FDA. We've seen the presentations of opioid-positive urines and rescue medication among the groups, and we've seen the plots with all of the dots. But has anyone just done a simple thing of saying what's the number and percent of patients by treatment group who used -- either had opioid-positive urines or self-report of opioid and had rescue medication use?

DR. SKEETE: So use of self-reported -- I mean, somebody who --

DR. KRAMER: Either opioid use by urine

positive or self-report, or rescue medication use.

DR. SKEETE: Or rescue medication use.

DR. KRAMER: Has anyone just done that simple calculation, so we see how many people had some type of evidence of need? Somebody else has an answer I think, someone from the committee.

DR. TRAVIS: I don't have the slide number, but it was --

DR. KRAMER: Slide 47? Is that -- it was a slide of dots, but it had a line on -- saw it quickly. I thought that was simple and quick, but maybe not.

DR. TRAVIS: If you go to the previous slide. That would be any missing or -- and go to the previous slide again. Sorry. These percentages here show the percentage who have either missed or supplemental rescue medication use of a certain number.

DR. KRAMER: Okay.

(Pause.)

DR. KRAMER: Perhaps we should go on --

DR. TRAVIS: I have the slides here. Sorry.

DR. KRAMER: -- and you could -- should we go on to another question and you could provide that?

DR. TRAVIS: Yes.

DR. KRAMER: Laura McNicholas?

DR. McNICHOLAS: Thank you. Did I understand you that we have documented in the subject's record that they have had 90 days of buprenorphine treatment, not 6 months, not 180 days, consecutively?

DR. SKEETE: Right. Consecutively, they all at least have 90 days because they had -- they also had to have the urine positive -- the urine positives -- urine negatives for the 90 days and the sublingual buprenorphine use. The question they were asked was, what was your lifetime duration? What I wanted to point out with that slide was that there appear to be -- there may be one patient who had less than 6 months. But overall, based on one data set, it looks like there were a few patients who had it, but those data were not reliable because they were using -- they were

being used to approximate it from another source.

They weren't actually ever directly asked consecutively, but those same patients had on average about 3 years of buprenorphine treatment over their lifetime.

DR. McNICHOLAS: Okay. Because there's a difference between a patient stabilized 3 months versus a patient stabilized for 6 months --

DR. SKEETE: Exactly.

DR. McNICHOLAS: -- and you're only looking at the last 3 months. That's what I was wondering. So we actually do not have data that everybody was consecutively treated for at least 6 months with buprenorphine and only on 8 milligrams or less for the past 3 months.

DR. SKEETE: So they were -- the patients to be enrolled were -- right. So they were supposed to be on buprenorphine for 6 months. The intent for that was 6 consecutive months. As far as we can tell, the majority of patients were on it for 6 consecutive months. We do have some data that are a very rough approximation that suggests that some

may not have been. But when you look at their lifetime buprenorphine treatment history as being 10 years for some patients, it's unlikely that that would have been the case.

DR. KRAMER: Dr. Dodd?

DR. DODD: These will probably require longer discussion, so I will put them in now, and perhaps we can come back to them during the later discussion. My first question to the statistician is, what do we know about the reason for missingness?

As far as I can tell, the handling of the missing data assumes that things were missing at random. And I can imagine scenarios where the missingness may depend on the treatment arm, which would be particularly concerning if I'm not adequately treated and go off and use opioids, and don't come in because I'm using opioids on one arm. And on the other arm, the pattern of missingness is different, that I'm not coming in for reasons not associated with having a potentially positive urine test. Did you examine that? Did you look into

what we know about the reasons for missingness?

DR. TRAVIS: There wasn't much detail on the data set. Usually, it was -- there were roughly three types. There were the issues with the analysis, which we think mostly would be missing at random. There are the discontinuations, so there were several -- the numbers were small. There were several that discontinued early on, and then -- we certainly don't think it's appropriate to treat the information after the discontinuation is missing at random. Then there are intermittently missing, which we would agree needs to be evaluated further, but no reasons were given. So we don't know.

DR. DODD: Then as a follow-up, were there any -- it looks to me as if all the sensitivity analyses follow the same sort of logic. When I do sensitivity analyses, I try to evaluate the extent to which the study weaknesses might have biased the results towards the null hypothesis. And when we're thinking about a noninferiority trial, the null hypothesis is different because we're saying that the treatments are different, that the

Probuphine is noninferior.

So what I read of the sensitivity analyses that I've seen presented would tend to bias towards the noninferiority hypothesis or the alternative hypothesis. And I don't know if there were any alternative sensitivity analyses that were conducted that would be more in line with what we would think of as a sensitivity analysis that would evaluate the extent to which things were biased towards the alternative.

DR. TRAVIS: I think the final sensitivity analyses I conducted, where I explored the use of rescue only in the Probuphine arm, would certainly address that, since that's only being -- the penalty's only being applied to the Probuphine arm rather than both arms. That was one of our concerns, and that's what we tried to evaluate with those analyses.

DR. KRAMER: Dr. Brady?

DR. BRADY: Yes. I was just wondering if you had done any further exploration -- I know it's a small group, but still that group that required

rescue medications, particularly maybe those that took more than 2 doses, just in terms of things like age, or what their maintenance dose was, or how long they had been on -- or history of psychiatric illness, anything like that, are they characterized in any way.

DR. TRAVIS: I know the applicant in their presentation looked at it by the previous dose. We didn't look at it, and we didn't look at any of the other baseline factors.

DR. KRAMER: Dr. Grieger?

DR. GRIEGER: Two hopefully brief questions. The first one, I'm not sure I understand the rationale for allowing an unlimited number of rescues in the sublingual arm, but only two in the implant arm. Why would you compare them two different ways if, in fact, you're looking at the same event, somebody who's having difficulty asking for more medication.

DR. SKEETE: I'm glad you brought that up. That's actually one of the things that we are asking you all here for to help us think through

some of these things. But the thinking behind that was we're comparing a titratable and a non-titratable product. So you can imagine that someone, when they're just switching over from the transmucosal form to Probuphine, maybe they need a few doses of extra transmucosal products at the outset of treatment, for example, as they're getting stabilized.

But if you are placing your patient on fixed-dose product, and you think that you might need to give them sublingual buprenorphine all the way through the treatment period, for example, we're wondering if that -- is that an appropriate way to manage that patient, for example.

The other thing is that it also takes into account the touted public health benefit. So if you have to continue a patient, say, for example, all the way through the treatment period, and you have to send them home with a bottle -- so some of these things that we're talking about with misuse, abuse, forgotten or missed pills, or accidental pediatric exposure, would still be evidence in that

case.

DR. GRIEGER: Okay. We can cover that in discussion later I guess. The second question is a little bit -- I meant to ask this of the industry representatives. Are these things radiopaque? You mentioned that one of these rods disappeared and was never found. I know Nexplanon's improvement was that it is actually radiopaque.

DR. SKEETE: Right.

DR. GRIEGER: So maybe industry can provide information this afternoon -- they're done -- on whether they could make it radiopaque or put tracer dots on it or something.

DR. SKEETE: I can --

DR. HERTZ: Well, Rachel, why don't you go ahead?

DR. SKEETE: So they're not radiopaque. So currently, if you are looking to find it, it's general via ultrasound or MRI. As you note, Nexplanon is, but that's been multiple iterations of various implantable contraceptive products. I can open it up to the company if you want to

mention anything.

MS. SHELDON: At this point, given the concentration of buprenorphine in each implant, it's very difficult to add anything else to the implant. So it would take another reformulation in order to be able to do that. However, what we've also heard from our experts is that x-ray is not necessarily the best method for both -- because of exposure to radiation, but also because of the number of x-rays you'd have to take in order to be able to correctly image because you're not going to get depth from an x-ray, what you really need in order to be able to find the implant. But you do get depth with MRI or other imaging.

DR. GRIEGER: I guess I go back to you can lose an implant and have no idea where it is. That's the bottom line. Because there may be people who can't get an MRI because they have metal from being welders or grinders, or something. There are people who can't get MRIs.

DR. SKEETE: Right. There have been some cases in the development program where they've been

unable to locate an implant even after ultrasound or MRI.

DR. KRAMER: On that same topic, the sponsor suggested that you need to palpate all 4 implants before you start the removal. If by chance somebody just doesn't do that first, and they've got an open wound, you can't really do an ultrasound over an open wound, can you?

DR. SKEETE: Well, that is a question I would probably want to ask our DBRUP colleagues to be able to help out.

DR. KRAMER: It's a small point, but all right.

DR. SEWELL: Hi. Catherine Sewell from DBRUP. You can use an ultrasound over an open wound. Ideally, you'd probably put some sort of sterile drape over it.

DR. KRAMER: Thanks. Next we have James Troendle.

DR. TROENDLE: Yes. I just wanted to clarify, whey we're talking about the different formulations of sublingual use, it sounded like you

wanted them -- do you want the sponsor to compare it to a different formulation? It sounds like you were --

DR. SKEETE: No, no, no.

DR. TROENDLE: -- hinting that this isn't the right comparison, and you want a comparison against something else.

DR. SKEETE: Oh, no. Sorry. If that is what came across, that's not what was intended. What was intended was that at the time of the study -- or I should say even at the time as we were thinking about the evaluation of this drug product for our clinically stable patients, there were Suboxone tablets on the market. Then in 2013 and 2014, Bunavail and Zubsolv -- Zubsolv and then Bunavail came on the market.

The point of what I was saying there was that if we're thinking about transferring a patient from a transmucosal form to Probuphine, there needs to be guidance about the differences in the variability that you might see in sublingual form. So even now with the Suboxone film, there's some

mention -- they're mentioned in there that -- there's mention in the label that there's some difference in the bioavailability. So you need to be able to consider that when you're transferring a patient over.

In other words, it's more for clinicians to be able to keep in mind that there are various forms, various doses, and to be able to transfer the patient appropriately over to Probuphine if they so desire.

DR. WINCHELL: If I might very quickly -- this is Celia Winchell -- it's almost a matter of the difficulty of expressing to the clinician. Eight milligrams is not 8 milligrams. So when we started the study, we said this is for patients who are on 8 milligrams or less, but it's become much more complicated to communicate what that means because 8 milligrams of Suboxone tablet, 5.7 milligrams of Zubsolv, it's just gotten a more complicated way to express the target population. I think that was the point of showing that the landscape has changed.

DR. KRAMER: Dr. Kotz?

DR. KOTZ: I'm wondering, what is the maximum number of times a patient can have continuous implants? I know you mentioned in one of the talks that it was 4 treatment cycles at 4 times, 2 in one arm and 2 in the other. What happens after that?

DR. SKEETE: Well, that's actually something that we need to think about as well because, actually, we don't know -- because only 4 sites are identified. Once those 4 sites are used up, we won't be able to say anything more about continued use beyond those 4 sites because it hasn't been evaluated for either safety or efficacy at this point.

DR. HERTZ: I think that would be a good question for discussion later on because it probably requires a bit more, and I see the sponsor interested. So I think perhaps after lunch.

DR. KRAMER: Dr. Pickar?

DR. PICKAR: Yes. As I recall -- and help me; I get older sometimes -- it was a small

percentage who were IV drug users in this sample. Do I recall that correctly?

DR. SKEETE: Yes, and that was actually in the sponsor's slide set, but yes.

DR. PICKAR: That's right. One of the questions that we're going to be asked to talk about is what is the population who would benefit and so forth.

DR. SKEETE: Absolutely.

DR. PICKAR: Now, I don't recall whether that subgroup who are IV drug users was large enough to analyze separately. And if it was, do you have any hint of it? Because that is very pertinent because it's really -- the majority of these folks are oral opioid -- a huge problem, no question, most of the time at least IV drug users. Got it.

But when the agency's here asking us to consider carefully who is the population and an indication, do we have -- and I'm just putting it out there. Do we have enough information for broadly on oral opioid use, or should we be talking

about oral dependency? They're asking me that question there, and that's what went through my mind. Do we have any data? Do we have anything in the stats, Dr. Travis? Anything there that can help us there?

DR. SKEETE: So we have --

DR. TRAVIS: I'm just going to say, I didn't evaluate anything like that, so --

DR. PICKAR: You didn't look at -- you didn't cover a covariant like we used to do in the covariant days, covariant for IV versus oral? Sorry. Because that's a huge, huge thing in the use of this product.

DR. HERTZ: So perhaps again we can look to see what analyses there may be. We'll check ours. The sponsor will check theirs and get back to that after lunch.

DR. PICKAR: Sounds great.

DR. KRAMER: Dr. Campopiano, can you quickly ask yours?

DR. CAMPOPIANO: I think it might be a yes/no question. Is there data available about the

alcohol or non-opioid substance use of these participants either prior to or during enrollment in the study?

DR. SKEETE: There are data. Unfortunately, I don't have that as a backup slide. I don't know if the sponsor has compiled for this substance the psychosocial history data. I don't know if you -- you all have it? So they apparently have it as I guess a backup slide, which we can display now or during the discussion.

DR. KRAMER: If the sponsor could get that ready so that they could show us that when we come back -- we still have a couple people who have questions for clarification from the sponsor. And we're going to adjourn now for lunch. We're going to come back at 12:45. We do need to have the open public hearing as specified on the schedule, a requirement. And as soon as that's over, we'll return to those few questions for the sponsor and see that slide.

Thank you. Remember, no discussing of the topic at lunch among members.

(Whereupon, at 12:00 p.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. KRAMER: Okay. If everyone could take their seat. Before the first person speaks in the open public session, I have a few comments to address to everyone.

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses

in connection with your attendance at 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, and 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. WILSON: My name is Sarah Wilson. I'm not being compensated for my time here to speak today, but the sponsor has covered my travel expenses to attend this meeting. I brought my mom here today for moral support as I share my experience with you.

Probuphine saved my life. I was hit by a drunk driver and had severe injuries. At that point, I lost my insurance when I was no longer able to work. The only treatment I could afford out of pocket were doctor visits and prescription painkillers.

By the time I was able to acknowledge my addiction, my husband and I had lost our home and everything in it. I was stealing from those that I loved. I wanted help, but was scared of suffering any more pain than I already was in. I was embarrassed. Addiction is prevalent in my family. I spent 15 years in law enforcement working with

the drug task force. I knew what to avoid. But there I was, addicted to painkillers with what I felt was no way out.

My husband found an ad in our local magazine for a research study for the treatment of opioid addiction. I called and made an appointment that day. The positive changes in my life were immediate and visible. All of my years of additional suffering were eased, and I successfully completed that first study.

I agreed to the implant study because I know there are risks associated with sublingual medication. I have four children. I keep my medication in a locked safe for their protection. I have to make sure the pharmacy keeps my medication in stock, and if I want to travel, packing my medication is the first thing that I have to do. The implant takes away the potential risks to my children being exposed to my medication. It alleviates the worry of a missed appointment, of the pharmacy being out, or forgetting my medication when I travel.

I realize there are no perfect answers for opiate treatment. There are variables, and every situation is different. But I believe that approving this implant will provide a method of treatment delivery that eliminates many of the secondary risks. Thank you.

DR. KRAMER: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and your organization that you're representing for the record.

MJR DEAN: Good afternoon. I am Major General Arthur T. Dean, and I serve as the chairman and CEO of Community Anti-Drug Coalitions of America. And CADCA does not have any financial relationship with the organization in discussion.

CADCA is a non-profit organization, which represents over 5,000 community coalitions and their affiliates. CADCA is a strong advocate for drug abuse prevention, first and foremost. The Office of National Drug Control Policy director, Michael Botticelli, has said that prevention remains the best and most cost-effective approach

to curving our nation's public health crisis of drug dependence and overdose. CADCA couldn't agree more with the director's statement.

At the same time, CADCA and our coalitions support a comprehensive approach that includes increased research, expanding options for effective treatment, and strengthening and support for all of those in recovery. CADCA and our members have a strong emphasis on preventing the misuse and abuse of medicines. We host on an annual basis National Medicine Awareness Month each October and provide numerous resources via our website, which is called preventrxabuse.org.

In 2015, CADCA co-convened the Collaborative for Effective Prescription Opioid Policies. We call it CEPOP. We visit and partnership with Mary Bono in Trust for America's Health. Because coalitions are uniquely positioned within their communities. CADCA members were first to recognize and be concerned about the grueling opioid crisis, and this came to our attention going back some 15 years ago.

Today, as you know, overdose takes more lives than car crises. We believe that increased leadership at the federal level can help expand research and healthcare coverage for an array of effective medicated assisted treatment options. CADCA does not endorse any single treatment approach or modality. However, we know that medication assisted treatment can be effective. It can help many patients return to caring for their family and their family members; maintain in gaining employment; and contributing to our society.

Of particular interest of our members is the advancement of technologies that can effectively treat opioid addiction while reducing the abuse potential of these medicines. Abuse deterrent formulations are critically important to us and our members, and the option of providing maintenance treatment of opioid dependence via subdermal implant is a promising approach.

CADCA applauds the FDA and this committee for focusing on expanding effective medicines for

the treatment of opioid dependence. Thank you very much.

DR. KRAMER: Thank you. Will speaker number 3 please step up to the podium, introduce yourself, and state your name and organization for the record.

MS. KNADE: Hi. My name is Susan Knade. I'm the mother of an opioid addict. I am not being compensated for my time today, and I am here to read a letter on behalf of David Sheff, journalist and author of Clean: Overcoming Addiction and Ending America's Greatest Tragedy and Beautiful Boy: A Father's Journey Through His Son's Addiction.

"Addiction is one of the biggest public health challenges of our time, one that's killing more Americans than any other non-natural cause. Today, the conversation around addiction is riddled with blame, stigma, and misinformation. This conversation needs to change.

"Contrary to popular belief, addiction is not a moral failing or a personal choice. It is a

chronic, progressive brain disease that is both preventable and treatable. My family and I have witnessed and battled firsthand the struggle that addicts undergo each and every day.

"My son Nick fought addiction for over a decade. His battle included rehab centers, residential treatment programs, and outpatient programs, numerous trips to the ER, and many relapses. There's not a day that goes by when I don't hear from people who have similar stories, including many that have a much less positive outcome than ours. They write long, heartbreaking letters about their children who didn't make it.

"It's alarming and inexcusable that as many as 90 percent of patients who enter addiction treatment programs in the U.S. don't receive evidence-based treatments, which includes one of the most successful treatments we have in our arsenal; medications proven to treat addiction, particularly, addiction to opioids, including heroin and prescription medications like OxyContin. It's no surprise that the patients leaving such

programs often relapse, and they never got the help that they needed.

"According to a report in Time, studies show that people addicted to opioids more than halve their risk of dying due to their habit if they stay on maintenance medication. There are other benefits to addiction medicines, but there are challenges. A major one is compliance, which is why I believe Probuphine will be a life-saving treatment for many of the people suffering from addiction.

"My son is alive today because of medication he was finally prescribed after almost a decade of failed treatments. He takes buprenorphine in combination with behavioral therapy and has been sober for six years. However, there are many people taking buprenorphine today who still struggle with relapse. Waking up every day, they are faced with a choice: take my buprenorphine or go get high.

"These people are often blamed for their relapse, but blaming an addict for relapsing is

blaming him for being ill. Relapse is a symptom of this disease. This is why medications that can prevent relapse are critical. Probuphine would take away the daily choice between taking their daily dose of Suboxone or returning to heroin or another drug.

"My son would have benefited from Probuphine as well as would countless children, husbands, wives, partners, and other loved ones. My son and our entire family suffered for a decade largely because innovative evidence-based treatments like Probuphine weren't available. It's encouraging to see progress in this area, and indeed I see Probuphine as a breakthrough step forward. I hope it's the first of many new options for patients.

"I urge you to make the right choice and approve this medication that has the potential to help alleviate the suffering of so many patients and their families, and the potential to save so many lives. Thank you for your time and consideration. Sincerely, David Sheff."

DR. KRAMER: Thank you. Will speaker number

4 step to the podium?

MR. JERNIGAN: Good afternoon. My name is Scott Jernigan, and I'm not being compensated for my time to speak here today. However, Braeburn Pharmaceuticals has expensed my flight and travel expenses, along with my wife's, to come up here.

I'm quite sure that my wife, when we got married, knew that opioid addiction was going to be a part of our vows. She's gone through so much with me, and I could never have gotten to the point that I am now without here. We all here today have one thing in common. We are productive members of society. I was not that way for a long time. In fact, I was in the depths of despair so bad that I never thought I would get out.

While my daughter was getting her undergraduate degree and her master's, while my wife was traveling the world for her company, I was trying to get high. I was trying to stop the pain of withdrawal. I was losing a company. I was everything that a dirty junkie is, except I didn't think of myself that way. I thought of myself as

white-collar businessman that does the right things, but I wasn't.

However, this drug has saved my life, and the implant and how it operates is great for a lot of different factors that I know we've all gone over and you've seen. As I said before, we're productive members of society. And with this delivery method, all I have to focus on now is my new normal. I don't have to be reminded every day that I'm a junkie, every morning. I don't have to be reminded every day or every month when I look into a pharmacist's eyes, and they're like, "Oh. It's one of you again."

I've started my own company. I'm president of my own company again. I'm not a dirty junkie, but I do need help. And this drug and with this implant is going to allow that to happen, I hope.

I believe we as addicts have hurt our families enough. And when I came up here today, I had to remind my wife once again that I was an addict. As we came to the airport, I had to look over to my wife and say, "Man, I hope I packed my

medicine," and bring that up, and what it brings to the table all over again. With the implant, we won't have to do that. It will be one less hurdle for us as addicts to get over. And I hope you look seriously at that delivery method. Thank you very much.

DR. KRAMER: Thank you. Would speaker 5 step to the podium and introduce yourself?

MS. KULKARNI: Good afternoon. My name is Shruti Kulkarni. I'm a policy advisor for the not-for-profit Center for Lawful Access and Abuse Deterrence, CLAAD. The sponsor is a member of the CLAAD coalition.

As you know, opioid abuse is a public health epidemic in the United States. In 2013, over 24,000 Americans died from opioid related overdoses. Over 16,000 deaths involved prescription opioid medications and over 8,000 deaths involved heroin. CLAAD works to reduce prescription drug fraud, diversion, misuse, and abuse while advancing consumer access to high-quality health care.

Thank you for the opportunity to provide CLAAD's input on the proposed buprenorphine subdermal implant for the maintenance treatment of opioid dependence. This medication advances two national goals set forth in CLAAD's national strategy and the White House's 2013 National Drug Control: increased access to high-quality care, including medication assisted treatment for patients with substance use disorders, and reduction in diversion, misuse, abuse of, and pediatric exposure to controlled prescription medications.

CLAAD supports and thanks the National Institute of Drug Abuse, the Office of National Drug Control Policy, and the Food and Drug Administration for their support for the development of novel therapies for the substance use disorders and medications designed to reduce the likelihood of diversion, misuse, abuse, and pediatric exposure.

The medication you are considering today is a result of public-private collaboration to support

the national priorities to advance high-quality treatments for substance use and to develop medications that pose lower risks to patients, families, communities, and traditional formulations. Today, I will speak to the issues of the population that will likely benefit from the implantable buprenorphine medication and the likelihood that the implantable medication could reduce diversion, misuse, abuse, and pediatric exposure.

A patient population that could significantly benefit from the use of 6-month buprenorphine implant consists of individuals in the maintenance phase of recovery who cannot routinely visit opioid treatment programs, addiction treatment providers, or pharmacies for geographic or other practical reasons.

A comprehensive medication-assisted treatment program includes both medications to treat substance use disorder and behavioral therapy. The implant medication offers patients the maintenance phase and opportunity to access

necessary treatment without additional burden so that they may focus on the psychosocial and other vital aspect of their long-term recovery.

Additionally, buprenorphine implant's novel delivery system offers several benefits to patients and addresses an important public health need. First, the implant support medication compliance over a 6-month treatment period, providing clinicians the confidence that the primary dose is administered according to the treatment plan.

Second, given that the buprenorphine implant would not be dispensed to patients for self-administration, it provides another avenue to help reduce prescription drug diversion, misuse, abuse, and pediatric exposure.

Finally, while patients treated with any form of buprenorphine may need occasional supplemental doses, access to treatment with a buprenorphine implant means ultimately there would be less oral buprenorphine available in the home for diversion, misuse, abuse, or pediatric exposure.

In conclusion, the buprenorphine implant is a product of and stands to further advance two national priorities: access to high-quality medication-assisted treatment and delivery systems that pose lower risks of diversion, misuse, abuse, and pediatric exposure. Thank you again for the opportunity. If CLAAD can be of any further assistance, please contact us.

DR. KRAMER: Thank you. Speaker number 6, would you step to the podium, please, and introduce yourself?

(No response.)

DR. KRAMER: Okay. We'll move on to speaker number 7.

DR. GINNAN: Good afternoon. I'm Dr. Shannon Ginnan, and I am the director of medical affairs for the not-for-profit Alliance for the Adoption of Innovations in Medicine, Aimed Alliance. Our organization works to improve health care in the United States by supporting development and use of novel evidence-based treatments. I have no financial relationships to declare. Thank you

for the opportunity to offer these comments on behalf of Aimed Alliance.

Compliance with a treatment regimen is key to success of any medical therapy. For acute conditions such as an infection or rash, compliance is relatively high because there is significant reward to the patient in relieving the suffering of that condition. Of course, "fairly high" is a relative term, as compliance drops to only 50 percent nearly because symptoms subside, which is often well before the end of the prescribed term.

Even convenience plays a large part in compliance. With adherence to medication regimens falling by 20 percent or more simply when increasing dosage from one time per day to 3 or 4. Now, as discussed, compliance for a chronic condition such as hypertension, diabetes, high cholesterol, and most relevant to today's discussion, substance use disorders. Compliance on oral therapies in these conditions fall as low as 50 percent in some studies, 50 percent compliance

for treatments that patients are well aware will decrease the risk of life-threatening consequences.

The patient with a substance use disorder may have every desire to get better given the statistics of medication compliance. in the best of circumstances. However, how can we possibly feel that we're giving these patients the best chance of recovery by using standard dispensing practices if Joe Smith and Susie Jones can't even remember to take their antibiotic when there's nothing in their brain fighting them?

How successful would they be if their brain were screaming, "No. Don't take that antibiotic. This raging bacterial sinus infection feels so good." That's what our patients with substance use disorders are up against. And as physicians and regulators, it is our duty to offer them every possible tool to win that fight.

Buprenorphine works. When the medication is taken as prescribed, it works. It has a proven track record, but compliance is key. A 2012 study in the American Journal on Addictions found that

addiction patients who were non-compliant with their buprenorphine medication regimens were 10 times more likely to relapse to opioid use than those who were compliant.

The buprenorphine implant solves this problem. It can be administered quickly and efficiently in a single visit, release a steady controlled amount of an effective medication for six months. Simply by adopting this new delivery method, we can bypass all the compliance issues: I forgot to take my medication. I left it at home. I don't want to take it. I don't need to take it. I can get by without it. I'd rather sell it for money.

It avoids issues of children getting into their parents' drug cabinet and finding the buprenorphine. It makes recovery more feasible for those who may have considerable socioeconomic or geographic challenges that get in the way of frequent physician visits. It prevents greedy physicians from taking advantage of the system and making money as pill mills. It can be a reliable

cornerstone to placing our patients down the path of sustainable recovery.

The risk associated with insertion and removal of implantable medications currently on the market are properly managed to the extent that implantable medications have become the standard of care. For instance, the American Academy of Pediatrics recommends subdermal implants as the preferred contraceptive method for adolescents that are not abstinent. Yet, unlike other implants on the market, the buprenorphine implant contains a controlled substance. And expelled buprenorphine implant could result in pediatric exposure, diversion, misuse, or abuse.

Aimed Alliance supports the use of REMS to manage the risks associated with medications. An appropriate REMS could address the risks of complications associated with the insertion and removal procedures to reduce the likelihood of pediatric exposure, diversion, misuse, and abuse.

Aimed Alliance has reviewed the summary of the REMS included in today's briefing materials and

considers the program adequate to address the anticipated risk of buprenorphine subdermal implant. The availability of a 6-month buprenorphine implant with the proposed REMS could provide tremendous benefit to an individual's overall well being as well as to families, communities, and the public. Thank you.

DR. KRAMER: Thank you. Speaker number 8, and I believe we have some one who's going to read that.

MR. GINNAN: And that would be me as well.

DR. KRAMER: Okay.

MR. GINNAN: I'm reading this on behalf of Amanda Wilson, M.D. I'm not aware of any financial relationships for her.

"I'm the founder, CEO, and president of Clean Slate Centers. I founded Clean Slate in 2009 to provide high-quality medical care and improved access to the underserved population of patients seeking addiction treatment. We currently treat nearly 6,000 patients on a monthly basis with buprenorphine in multiple states.

"As a practicing physician, my life's mission is to help people struggling with the opioid addiction so that they can lead healthier more fulfilling lives, so their families and loved ones may also experience some release from the collateral and often tragic burden of this chronic brain disease.

"I wanted my thoughts heard today because I know firsthand how desperate the need is to expand the range of medication treatment options for opioid addiction, and because I know that this community is currently evaluating potential new therapy that I believe effectively addresses significant unmet needs.

"In 2012, Clean Slate was the first recipient of the SAMHSA Science and Service Award for Office-Based Opioid Treatment. Our treatment model at Clean Slate applies a holistic approach that integrates behavioral counseling with safe and effective prescription medicines. We are deeply aware, based on real-life experience, that medication-assisted treatment with buprenorphine

can make a significant difference in helping patients attain recovery, yet we are also profoundly aware that an opioid addiction-sustaining recovery is not defined by the concept of cure. It is a lifelong struggle typically marked by occasional relapse, interim neurological cravings, and the challenges of adherence to both medication therapy and counseling.

"Given these challenges, we need to expand the range of treatment options so that more people and families can be helped. While there's no cure for this chronic disease, the subject of today's meeting illustrates that there are immediate opportunities to make tangible, life-changing progress in this horrific struggle.

"Medication-assisted therapy has been enormously beneficial to patients, and the advent of office-based treatment with oral daily buprenorphine was a tremendous step forward. It is our collective and continuing responsibility to address any limitations with current treatment

options that may pose challenges to recovery or correctable risks to household and family safety.

"Adherence to daily medication therapy, including oral forms of buprenorphine, is an ongoing challenge to recovery for many patients. First and foremost, an implant that delivers 6 months of continuous buprenorphine treatment can eliminate this variable for patients challenged by adherence.

"We are also aware that opioid addiction presents extended dangers to family households and society at large. Tragically, some of these potential dangers are inadvertently posed by the treatments themselves. Medications that must be stored in patients' homes are vulnerable to the potential for accidental ingestion by children, recreational experimentation by their family members, or diversion to illicit commerce on the street. The Probuphine implant presents no such risks or dangers.

"Based on the Probuphine clinical trial results, I and many of my medical colleagues are

excited and optimistic about the potential of the proposed buprenorphine 6-month implant to effectively address these patient adherence, household and safety, and diversion challenges.

"The current innovation gap that exists in the treatment of opioid addiction is unacceptable. According to the Pharmaceutical Research and Manufacturers of America, right now, there are more than 1200 medications in different stages of development for diabetes, cancer, and heart disease.

"Opioid dependence is not even recognized at this category, in which the organization is tracking new medications and development. Given the stigma and shame surrounding addiction, it's sadly not surprising that the research and development around this complicated, life-threatening disease pales in comparison to other serious diseases. This has to change.

"We urgently need to see society -- new opioid addiction as equally deserving of new treatment advances and understanding. Yet, despite

its broadening in epidemic scale, opioid addiction continues to be misunderstood as a choice or moral failing instead of a chronic disease whose basis is in brain chemistry. Sufferers and their families too often secretly bear the burden of shame and stigma, which further discourages recovery.

"Thank you for the opportunity to share my perspective at today's important meeting."

DR. KRAMER: Thank you very much. Speaker 9?

MR. MENDELL: Good afternoon. My name is Gary Mendell. Thank you for the opportunity to be here today, and I have no financial interest. I'm here speaking first and foremost as a father, a father who has experienced something that no parent should ever have to experience.

My son Brian died at the age of 25 due to addiction of opiates. But even more tragic, his death was preventable. My son, after being addicted for many years, was prescribed buprenorphine in his treatment program. And then he was sent to a halfway house, and there the

doctor in the outpatient program didn't believe in buprenorphine, and he tried to titrate him down, of which I objected.

While my son was on it, it was the best he had ever done in years. He was happy. He was working. He was doing great. And several months later, he died. I found out, after he died when I saw his papers, that they were titrating down. And there were a bunch of emails between my son and the doctor, my son complaining, "Stop titrating me down or I'm going to tell my parents."

A week after my son died, his sponsor called me up crying hysterically. He said, "Gary, I'm so sorry. I'm so sorry, Mr. Mendell. I loved Brian. I tried to get him off that damn buprenorphine, but he was not going to be able to reach his higher power. I tried so hard to get him off it."

The months to follow Brian's death, I learned that for every major disease in this country, there is one well funded national organization, pioneering research; advocating for changes in public policies; getting information and

research that's proven to work; implemented in our communities and our healthcare system; reducing stigma associated with their disease; and providing information, support, and hope for so many families. And from that, a vision emerged of uniting millions of Americans to combat addiction and empowering them to help others. And from that, an organization, this organization, Shatterproof, was formed.

I'm proud to be here today representing Shatterproof, an organization that I founded and the millions of Americans across this country who have joined with us on this vision to combat addiction and the stigma associated with it.

We must choose to treat addiction as a disease, a disease just like cancer or diabetes, and treat this disease accordingly. A recent study in the Journal of American Medical Association found out that 80 percent of those with these disease are not treated with evidence-based protocols, 80 percent. I meet families every day across this country who have loved ones struggling

with addiction, and struggling with opioid addiction, who are desperate for treatment, anything that will help their loved one recover with a better chance of success.

You all here today have an opportunity to change this. Approving Probuphine will increase the treatment choices physicians have to treat this disease, a chronic, life-threatening disease. If we as a society can change the way we think about addiction, the way we think about other diseases, then more of our loved ones will feel loved and connected. More will seek treatment. Fewer will die, and fewer families will be shattered beyond repair.

I thank you. I thank you as a father, as to my son Brian, I owe all that I am and all that I have to end this disease. Not just addiction, but attitudes. Not just a sickness, but this stigma that took his life. Thank you.

DR. KRAMER: Thank you. Speaker number 10.

MR. CAMPBELL: Hi. My name is Wayne Campbell. I'm the president of Tyler's Light. I'm

not being compensated for my time here today, but the sponsor has covered my travel expenses to attend this meeting, which is Braeburn Pharmaceuticals.

Good afternoon and thank you for letting myself and the public speak. Each day, nearly 70 Americans die from opioid overdose. To me, this isn't just a statistic. This is how I lost my son also. My name is Wayne Campbell, and I founded an organization called Tyler's Light. We're a non-profit, based in Columbus, Ohio, aimed at equipping our communities with information and resources to help choose a drug-free life and battle addiction.

I began Tyler's Light two weeks after my son Tyler passed away from an accidental heroin overdose. As in the case of many addicts, Tyler path through addiction started very innocently. As a Division 1 football player, Tyler was introduced to opioids after a football injury. His doctor prescribed Percocet to manage his pain after surgery. From there, Percocet led to OxyContin,

and then OxyContin led to heroin.

This trend we are seeing more and more frequently among athletes of both high school and college level. More often than not, athletes experience injuries that require pain management or even surgery. When doctors prescribe painkillers to manage the pain, athletes and their parents are not adequately warned or even cautioned at all, in many cases, about the risks involved in taking opioids, including the potential for addiction.

College students are particularly susceptible to develop opioid addictions as it's incredibly easy to access painkillers, which are typically just a call or a dorm room away. With football players and athletes, these addictive pills are discretely exchanged in locker rooms because they're expected to play through pain. As these players continue to take painkillers throughout the recovery process, their addiction can escalate, and eventually they may become more and more dependent on stronger and cheaper drugs such as heroin.

My wife Christy and I never thought that our loving, energetic, football-fanatic son would fall victim to addiction. It was devastating. We witnessed Tyler go from a competitive athlete who live for football to a kid who was focused only on where he was going to get his next fix. Our lives became consumed with helping Tyler get clean and back on the right track.

We took him to counseling, supported him when he took a break from school to try to get healthy. We enrolled him in six-week programs, helped him through a total of six different rehabilitation attempts. He relapsed after each stint, something that is a very common occurrence. In the end, it wasn't enough to save him. Tyler died within 12 hours of a 30-day inpatient stay.

After our son passed, my wife and I made it our mission to learn as much about opioid addiction as possible to try and prevent other families from experiencing the same pain. One of the things we realized was how few resources exist to help educate people about the ways to prevent opioid

addictions, its warning signs, effective interventions, and treatment options available.

Tyler's Light been to seven states, 200 schools, and spoken to 100,000 students so far in a matter of four years. The reality of this opioid addiction is a brain disease that doesn't discriminate based on age, race, economics, or education. The disease is running rampant in our very own communities, yet people turn a blind eye to it, ignoring it that it might go away. We can't wait for our kids to die. We have to intervene early and deliberately. Take it from me.

Death due to addiction can be prevented. Looking back, I wish I would have had access to effective medications to help prevent his relapses after completing addiction treatment programs. None of the six addiction treatment programs that Tyler attended emphasized prescription medication as a central part of maintenance after the program.

While behavioral therapy can be a great way to help patients recover from addiction for most, it's just one piece of the puzzle. Addiction

impacts every part of a person, and it doesn't stop there. The whole family's impacted.

As a brain disease, addiction is not a choice or a sign of weakness. It has emotional, psychological, chemical repercussions. As such, it needs to be tackled from all angles, including biologically with medication. Given the option, we definitely would have encouraged to him to adhere to a medication after completing rehab, as there is irrefutable evidence that long-term use is effective in treatment opioid dependence.

Today, we're here to discuss Probuphine, a drug that has the potential to change the outcome of millions suffering from opioid addiction and their families. This long-acting implant may have been the antidote that son needed. As you deliberate, I urge you to consider how treatment options like Probuphine can help move the needle on reducing opioid addiction in this country, given those suffering a fighting chance of recovery.

The opiate epidemic is consuming a generation in our country. There is no one answer,

no magic bullet to solve this problem. Short of banning the production of prescription opioids --

DR. KRAMER: Mr. Campbell, I'm sorry. The light's on. Could you try to wrap up quickly?

MR. CAMPBELL: It's one sentence.

Short of banning the production of prescription opioid, it's incumbent upon all of us to provide every tool we can to try to save lives in opioid addiction. Probuphine can be, and should be, one of those tools. Thank you for your time and consideration.

DR. KRAMER: Thank you. Speaker number 11.

DR. RUPP: Thank you for the opportunity to speak today. My name is Dr. Tracy Rupp. I was previously a clinical pharmacist at Duke University Medical Center, and I'm now the director of public health policy initiatives 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.

We strongly support access to safe and effective treatments for opioid dependence. In 2014, more Americans died of opioid overdose than any other year on record, so we need safe and effective treatment options. Currently available medications for opioid dependence are effective but could be improved to make them more difficult to divert and abuse and less likely to be accidentally ingested by small children. A long-acting medication could help improve adherence with therapy, potentially improving treatment success. However, in seeking to solve these problems, we must be certain we are not creating new problems.

First, we do not have substantial evidence of Probuphine's efficacy as required by statute. In fact, the evidence for efficacy comes from a single controlled trial with multiple design flaws. For example, patients requiring a significant amount of supplemental sublingual buprenorphine, after the first month, should be considered treatment non-responders due to the non-titratable

nature of the implant. However, the study's sponsor did not consider these patients as non-responders.

Patients who received study drug but discontinued the study without providing any efficacy data were not included in the sponsor's intention-to-treat analysis. Appropriate statistical analysis requires that these patients are included in the intention-to-treat population. Some missing urine toxicology tests were counted as negative tests. However, it is well known that opioid-dependent patients often skip urine tests to avoid a positive test. Missing tests should be counted as positive.

Second, we also do not have substantial evidence of Probuphine's safety as required by statute. The lack of information regarding how to safely transition patients from oral buprenorphine to the implant increases the risk that patients will suffer a dangerous relapse during this critical window. The risks of a poorly managed transition cannot be overstated since a relapse for

patients who were previously stable would be particularly devastating.

The study protocol instructed patients to stop their oral buprenorphine 12 to 24 hours before placement of the implant. However, the pharmacokinetics of the Probuphine implant indicate that it takes 3 to 4 weeks for drug levels to reach steady-state concentrations. Therefore, to ensure patients are adequately treated and decrease the risk of relapse, continuation of oral buprenorphine for the first few weeks of therapy would seem to be necessary to maintain drug levels.

Because the transition was not properly managed or studied, we don't have the information needed to instruct providers and patients on how to manage the transition, period, to decrease the risk of relapse. This is an unacceptable risk for stable patients.

Lastly, 84 percent of the patients studied were white and very few were studied beyond six months. This is not the real world of opioid addiction. Many of these patients will require

treatment for years. We need long-term safety data from diverse populations. Patients will require a new incision every 6 months, creating an ongoing risk of harm due to bleeding and infectious complications. The Probuphine implant has a higher risk for bleeding and complicated removal and infection compared to contraceptive implants, so we need a better understanding of its long-term safety profile.

In conclusion, based on the data presented and discussed today, I'm disappointed to conclude that the risk-benefit profile of Probuphine does not support its approval for the population studied. Thank you for the opportunity to comment today and for consideration of our views.

DR. KRAMER: Thank you. Speaker number 12.

MR. HARROLD: Good afternoon. I'm Mark Harrold. I serve as law enforcement liaison and legal consultant for the Center for Lawful Access and Abuse Deterrents, or CLAAD. I'm an attorney, former federal prosecutor, and former City of Atlanta police officer. I should note that I

appear today in my personal capacity, and I have no financial relationship with the sponsor.

Whenever this committee seeks to make crucial recommendations related to new drug applications, it is important to consider the manner in which the new treatment can assist law enforcement in exercising discretion towards individuals struggling with addiction and those involved in drug possession as opposed to trafficking and violence.

Specifically to the consideration here today, any effective treatment aimed at opioid addiction is advantageous from a law enforcement perspective because it helps remove individuals from the cycle of possession, sales, trafficking, and related criminal activity.

More specifically to the type of implantable treatment, I note three primary advantages that will assist law enforcement. First, if an individual goes to jail or rehab during the time the implant is working, there won't be an interruption in medication access or risk of

withdrawal, which creates chaos for the individual as well as those around him or her.

The treatment cannot be readily stolen, sold, or traded illicitly, which is especially important given that oral medications are common contraband within correctional institutions. Fewer oral medications in the hands of patients means fewer drugs available for the diversion of the black market.

It is of course much easier to remember to renew medication every six months, for example, than to go to a methadone clinic or take an oral drug every day. Better medication adherence can reduce relapse, risk and, recidivism, and it can allow individuals to focus on the psychosocial supports necessary to live a healthy, productive life outside of the criminal justice system

Thank you very much for letting me share my thoughts with you today on this very important issues. Thank you.

DR. KRAMER: Thank you. Speaker number 13.

DR. MALIK: Thank you very much. I'm

Dr. Azfar Malik. I'm a psychiatrist, addiction specialist, and I am a chief medical officer and CEO at Centerpoint Hospital. I'll talk about the hospital a little later, but first I want to clarify that I'm not being paid, compensated, to speak over here. Of course, the sponsors have covered my travel expenses to be here.

It is because of my passion to treat patients with addiction and psychiatry that brings me here, and I feel it's an honor to present this to my colleagues and to this community regarding this very important subject.

It has been on our mind. My interest and passion has been psychiatry. I graduated from my residency about 30 years ago, and psychiatry was exactly where addiction psychiatry is today. There were not enough medications. We had very similar primary medications that we use infrequently, and patient and outcome and treatments were not as good. I see addiction psychiatry exactly where we were 30-35 years ago. There are not enough significant treatment, efficacy, and we talk about

comparative analysis of what psychiatry did and where we are.

First of all, a lot of our patients, at least who we admit, about 60 to 70 percent of these psychiatry patients have comorbid substance use disorder, and they blend together. Just to go to some statistics, about 16,000 patients -- people, I would use the world -- died in the U.S. in 2013 using opioid pain medications. That's about 4 times higher than 1999.

Prescriptions have increased over 300 percent since 1999, and that has resulted -- there is a very comparable proportion today, increase in addiction, too, at the present time. CDC reported that in 2012, most of the medical practitioners wrote about 259 million pain prescriptions. That certainly leads to what we see. We have heard our speakers number 1, number 4, and so on and so forth.

At Centerpoint Hospital, our goal is to treat the whole health problems, including psychiatry and addiction. We see about 30 to

40 percent of patients coming in to our hospital systems who have addiction. We do detox. We do rehab. With the IC, we have four addiction psychiatrists in our system. We treat about 500 to 600 patients with buprenorphine. But the problem is there's a restriction, and we certainly cannot provide more treatment, and we would love to.

I've been practicing psychiatry for over 30 years. At best, our treatment for addiction at this time is mediocre I would say. People don't seek treatment because there is less effective treatment. My experience has been with trials, and we have done the Probuphine trial implant.

I consider this very similar to how we had Risperdal pills or atypical antipsychotics, leading to long-term LAIs, which are long-acting injectables, which last for a month. Now, we have LAIs, which are lasting for 3 months, which is Invega Sustenna; I don't know if you may know about it. I consider this as very similar. We treat patients who are taking Suboxone or various products. There is a problem getting them

refilled, getting them checked. I do feel long-term maintenance treatment is something we should consider, seriously.

We were a part of the 814 study. Most of my patients who were in the study loved it. They would want to continue with that, but certainly I have no options at this time. I will certainly consider more drugs and more new technologies to be brought in. Thank you very much for giving me the opportunity.

DR. KRAMER: Thank you very much. Speaker 14.

MS. TUOHY: Good afternoon. Thank you for this opportunity to speak before you. My name is Cynthia Moreno Tuohy. I'm the executive director for NAADAC, the association for addiction professionals. I have no financial interests.

NAADAC represents over 85,000 addiction-focused counselors, directors, managers, educators, and researchers across this country and abroad. I'm an administrator, a clinician, a treatment program developer, an addiction

curriculum writer, a trainer, an educator, and I have the honor of doing that all over this world, and that doesn't matter.

I have been in the addictions and social work profession for over 40 years now, and every time I hear stories, as we have heard today, of someone overdosing because they have an addictive disease, or a family member in deep sorrow over the loss of their family member to an overdose, or the fear of a parent who will lose or may lose their child to an overdose, it reminds me why I do what I do, and why I've done it so long.

It reminds me why this hearing is so important. And it reminds me why I represent counselors across the United States and abroad who work with addictive diseases in order to try to make a difference, to try to assist people's lives, either the person who is addicted or their family member.

So you see, when you work in this profession, it really doesn't matter how many years you do this work because there are stories like

this that we hear every day, and more so now that a person in the United States, now, is overdosing and dying from opioids every 2 minutes of every day.

Oftentimes, we don't have the medications available for long-term recovery. Yes, we hear the stories from the people we serve with an opioid addiction. "Oh, I started my treatment. I'm doing well. And my brain starts to crave my addiction, my drug, and then I want to use again. And then I go out and I find a way to use."

Without the medications that will serve the addicted brain and in a method that works for a variety of persons who are addicted to opioids, there is a higher percentage of relapse and a higher chance of death. NAADAC strongly supports the concept that medication is a tool that can suspend the craving or desire to use and gain time and perspective for the person with an addictive disorder to make a different choice, to make a choice not to use again.

In this presentation, you may hear me say this word "medication" versus a drug. In the

addiction treatment and recovery world, we don't use that term "drug" because it refers to a street drug. We don't want the brain to go there, so we refer to this as a medication. And an medication is a tool that will assist a person in their treatment and recovery process, then we understand that it's helpful. We understand that this drug -- no, this medication -- is a safe and effective medication. We understand that it's helpful for opioid dependence. We understand that it has a place in the treatment world.

This work is my personal as well as my professional mission. I lost my mother -- sorry. I lost my mother to a drug overdose. Would it have made a difference in her journey had she had the opportunity to be on a medication that could change the way her brain reacted. I hear it.

(Chime sound.)

MS. TUOHY: Do you know that my wish is that every addiction counselor, every family member, has the opportunity to give a medication -- I'm so sorry -- that could change the brain? So I urge

you to consider this medication, and I thank you.

DR. KRAMER: Thank you very much. Speaker number 15.

(No response.)

DR. KRAMER: Speaker number 16.

MR. EMSWILER: My name is David Emswiler. I'm not being compensated for my time to speak here today, though the sponsor has covered my travel and lodging expenses to attend the meeting. I also brought my wife Cindy here today for moral support as I share my experience with you.

Thank you for this opportunity to speak. It has been said that I'm in remission. The dictionary defines remission as a period in the course of a disease when symptoms become less severe, a temporary recovery. Addiction is the disease, and it can come back. I've been clean for four years this month, and only I can control if I remain in remission.

I remember all too well the sickness of withdrawal from opioids, and I don't want to feel that way again. It's one of the factors that

drives me to make my remission permanent. One of the other factors is my wife who's here with me today, and the other one calls me Grampy.

Opioids took over my life, and I am one of the fortunate ones who decide I needed help before it was too late. I've been a firefighter for more than 20 years. I'm the poster child for it can happen to anybody. I've seen addiction from both sides as a patient and as a provider.

My addiction cost me more money than I care to know. I hate money. I lied to get money. It affected my life at home and took a toll on my wife and kids and my parents, though none of them knew until I told them, and I decided to get help. Thankfully, they all stood by me, and I did not have to suffer through what would have been my greatest loss. I am blessed to have a wonderful support system at home as well as in the clinical setting.

After starting my medication, I felt normal for the first time in years. I wasn't high. I wasn't withdrawing. My head was finally clear, and

I could function on a day-to-day basis. Medications like buprenorphine and Probuphine allow that state of normalcy, Probuphine on an even higher level because I don't have to worry about a pill every day that taken correctly takes 45 minutes. And I don't have to leave that pill that could kill the love of my life, my granddaughter, if she found it and took it.

I'd also like to add that neither Suboxone or Probuphine alone will work without the proper support system consisting of the appropriate prescribers who understand how the medications work, as well as some form of counseling. I chose one-on-one counseling along with visits to a clean site every two weeks. Others may choose one of the 12-step programs or counseling with their prescriber. Whichever method is chosen, it is imperative that everyone involved works together with the common goal of constant remission and recovery.

I'll deal with this for the rest of my life. Right now, my medication is a safety net for me,

and the thought of not having that net scares me. It's a comfort to know that I have treatment available to me and there is potential for Probuphine to be approved. One day, I may have to stop using medication for my recovery, and I will cross that bridge when I come to it. But until that time, treatments like Suboxone and Probuphine are literally saving lives every day, including my own. Thank you for your time.

DR. KRAMER: Thank you. Speaker number 17.

DR. MALIK: Thank you again. I'm here presenting for Dr. Amit Vijapura. He's one of the other investigators who I know, but he couldn't make it. He was a principal investigator in multiple trials, 5 trials, 805, 807, 809, 811, and 814. I'll just read his statement. He claims:

"I've been working with the compound for the past five years in 3 different double-blind studies and 2 open-label studies. I've seen significant improvement in the level of functioning for each individual participants in the clinical trial. Each participant in the open-label phase showed a

significant improvement and steady maintenance of their symptoms, without any craving or withdrawal symptoms.

"Inserting and removing of the implant is a simple procedure that can be done by any qualified physician in an outpatient setting. As a clinician treating opioid dependence in my clinical practice, I've seen many of my patients struggling to stay compliant with the current available buprenorphine products. It is my belief that having the Probuphine implant available to those patients could be a life-changing experience.

"I have surveyed many of my patients in my practice to ask them if they would be interested in a 6-month implant as a treatment option, and most of them said they would consider this treatment option when hopefully approved by FDA for the maintenance treatment of opioid dependency. I've asked similar questions to physicians who are treating opioid-dependent patients, and I've found the same level of interest from my colleagues as well.

"Thank you for your time and consideration. Amit Vijapura, board certified psychiatry, addiction, medicine." Thanks.

DR. KRAMER: Thank you. Speaker number 18.

DR. GAY: Thank you. My name is Joe Gay. Braeburn Pharmaceuticals has paid for my travel expenses and lodging, but I'm not otherwise compensated for my testimony. I am a clinical psychologist by training and the executive director of Health Recovery Services, Incorporated, which I'll refer to as HRS, based in Athens, Ohio. HRS is a private, non-profit behavioral healthcare agency specialized in addiction treatment and prevention.

The committee is undoubtedly aware of the dramatic increase in problems related to opioid use. Ohio feels as if it is in the center of the storm. Opioid related deaths in Ohio have increased tenfold, from 198 in the year 2000, to 1988 in the year 2014. In 2014, Ohio recorded the second highest number of overdose deaths of any state in the U.S., and depending on the method of

calculation, the third or fifth highest death rate.

HRS is an area of the state that has been highly impacted by the increase in opioid use. During the year 2000, only seven-tenths of 1 percent of our admissions were opioid related, whereas now, they comprise about 50 percent of our admissions.

For several years, we struggled to treat the rising number of opioid-dependent individuals without the use of medication-assisted treatment, also know as MAT. Without the use of medication, only about 15 percent of opioid-dependent clients even successfully completed a course of treatment.

In 2000, we began utilizing medication-assisted treatment. Since that time, we have provided MAT to close to 900 individuals utilizing primarily buprenorphine-based medication. Our overall rates of treatment, retention, or successful completion have increased to roughly 40 percent. We are convinced of the efficacy of opioid agonist treatment so long as it is delivered appropriately. However, significant problems have

arisen in the delivery of such medication. Probuphine has the potential for addressing some of the key challenges.

The diversion of buprenorphine-based medication has emerged as a significant issue. Individuals typically use diverted medication to avoid withdrawal and to reduce drug craving, obviously uses for which the medication was intended. However, often the medication is used only temporarily with the intent of resuming the misuse of opioids.

Buprenorphine, which has the potential for being a major adjunct to treatment and recovery, thus because a component of the addictive pattern of use. The individual for whom the buprenorphine is prescribed remains engaged in addictive related behaviors, including drug trafficking, and immersed in the drug subculture. The customer receives prescription medication with no medical oversight.

Diversion has also seriously undermined the credibility of opioid agonist treatment and rendered the use of buprenorphine in its current

formulation unacceptable to important referral sources, particularly in the criminal justice system.

As a result of the circumstances described above, we would welcome the availability of a product such as Probuphine, primarily because it reduces, if not completely eliminates, the potential for medication diversion. It also reduces certain barriers to treatment, including the transportation challenges faced by those receiving medication and the difficulties in accessing physician time to prescribe medication.

Thank you for the opportunity to testify.

DR. KRAMER: Thank you very much. Speaker 19.

MR. MENDELL: Hi. My name is Gary Mendell, and I'm founder and CEO of Shatterproof. And I'm here -- I'm reading a letter written by Patrick Kennedy, former U.S. Representative, Democrat from Rhode Island, founder of the Kennedy Forum and co-founder One Mind.

"I'm humbled and honored to write in support

of something that is absolutely critical to the future of this country, expanding access to addiction treatment for opioid dependency. A you know from recent news, opioid overdoses are at epidemic levels in many parts of the nation. People are dying every day, and the public health and criminal justice systems are stretched to their limits. And this isn't happening in a vacuum.

"A recent public opinion poll out of New Hampshire cites heroin overdoses as the number one concern of voters in that state, not the number one health concern nor the number one crime issue, the number one issue overall. We need solutions now. Why? Addiction is a disease that does not discriminate based on race, gender, economic status, or geography, yet solutions to this epidemic are sparse, or worse, non-existent for millions of Americans who need them. Addiction is a progressive disease with a trajectory marked by death and disability if untreated. That must change.

"I write to this panel not only as a former

member of Congress and author of the Mental Health Parity and Addiction Equity Act, but as someone who has lived the experience of opioid addiction. My addiction began as a result of treatment for back pain. Just like many others who originally sought relief for an injury or chronic pain, as my symptoms subsided, they were replaced by addiction.

"I have been opened about my struggle with prescription painkillers and mental health issues, which often co-occur, in the hopes that I will set others free from living with this all-consuming disease and silence. The stigma of seeking treatment is a burden no one should have to bear.

"Today, millions of people are living with the very same scenario, the one that I have dedicated my life to understanding, fighting, and advocating to solve, whether as a private citizen or through the passage of the parody law.

"Now, we have new treatment options at our disposal which are worth consideration for this panel. To that end, the abundance of clinical research shows that medication is a critical part

of the recovery process. Buprenorphine in particular is highly successful in helping people like myself who have struggled with opioid addiction. It allowed me to live to the point where I live now, in stable recovery without medication-assisted treatment.

"That said, there were many points in my early recover where I relied on medication-assisted treatment in order to function free of the debilitating effects of my full-flown addiction. That is why I am excited to learn about the long-term treatments, like a 6-month implant, as well as weekly and monthly injectables. Stricter adherence to a course of therapy means a greater chance of achieving a long-term recovery, a goal that is essential to these medical advances and why this panel should approve any new form of this treatment.

"I feel strongly that injectables and other similar medical interventions are critical and noteworthy interventions of an existing medication. My expanding currently available options for

treating this illness, you'll be offering the same personalized medicine for addiction as we have come to expect for treatment of other diseases. In other words, we will be treating the disease of addiction in an equitable way backed by complementary medical practices, which is the cornerstone of the Mental Health Parity and Addiction Equity Act. It's good medicine, and it's part of the law. Thank you.

DR. KRAMER: Thank you very much. Is speaker 20 here?

(No response.)

DR. KRAMER: If not, speaker 21.

MR. CAMPBELL: My name is Wayne Campbell, and I'm going to read a letter from Timothy Lepak. And neither Timothy nor his organizations have received any financial support from Titan Pharmaceuticals or its affiliates.

"Timothy represents the National Alliance of Advocates for Buprenorphine Treatment, NAABT, which is a 501(c)(3) non-profit organization formed in 2005 to educate and help connect patients to modern

evidence-based addiction treatment. Our membership includes over 4,000 buprenorphine prescribing physicians, and outpatient physician-matching service has been used by more than 93,000 patients seeking evidence-based addiction treatment. I am in strong support of the FDA approval of Probuphine.

"Since buprenorphine was approved for the treatment of opioid addiction in 2002, it has become the standard of care. We now have over a decade of clinical experience with millions of patients, which has shown buprenorphine to be safe and effective when compared to alternative treatment or untreated addiction.

"Over 76,000 people have died from opioid overdose since the FDA rejected Probuphine in 2013. We can't know how many lives would have been saved by Probuphine, but we can be virtually certain it outnumbers any lives saved from withholding it. The need so enormously outweighs the risks. It's baffling that this tool has not been rushed in the hands of doctors already.

"Probuphine is unique among buprenorphine medications as it has many attributes currently unavailable in the current offerings. It provides 6 months of stable-state medication, which virtually guarantees 6 months of compliance. It's difficult to divert, eliminates axonal pediatric exposure, dosing errors, missed dose, and lost medication.

"Although it lasts for 6 months, it contains about one-sixth to one-third of the medication required for taking tablets or film during the same time period, thus further reducing the risk from diversion. It eliminates the risk or the ritual of taking a pharmaceutical daily, which can be a trigger for people addicted to prescription opioids.

"Clinical trials with buprenorphine titrated the initial dose up over the course of several days. This method was initially adopted by clinicians, but it led to patients dropping out of treatment before stabilizing, with some relapsing and dying. It took clinical experience to

recognize that patients could be retained if they were dosed to affect on the first day, thus suppressing cravings and withdrawal as quickly as possible.

"The sooner Probuphine gets to clinicians, the sooner its particular best practices can be determined, something that cannot be ascertained and limited preapproval clinical trials. With 78 opioid overdosed deaths a day, we need this unique tool in the hands of physicians as soon as possible. Please recommend the approval of Probuphine. Thank you very much."

Clarifying Questions (continued)

DR. KRAMER: Thank you. That concludes the speakers.

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

Before we go any further, we are going to

give the sponsor a chance to answer the questions that have been posed to them. And when they are finished, we will go to the three people who have a question for clarification for the sponsor earlier. Then we'll take a break.

MS. SHELDON: We'll start with the discussion on route of administration. Seventy-five percent of patients in PRO814 had a history of prescription opioid versus 25 to 30 percent on heroine. And we've taken that data and looked at both kinds of drug abuse by method of administration.

If you could put slide RR-5 up please? Both for heroin and for prescription, people inject and inhale. In the -- slide up -- in the heroin -- it's not up. Okay, here we go. Fifteen out of 22 heroin patients on sublingual were injecting; 12 out of the 15 Probuphine heroin patients were injecting. You can see the inhalation numbers. I was sort of surprised. Actually, 10 percent of the prescription abuse was also via IV injection.

In terms of response rate -- we have the slide made? If we don't, I'll just tell you what those are. Sixteen out of the 21 sublingual IV users, or 76 percent, were responders, and 17 out of 18 Probuphine IV history --

DR. KRAMER: You lost the slide?

MS. SHELDON: Yes, because that slide -- I have gone on to the response rates, sorry, for which apparently, a slide is not made yet. But 94 percent of the patients in the Probuphine group, who were in their history using their either prescription opioid or heroin by an IV route, were responders versus 76 percent of those in the sublingual group.

We do have some data on both IV use of heroin, IV use of prescription opioid pills, as well as inhalation. It does not appear that, overall, there's a difference in response to Probuphine or to the sublingual group depending on prior history of use.

There was also a question about length of stability, I think, between the 6 months and the

3 months. Just to clarify that while we wanted people to have been in buprenorphine treatment for 6 months prior to entry into the study, the stability criteria was only for 90 days.

That 90-day stability criteria involved no evidence of illicit opioid use by urine toxicology or self-report, as well as the physician attestation that they were clinically stable, as well as being on a dose of 8 milligrams or less for that 3-month period of time.

We had a question also on predictors of supplemental use. We actually, at the request of the agency previously, did a multivariate analysis to see if there were any predictors. And we looked at all the typical things -- age and sex, and history of abuse, daily dose prior to entry into the study -- and we did not see any predictors of response. There were no variables that seem to be able to predict who was -- I'm sorry, not predictors of response, but predictors of supplemental use. There do not appear to be any variables that would lead you to be able to pick a

priority who was going to become a supplemental user.

DR. KRAMER: Could you clarify?

MS. SHELDON: Sure.

DR. KRAMER: Did you just look at prior dose, or did you look at dosage form with this question of whether the formulation had a different --

MS. SHELDON: There were definitely patients in our trial that came on film, on tablets, and on different -- on the new products as well, Bunavail and -- again, that was also a requested analysis that we did for the agency, and there were no differences depending on what prior medication patients were taking.

We saw earlier the slide that the prior dose also did not predict response between the two arms, although in general, the patients who were taking lower doses before they came in did a little bit better. I think those are difficult to determine from a statistical standpoint.

I think I have -- yes, I have one more

deliverable to you guys. You asked about history of other illicit drug uses. We did not actually collect alcohol, or cigarettes, or nicotine but we did -- slide up -- look at entry criteria at screening at other types of illicit drug use.

In general, they were below 10 percent of the various illicit drugs that you can see on the screen with the highest, as again maybe expected, being cannabis at about 16.2 percent across the entire study population.

Last one, the question of -- again, for clarification and for your deliberations, the question of what happens after two years has come up. Previously, as part of the previous submission, we had made commitment to doing a same-site study.

As soon as we would have approval, we would immediately start a PK study to show that you can insert into the same -- into a previously inserted site so that, as is common with the contraceptive implants, you'd be able to go back in. Certainly, well before the two-year mark is reached, we would

be able to provide that PK data.

Alternatively, other sites have been considered and recommended by some of our expert clinicians, so it's possible to insert into other parts like the abdomen or the lower back.

DR. KRAMER: Just to clarify that. You would say that the overall strategy that the company has is to provide a maintenance treatment that would be long term, since these people, by your own survey, have been on it for years and some of the people up to 10 years?

You're not talking about withdrawal people. And all of the data, subsequent to what we have now, is to conduct -- all the study of that is to be conducted in the future after approval; is that what you're saying?

MS. SHELDON: The only study that we would do after approval would be to show that you can insert into the same site, so that you can go beyond two years by inserting into the same site. However, other sites are also possible for insertion beyond just the arm as has been done with

other products and occasionally, even in our studies where it's been more acceptable for the patients. The abdomen and the upper back are other possible sites for insertion of the implants.

We've asked clinicians how long they expect to keep patients on Probuphine, and 4 percent said once. The vast majority said as long as the patient needs it, and then there were sometimes in between. It seems, based on what everyone has been saying, that buprenorphine is a product that, of course, should be used for the long term. We have data for up to one year and a possibility to go to two years with the sites that are available in the arms.

DR. KRAMER: Okay. We have questions from Dr. Brady first.

DR. BRADY: Yes. I was just curious about the REMS, the training plan. It looks like it has kind of two components: one which is just for the prescriber, which looks like it could be done online, but then the other part of the training that's for the person doing the procedure, it looks

like that's pretty intensive hands-on training.

Have I got that right?

MS. SHELDON: So the 4-hour competency training is actually required for everyone, whether you're a prescriber or whether you just intend to implant or you have a dual role.

The difference will be that the prescribers who don't intend to implant, they'll still go through the practice so they understand the procedure. They just won't have to take the competency assessment test.

Slide up. Just to reiterate, in terms of the ability for the training program to fully prepare people for difficult removals, in the human factor study and in the training programs, as we've done them even for preparing the investigators, we actually made it pretty difficult.

There was only one that was pre-inserted properly for the trainees to remove. One was fractured. One was superglued, as Dr. Chavoustie explained. And one was intentionally inserted way too deep so that the intention was that they would

not be able to remove it. And then the appropriate thing at that point would be to say, I can't find it; I need to send this for imaging.

Obviously, all those 4 things will not happen in the same person, but we wanted to make sure that people are fully prepared for difficult removals.

DR. BRADY: What's the general plan in terms of ramping up that training to make it -- will it be done by Braeburn -- to make it accessible and frequent enough to accommodate the needs of the prescribers?

MS. SHELDON: We have 20 master trainers as of this time, and we have a 5 to 1 ratio, so we can train a hundred at each session. We plan to run a couple of sessions a day. Actually, we can do some pretty intensive training, and plan to, if approved, be able to train 1500 people in the first 6 weeks or so and have already assessed where the locations would be, kind of mirroring where the current use of buprenorphine and buprenorphine prescribers are.

DR. BRADY: Thank you.

DR. KRAMER: Dr. Kotz, did you still have a question?

LCDR SHEPHERD: It was from this morning.

DR. KRAMER: For the sponsor.

DR. KOTZ: I don't know whether this is appropriate now for discussion, but I'm wondering if the implant obviously is going to count under the regulation that we have now of a hundred cap per physician. The implant would be -- conceivably, one physician could have a hundred people on implants.

MS. SHELDON: We've been discussing the potential for the -- obviously, when DATA-2000 was initially put out, there was no contemplation of an implant. It'll be yet to be determined exactly how the implant will be treated.

One interesting finding so far is that many of the clinicians who are interested in Probuphine actually like buprenorphine but don't like some of the diversion aspects. So they actually happen to be people who are below their cap, so this actually

will result in an expansion of access for patients because these physicians are not taking more patients. But exactly how the cap will apply to Probuphine is a matter we're still discussing.

DR. KOTZ: But currently, the law is, right, that Probuphine counts as a --

MS. SHELDON: Yes, based on the current law, that would be the case. Obviously, we're all eagerly awaiting some new HHS announcements of potential changes to increase access.

DR. KOTZ: Thank you.

DR. KRAMER: Adam Gordon?

DR. GORDON: Good afternoon. I have a question about the urine test results for PRO814. I noticed that in the quantitative analysis of your urine drug test results, you're not measuring buprenorphine at all. I'm wondering whether you specifically assessed in the self-report data whether patients were taking illicitly diverted buprenorphine products.

MS. SHELDON: The self-report for illicit drugs was limited to non-buprenorphine products.

DR. GORDON: So then I could surmise that we would not have any results that indicate that patients may be taking supplemental buprenorphine off the streets in the data presented in the results?

MS. SHELDON: Obviously, not from the results that we have. However, based on personal experience with these patients, I think Dr. Torrington could add little something to this conversation.

DR. TORRINGTON: Hi. Matt Torrington. We didn't really think it was very realistic that patients would be taking illicit buprenorphine when they could get it free from their study provider just by asking for it. It is possible, but it was not something that we thought was very likely.

DR. KRAMER: Dr. McNicholas?

DR. McNICHOLAS: Thank you. I just have a follow-up on the issue of the 3-month stability versus the 6-month because something occurred to me over lunch, frankly.

Were subjects, in order to be recruited into

the study, did they already have to be in buprenorphine or could they be recruited, maintained for 3 months or 4 months or 5 months, and then put on to the buprenorphine?

MS. SHELDON: They had to already be in on buprenorphine for 6 months, but they had to only have demonstrated the stability criteria by the 90 days clean and physician attestation. Slide up.

DR. McNICHOLAS: My other question is, do you know if there were any incentives to keep the dose below 8 milligrams other than clinical judgment?

I know some insurance companies and stuff kind of recommend a lower dose than sometimes the clinician would like, and I don't know if you know if there were any incentives in play at your various sites that might have resulted in a lower than optimum dose for the patient other than clinical judgment that this was in fact the optimum dose.

MS. SHELDON: We are not aware of this particular effect having been in our study.

Dr. Lofwal?

DR. LOFWAL: I can just add as one of the study sites and knowing several of the other study sites, that most of the volunteers who enrolled were actually our current clinic patients.

The vast majority of the patients at my site were previous patients and had been for years. Also, I just have an interest in policies and what states are doing. I've not seen anything with insurance companies where they're requiring people to go below 16.

We do in our state have this attestation that we have to have every 6 months, if they are at 16 or higher, why they are on that and why we're not decreasing that dose, but I have not any state or policy below that.

DR. KRAMER: Dr. Campopiano? Did I pronounce it right?

DR. CAMPOPIANO: It's Campopiano. I have a follow-up question to the data that you just presented about other substance use. The numbers that you presented, was that what was reported

prior to enrollment or was that also what you found during enrollment?

That's kind of the first question. Go ahead. I just want to give you a heads up, and I have a follow-up question.

MS. SHELDON: Those are the data at screening. We can show kind of one by one, if you would like, the data as the study progressed. Generally, other substances of abuse did not change. But if we -- sorry, can you go back to the other one? I was just looking at the amphetamine ones as an example.

Slide up. Thank you. This is just the example for amphetamine, and the percentages more or less stayed about the same.

DR. CAMPOPIANO: Was there a reason you didn't test for cocaine?

MS. SHELDON: We did.

DR. CAMPOPIANO: Oh, I didn't see it.

MS. SHELDON: It's just we have to go back -- we did test for cocaine as well.

DR. CAMPOPIANO: You did. And then I

noticed that people were testing positive for benzos. Did you distinguish whether this was prescribed or illicit benzodiazepine use?

MS. SHELDON: We allowed prescribed benzos as part of the study. Any of the results that you saw were at screening and they were illicit use.

DR. CAMPOPIANO: I guess I'm forced to conclude that people who were using illicit benzos and marijuana were considered clinically stable by the --

MS. SHELDON: For their opioid dependence. The criteria required that anyone who met a substance use disorder for other substances be excluded. But if they were using but they were not assessed to actually have that substance as their primary substance use disorder, then they were allowed in the study.

DR. CAMPOPIANO: Okay. Before you presented the substance use data, you said that you did not find a correlation between any of the patient variables and whether or not they required supplemental use, and then you went on to present

the substance use data. Did you check for any correlation between the substance use data and any -- did you check for correlation between that and supplemental use?

MS. SHELDON: That was not a parameter that we checked, no.

DR. CAMPOPIANO: Okay. Thank you.

DR. KRAMER: We've had a few people that have some questions, the ones we have from before. We'll take Dr. Preston, Dr. Conley, and then we're going to -- I had a question as well. I'll be last, and then we'll take our break.

DR. PRESTON: I've read that, occasionally, one of the implants came out just after being implanted, and I could imagine this could happen if it went on the market. Is there a recommendation for that? If that were to happen, would you recommend that it be replaced or supplemented with some other replacement buprenorphine?

MS. SHELDON: In the clinical trial, when one case did occur where the implant was -- all 4 were removed, and they were reinserted in the

contralateral arm. In the real world, it may be possible to just reinsert one.

DR. KRAMER: Dr. Conley?

DR. CONLEY: Yes, thanks. Rob Conley. This was based on the new presentation of your data. You implied that in training on the insertion and removal techniques, when you mentioned the that was inserted too deep, that there was sort of a right answer that you're supposed to ask for imaging.

MS. SHELDON: In training, yes.

DR. CONLEY: What I didn't really see in training is two things. One is during the insertion technique. So the first question is, do you assess how well people do that, and is that part of the competency?

Secondly, on the removal, like for example, the broken one, obviously, the U-shaped technique didn't work or wouldn't work. I assume there's some other technique you trained during that time?

MS. SHELDON: Yes, so slide up, and I'm going to have Dr. Chavoustie come up and discuss in a bit more detail. But the 21 insertion critical

tasks do include the proper angle which is a 20-degree angle, and that's intended to prevent the too-deep insertion.

DR. CHAVOUSTIE: The Competency Based Training program, when we do the deep insertion, the correct response that we're anticipating from the trainee is to stop and say I cannot palpate that implant or I cannot find that implant. I'm going to suture up the incision, and I'm going to schedule the patient in 3 weeks for an ultrasound, and then bring the patient back. That is the correct way to handle it.

The U-technique, the second part of the question with the U-technique, when an implant -- fibrosis and fractures, and most of the fractures are iatrogenic.

When you grasp a hold of the implant with the actual atraumatic clamp, if you're a little bit too overzealous, which somebody like me could be with my biceps, if you pull too hard, you could fracture the implant.

However, a fracture is in the same plane,

almost like a cocoon, like the caterpillar in a cocoon. It's in the same plane, so then you would reach in with -- by the way, you have two of these clamps on the field, so if you fracture one, you grab it and take that one out, and then take the other one. The U-technique works perfectly in that situation.

DR. KRAMER: Okay. I just have one question. It gets back to the issue of study quality. And it's a question specifically on the safety, PRO814 and the information, I think it was presented in your Appendix A of your original packet. I didn't see it presented today.

I was a little confused because despite reporting that 93 -- let's see -- 93 percent of the Probuphine and 94 percent of buprenorphine patients completed the study, it also stated that the proportion of patients who received study treatment for at least 24 weeks was 68.5 percent and 65.5 percent in the two arms. Maybe I'm missing something. But if they completed the study, why did they only get 68 percent of the treatment?

MS. SHELDON: Each study assessment period had a 7-day window, so it was possible for a few patients to come a little bit earlier. In the database, if it wasn't 24 weeks, it got captured as less than 24 weeks. If it was 23 and a half weeks because they came early or they came early on 2 or 3 of their visits, and therefore, their end-of-treatment visit was at week 22, that ended up not counting as 24 weeks.

DR. KRAMER: Thank you.

Okay. We're going to take a 10-minute break. Just to prepare you, number one, we can't talk outside during the break; you know that. But when we come back, it's going to be quite a challenge because if you're looked ahead, we have a lot of discussion questions. The FDA really -- we only have one voting question but we have a total of nine questions.

They really want to hear from the members of the committee, so I'm going to ask for your patience and cooperation. We are definitely going to go to the end, I think, of the time. Thank you.

Promptly at 2:35.

(Whereupon, at 2:23 p.m., a recess was taken.)

DR. KRAMER: Please take your seats. We're about to restart. The prompt people will get to speak first. Dr. Hertz is going to give a charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Hi, all. Thank you to everyone here today. I just want to say that I appreciate the time it takes for our committee members to come and participate and help us at these advisory committees. We really value your efforts.

We have the first implantable buprenorphine product that has potential benefits stemming from a form that cannot be as easily diverted or result in accidental exposures in the home compared to existing formulations. We heard about some other possible benefits during the open public hearing.

However, there are also some novel risks, and they center around the surgical implantation and removal. Plus, we have heard that

buprenorphine comes in one strength, and it cannot be titrated.

You've heard presentations about the objectives and results of a novel study design. And as can happen with a novel study design such as this, we did not fully anticipate all of the factors that could influence the outcome. And as can happen, not all of the investigators in study sites completely carried out the protocol as expected with regard to some of the criteria.

You've heard the sponsors and our interpretations of the results and how they differ, particularly why we disagreed with any claim of superiority and with the overall responder rates.

The questions we have for your discussion and vote begin with defining the appropriate patient population for treatment and how to define successful treatment, particularly with respect to the use of sublingual buprenorphine and the results of urine toxicology.

Defining the intended population, and not just whether it works or does not work, but also

what the responder rate is, these are important so that clinicians have the information they need when deciding whether to use buprenorphine for a given patient.

If you think this sponsor has succeeded in demonstrating that buprenorphine is effective for a particular group of patients, help us understand how to identify those patients, how clinicians should be guided to provide rescue use when needed, and how to tell when a patient is not benefiting from Probuphine. If you think the study has missed the mark, then let us know that, too, and if you think that additional work is needed.

While, we don't think that Probuphine presents any greater systemic risk than sublingual buprenorphine, we do have some concerns about the potential adverse events associated with insertion and removal and for what might become of Probuphine rods that come out, where they may pose a risk of misuse in accidental exposure.

The proposed REMS is intended to minimize these risks, and we would like your thoughts on

that approach as well, the approach to risk management.

We recognize the public health value of having an implantable buprenorphine product as a part of medication-assisted treatment options, and we need your assistance in determining whether this product will provide the anticipated benefits.

We'll go to the questions now. Thank you.

Questions to Committee and Discussion

DR. KRAMER: Given the number of questions we have and given the urgency to get to the voting question with all of you present -- and if people start leaving, it really defeats the whole purpose of why we're here today -- we want each of you to have a chance to weigh in to the final vote -- we really need to try to keep the discussion on each one of these to about 10 minutes, at the most 15 minutes.

So the way we're going to go about this is I'll read the question, and I think it would be best for those people who feel motivated to address a particular question to have the opportunity

voluntarily as opposed to forcing around the table kind of discussion. I think it becomes more meaningful.

Then I'll make sure at the end of that discussion, in a particular question if there is anyone who has an urgent comment that they want to make, then they can make it.

It's very important, I think, to understand the FDA is as interested, not just in your vote, but is as interested in your thoughts on each of these questions they've carefully developed to explore your interpretations.

We've got a background buzz on the microphones.

Please do comment. Don't feel that the only thing that counts is a vote. Okay?

The first question, buprenorphine is non-titratable product that provides a fixed plasma level of buprenorphine. The original studies raise concerns about the appropriateness of the dose for a broad population.

The applicant has now specified a

population, namely stable patients on a relatively low dose of sublingual buprenorphine for whom they believe the dose provided by buprenorphine is adequate.

The discussion is around A) whether there is a population that would benefit from the use of buprenorphine and how to define this population; B) if there is a population that would benefit from buprenorphine, if there is one; discuss whether the study entry criteria that the sponsor used adequately defined this patient population, and discuss whether the population studied actually reflected the population they defined.

I'll open it up, and let's continue to have you put your name tags vertical and get your Jennifer's eyes, so we can keep a list of anyone who wants to comment.

Dr. Carroll, on the phone, I'm told has a question. Dr. Carroll, your name tag has been properly placed upright by Dr. Gordon.

Are you there?

DR. CARROLL: Hello?

DR. KRAMER: Dr. Carroll, we're ready for your question.

DR. CARROLL: Hello? Can you hear me?

DR. KRAMER: Now, we can hear you. Go ahead.

DR. CARROLL: Okay. I was wondering if -- the sponsor, I note, had provided some sort of estimate as to the population of buprenorphine patients that actually might be appropriate for buprenorphine because it strikes me as it would be relatively small, which could affect the impact and might make us look at the risk a little bit differently.

If we have an array of -- large sample of individuals on buprenorphine, but in clinical practice, it's something like 60 to 70 percent of them drop out within the first 6 months. And of those, a lot of them aren't stable. It seems to me we may be dealing with a very small, very specialized sample of individuals who are appropriate.

Then if we think about how the study was

done and make some comments around, maybe those who aren't using a lot of benzos and cocaine are appropriate for this, it might be a very, very small number. So I'm just wondering if we had considered sort of the size of the population for this.

DR. KRAMER: Okay. Dr. Carroll, because we actually didn't give you a chance to ask your clarifying question earlier, we're going to allow the sponsor to address, answer your question before we go on to further the discussion and press you on whether you think there's a population that would benefit.

Sponsor, if you could address the size of the population that you have estimated would be appropriate for this product.

MS. SHELDON: Sure. We've looked at it a couple of different ways. There's no easy way to figure this out, obviously. And Dr. Walsh asked the same question, so we figured she could now give the answer as we've investigated it.

Slide up, please.

DR. WALSH: Thank you. Hello, Dr. Carroll. There really is no easy way to answer this. There's no one single data set that captures everything. Of course, we also know that there are many practices that are cache-based that are not going to be captured in any data set probably.

What you're looking at here are data that are proprietary data from Symphony Health Solutions, and they were asked to assess the number of patients who are receiving doses of 8 milligrams or less as the potential starting point for defining the population that would be appropriate for Probuphine.

You can see in the figure on the left-hand side, from a patient chart study, that was just a random selection of patient charts from some of the larger insurance companies that contain 652, the estimate there is about 47 percent of patients across doses are on doses of 8 milligrams or less.

But when looking at a larger claims database of over 72,000 individuals, the estimate there is about 24 percent. Based upon other data, we

believe that probably about 25 percent or so is about the right number of patients who are being maintained on 8 milligrams or less.

I think in the FDA slides this morning, they mentioned that in 2014, that 1.3 million persons, unique persons, received buprenorphine for the treatment of opioid dependence.

DR. KRAMER: Thank you very much. Okay. Dr. Carroll, did you want to comment on the first discussion question, whether you think there's a population that would benefit from the use and how you would define it?

DR. CARROLL: In light of --

DR. KRAMER: I've lost you again. Dr. Carroll?

DR. CARROLL: I'm sorry.

DR. KRAMER: We didn't hear anything.

DR. CARROLL: It seems to me we might want to discuss carefully what clinically stable actually means. I might define it a bit more narrowly that that's done in this particular study, specifically around -- with this drug use, the

clear demonstration of stability given the potential risks here, especially for other drug use.

DR. KRAMER: Could you tell us what you think the population would be?

DR. CARROLL: I think the stable for 6 months is probably smaller than estimated, but I would also look for sort of a demonstration through urinalysis of no other use of illicit drugs that are contraindicated for buprenorphine. The benzo use is a bit of a concern to me.

DR. KRAMER: Okay. Thank you very much.

Dr. Grieger?

DR. GRIEGER: I think the criteria, as the sponsor has laid out, are reasonable as guidelines for patient selection. As you look their data, not every patient met every one of their criteria, but it sets the groundwork for who you would start to think of as a clinician.

I wouldn't prescribe an exact set of criteria or proscribe another set of criteria, but rather to leave these as being guidelines because

this is a dirty population in terms of comorbid substance use, comorbid psychiatric disorders. You're never going to have a clean population of people that aren't abusing other things, and yet you don't want to deprive them of a potentially beneficial long-acting agent.

I think the company actually laid out, with their physician or prescribers certification form, reasonable guidelines for who you would think of to use this medication with.

DR. KRAMER: You're referring to clinical stability checklist?

DR. GRIEGER: Yes.

DR. KRAMER: Okay. Dr. Ionescu?

DR. IONESCU: I'm going to agree with Dr. Grieger, too, because I'm just thinking about other chronic conditions that we as physicians face all the time, like diabetes, hypertension. Certainly, our patients don't come in with blood pressures that are perfect every single time or blood sugars that are perfect every single time.

Similarly, this is a chronic condition that

I'm trying to equate to it, and I think the guidelines outlined by the sponsor seem reasonable from a clinical perspective. It's not perfection, but as we all know, clinical work certainly isn't perfection.

DR. KRAMER: Dr. McNicholas?

DR. McNICHOLAS: Thank you. I'm going to have to disagree a little bit. I definitely think there is a population for whom this medication would be a godsend, but I'm not sure if 3 to 6 months of stability, and particularly with positive for other drugs of abuse, is really the criteria that we should be going by.

Having a lot of experience with this population, there's a honeymoon phase, and that can last a good 3 to 6 months, and then it's, "Oh, well, let me see what I can do." So I think I would like to see them stable a little bit longer.

The other thing is, in my clinical experience, most patients early in treatment are not at 8 milligrams. They're at 12 to 16 milligrams. And then as they stabilize and as

they get into regular therapy and their cognitive behavioral therapy and their supportive therapies and stuff, then they start backing down on the dose.

I think the 6 months is probably a little bit light for my -- in general, for the patient that I would think would be good for this medication because they're really complex, and a lot of them have major issues when they come in, and you've got to get that under control before you give them, according to them, a lot of them, permission not to come in for all of their counseling therapies.

DR. KRAMER: On the third part of the question, discuss whether the population studied reflected the population you're describing, what is your assessment of that?

DR. McNICHOLAS: I think that would have to be questionable to a no.

DR. KRAMER: Okay. Dr. Campopiano?

DR. CAMPOPIANO: Focusing on the question the way FDA has phrased it, which is this product,

which is non-titratable and at a relatively low dose, my assessment of the population that would be ideal for would be one that is behaviorally stable.

With the understanding that the pharmaceutical product that we're looking at is only treating the opioid use disorder, rarely do you see that by itself. A person who is self-medicating or has not gained the insight into their behavior enough to abstain from other substances is going to be inadvertently inducing symptoms of withdrawal in themselves or similar to withdrawal, making themselves emotionally unstable, psychiatrically unstable.

It would be very difficult to expect a person who is still struggling with poly-substance use to be able to function well on something roughly equivalent to 8 milligrams or less of buprenorphine.

A behaviorally stable population where -- again, you're going to have people who become unstable while they're on it, and that's not fault of the product. But I think maybe that's the

element of the consideration for enrollment or treatment with this product, should it be on the market, that maybe needed to be tweaked a bit.

DR. KRAMER: Did you feel that that was not verified in the study?

DR. CAMPOPIANO: I can't say -- it could be verifiable if there's additional data that could be looked at for correlations between substance use, other substance use, and completion or need for supplemental dosing. We certainly could inform clinical use of the product if that data as analyzed and proves useful.

DR. KRAMER: Thank you. Dr. Dodd?

DR. DODD: As a follow-up to that, it's very hard for me to address this question without really looking into the missing data more. It really concerns me. And I'd like to see some analysis of predictors of missingness in conjunction with the analysis that you were talking about to really add to a better understanding of what the potential population it might benefit would be.

DR. PICKAR: Boy, that's a tough one. I'm

enjoying hearing the conversation. This is a tough patient population. My goodness. You're addressing probably a quarter of the population out there. That feels reasonable to me.

Since the study was done with these guidelines and you start moving outside that, you sort of taking away a little bit from the study. The study, I thought everybody agrees, showed comparability -- what's the correct term? Noninferiority. I thought it showed that, non-superiority.

Now, I don't know what that does that to the study if you start changing the patient population towards an indication. I don't have an answer to that. These are tough studies to do. I mean, who's doing them? Everybody who deals with this patient population

So having said that, I'm right with you, but I don't want to miss a chance to save some people's lives. I don't know how realistic it is to go around and changing the study population post hoc, and then making assumption from the data. It's a

toughie, and you're dealing with a life-threatening condition.

I both agree, and then I'm wondering whether, all things being, you know, whatever, that we go ahead as Tom suggested of going with the way they laid it out. It's how they did the study. If we change it, I don't know what happens then.

DR. KRAMER: Do you think that the sponsor did define their population adequately and enrolled the population they defined?

DR. PICKAR: It would seem that the sponsor defined it in a way that was pretty clear, and I think that they probably got what they were looking for, and it's probably a good, solid data that represents about 25 percent of the seriously addicted population, which I think that would be the case.

You're so right about the early phase, and it's behavioral; all that's true. Just tell me -- I hate to be so whatever -- except that we're dealing with a specific question in a drug approval.

I don't know what you'd do if you change the game in terms of the patient population with the data, although I'm open to fudge also to things, if you want, but it just seems a little odd to me. That's all.

DR. KRAMER: Dr. Kotz?

DR. KOTZ: My concern is that this isn't a stable population because there are many patients who did use supplemental buprenorphine after they entered the study. In fact, some used it throughout the study, and there was a wide variety: some used a little, some used a lot.

Leaving out the behavioral part, just from a medication perspective, I don't see this as a stable population. If they had been on for 90 days, stable on 8 milligrams of buprenorphine, then what happened? What changed?

Were they using illicitly at the street during that time of the 3 months or -- but I don't understand how they can go from stably using 8 milligrams, and then start using supplemental Suboxone after that.

DR. KRAMER: I think Dr. McNicholas had a follow-up to Dr. Pickar's.

DR. McNICHOLAS: Yes. I just wanted to say I think that they defined their study population. I'm not sure it was the correct population. That's where I'm struggling here because I think that they may have put it to not taking it out far enough in terms of stability of the patient.

DR. PICKAR: Right. That's a little bit of what Dr. Kotz is saying as well, is a question about that study population. Now, you're getting to the heart of the study and was the study valid in the way that you wanted it to be to tell us -- direct us properly.

So now, you're talking about the study; that's what we're talking about; your question whether the study group was appropriate and a fair group to study for this purpose.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: I would kind of have similar concerns that the study population as defined, less than 8 milligrams, they were probably getting once-

a-month urines or whatever. But easily, you could have used heroin and gone undetected before, and you could have used it later and gone undetected as well.

I think if we were to say that they defined the study population, it has to be narrowed down because these were mostly prescription opioid users, primarily people who have been diagnosed for only five years, not really severe addicts, because my fear would be we know that this drug at 8 milligrams doesn't occupy a lot of receptors as 16. It's probably medium occupancy, so there's a lot of range to continue to use drugs.

I would suggest that most likely, it should be narrowly defined of who should go on this therapeutic because if you put a lot of serious heroin addicts on this, they're probably not going to get enough, and then they're going to continue to use and require more and more sublingual dosing.

DR. KRAMER: How are you proposing to narrowly define it?

DR. NARENDRAN: Mostly strictly try to fit

in the box that they propose or what they recruited, which is people who have been extremely, 6 months. But I would have liked to have seen some hair analysis or something that can confirm that they didn't really use before. I do have suspicion of why did they use so much sublingual later than if they were stable. So I think there are some issues.

DR. KRAMER: Okay. Dr. Gordon?

DR. GORDON: I'll just keep it brief. I think whatever we decide, I think the FDA needs to be very clear on this indication about what they believe stability is. I say that because there's a lot of definitions out there, even among this room.

If it's left up to the practitioner about what is a stable patient or not, we're going to have a lot of supplemental buprenorphine probably on top of the Probuphine in practice, and that may defeat the purpose of having that medication in the first place.

The one indication, I think, that's really important and it's this idea of being below

8 milligrams or 8 milligrams for a long period of time. Actually, I think 3 months is a little bit short. I would probably go out to 6 months or even a year, but we need data on that. In clinical practice, that population who's been stable on the 8 milligrams for a long period of time is the indication that I would use for this medication.

DR. KRAMER: Dr. Bickel?

DR. BICKEL: I'd like to just suggest that we look at this in terms of the reality of treating opioid-dependent individuals. How many people on buprenorphine, when they get on buprenorphine, continue to ask for additional medication? How many abuse other substances? I think a large proportion.

As I look at the number of supplemental patients who use 2 or more times, this is CE-56 on page 28, I count 10 -- or I count 8, I'm sorry -- 8 who used it more than two times. That's out of 84 participants. That's 10 percent.

Tell me what medication we've got that's really working well, that exceeds a 10-percent

challenge of some of the patients not doing well? I say we have to think, balance this against our epidemic and the challenges that we're really facing in the real world and think about where we're going to do the most benefit. I would ask us to calibrate our comments in terms of the real world of opioid dependence.

DR. KRAMER: Dr. Troendle?

DR. TROENDLE: I was just basically agreeing with Dr. Pickar in that we only have one study, so I'm not really sure I understand the FDA's question to us because it's just completely speculation as to what other groups would do.

The second point is a lot of the supplemental use, I suspect, would be largely the fact that you've entered these people in a clinical trial and made it really easy for them to get supplemental drug; one-fifth of them. Less than one-fifth got supplemental drug. I suspect that's pretty much --

In terms of whether they're very stable or not, I don't know exactly, but they seem like

that's pretty stable. It could be pretty stable, but it could be the effect of just being enrolled in a clinical trial where they made it very easy to get the drug.

DR. KRAMER: I have Jennifer timing us here, so I think we've gotten a good sense on this question. Let's go on to the other questions. A couple of people had -- I'm giving people who have at least not addressed the question a chance to speak. I'm not giving people two times unless it's a follow-up clarification and try to see if we can get through this.

The second question, in general, occasional dose adjustments for patients on sublingual buprenorphine can be expected over time. The sponsor chose not to include rescue medication as an element of the responder definition because there was an expectation that patients would require little to no rescue medication. However, that was not the case, as a rescue medications was used by a number of patients, some throughout the 6-month treatment period.

Discuss whether the use of rescue should be considered in defining a responder for a long-acting formulation of buprenorphine such as Probuphine, where the dose cannot be adjusted over time. If rescue should be part of the responder definition, should the use of rescue buprenorphine be differentiated based on the pattern or the frequency of rescue use over a 6-month period.

Consider the following patterns of use, the first being used primarily after initiating buprenorphine; the second, use throughout the 6-month period; and third, use only at the end of the 6-month treatment period.

Dr. Conley?

DR. CONLEY: Thanks. Rob Conley. A couple of things. One is first, for the overall definition of a responder versus a non-responder and then conflating it with the rescue medication was a problem for me because, as was mentioned here before, there are a lot of things that lead to non-response and opioid addiction. Certainly, rescue medication is a concern; there's no doubt

about that. But that's not the same as failing and non-response.

I realize there's only so many things you can do in a study when you're looking at it statistically and you're trying to see whether or not you have equivalence. So I get why you're doing it, but I think you may be taking it too far to actually say, more or less, any rescue medication is a failure.

Specifically now, speaking more as a clinician than sort of a fair balance on the industry side, I've both treated opioid addiction as soon as use Depo medications, of course, not for this, which is not indicated, but in psychosis. And there, the use of rescue medication is real. And I think using rescue medication after first initiation would be relatively common for lots of conditions.

I would begin to be concerned if I continue to have to use it all the time. I realize that really wasn't part of the study, so it's hard to address it from the context of the overall study.

You said, Dave, the study is as it is. It's hard to change it all around. But right now, just in counting up the number of cases, they didn't seem large to me. It would seem to me that, again, thinking about what you might do in postmarketing surveillance is to understand whether or not people come off, or maybe it is labeling. I think this is a labeling issue of how much rescue should be allowed before the clinician considers it. But to me, it felt as if it might be a question that could be answered in that way.

DR. KRAMER: Dr. Grieger?

DR. GRIEGER: I deal with the chronically mentally ill population on a day-to-day basis, and I have a lot of patients on decanoate injections because they're noncompliant when they're discharged from the hospital. Some of those patients, I also discharge on oral.

Now, the state guidelines are you shouldn't have somebody on oral and decanoate at the same time. The rationale is that even if they go off the oral, their time to decompensation will be much

slower if they are on the decanoate as well, and that's the rationale for doing it when I dictate the discharge narrative.

I don't even like the term "rescue medication." I call it "augmentation medication" because that's what it is. You've got some on board that's long lasting, and it's not quite enough at various points and treatment, and you augment treatment either with the same agent or another agent.

DR. KRAMER: Dr. Troendle?

DR. TROENDLE: My answer is no. I don't like incorporating the supplemental medication into the outcome, but I do think it's a good argument for why you should consider smaller NI margins. I felt we were going to be asked about that, but I see it's not one of our discussion questions about the size of the NI margin.

But I think it does raise of -- if there's a real lot of use of the medication, it would make one want to see a smaller NI margin because it does tend to bring the groups together and make it

easier to show NI.

DR. KRAMER: Any suggestion on the NI margins?

DR. TROENDLE: It's very arbitrary. I think 20 percent is extremely large, though. You wouldn't consider a proportion of 0.8 equal to a proportion of 0.6. It's a huge difference. It's an absolute difference of 20 percent, right? It's not a relative difference, I believe. I think it's very big, but I think, regardless, most of the analyses show it's quite a bit. It's not very close to 20 percent. It's actually quite a bit better than that, it looks like.

DR. KRAMER: Okay. Dr. McNicholas?

DR. McNICHOLAS: This is not what I would do in clinical practice, but looking at the study itself, I do think that the use of rescue or augmentation -- I like your term better -- should be considered in case B, throughout the study.

I think if it takes 2 to 3 weeks for the blood levels to come up and patients need something initially, you don't count that as a non-response.

But somebody who needs it for the entire 6 months they're on, that's a problem for me. So I think that is a non-responder.

DR. KRAMER: Okay. Thank you. Dr. Kotz?

DR. KOTZ: This is just a little bit of a different aspect on it, and I like the way that you called it augmentation. But the difference for me between other injectable antipsychotic drugs or meds is they're not controlled substances, and they're not having problems with diversion.

So for me that makes it very different, and it's like comparing it to insulin and blood pressure medication; again, they're not diverted. And one of the reasons this study is being done because it will hopefully decrease diversion because it's implanted.

So if somebody, as Lori said, is using -- again, I don't know what the average was, I'd have to go back and look at a graph -- so many additional Suboxone pills or film during the entire 6-month period, my question is, in the clinical real world, okay, if we give somebody extra

buprenorphine or film, we ask them to bring in the wrappers so that we can see whether or not they used them or whether or not they diverted them, or gave them away, or lent them to their buddy.

I don't know -- again, with pills a lot of clinicians in the real world do pill counts. They want to know if they prescribed extra buprenorphine in order to adjust the dose that their patient actually took it and not somebody else.

So I think in the study there was something like over a thousand extra supplemental doses given. I don't know how many milligrams that turns out to. And even though it was a relative fraction of the total number of buprenorphine that was given without the implant, for me, if one of the purposes of the study is to figure out how to decrease diversion, then that would be a consideration of mine.

DR. KRAMER: Dr. Campopiano?

DR. CAMPOPIANO: You're getting really good at pronouncing my name. I'm generally in favor of how a non-responder was defined by the FDA

analysis. I'm concerned about including any use of supplemental buprenorphine as a non-responder because I think it's reasonable to expect in that first month, when blood levels are stabilizing, that people may need that.

I don't want to create an expectation for Dr. Joe out there in the world somewhere that any supplemental use is a bad thing. But I also want to be cautious because the study is not designed to demonstrate whether this reduces diversion, yet that claim is being made by a variety of stakeholders.

So we have to be sensitive to that. And nobody's trying to say that we're hoping that this increases access and reduces, or does not augment diversion, but we don't have any evidence to base that on. So I just would like to see a cautious path between saying any supplemental use equals non-responder -- allowing some clinical judgment and encouraging the clinician to have a cautious and supportive attitude in transitioning that person from stable sublingual or transmucosal use

to stable implant use.

We don't want to cause relapse. We don't want to cause people to think that I can't give this person any buprenorphine or they're a non-responder.

DR. KRAMER: So you're touching on two things there. And on the second, a communication of what the data we have really show, were this to be approved on the market, is going to be something I hope we'll discuss throughout the remaining discussion questions.

On the first part where you were commenting on not wishing to have any use be a non-responder, I personally read the analysis the FDA did as sort of a what-if scenario, where they were trying to say the worst case would be to consider it, and would it still be non-inferior.

So I personally didn't take it literally, so maybe the FDA could correct us if I've taken it wrong and you were being -- but that's just one way to look at it. Any comment?

DR. WINCHELL: Some of the analyses we did,

yes, were exactly as you say, a what-if analysis to consider the worst case scenario. The final analysis that Dr. Skeete explained, in which we saw that patients who needed supplemental dosing more than twice if they were in the Probuphine arm, were not being adequately treated with Probuphine. That was the analysis that we thought was the most persuasive, or the most appropriate, captured the story the best.

DR. KRAMER: So the question you posed to us of whether it's dose, 2 times using it, versus pattern, it looks like you chose dose, but I heard around the table many people saying pattern makes more sense early on after initiation.

DR. WINCHELL: Right, it was two occasions.

DR. KRAMER: Yes, but we did not specify --

DR. WINCHELL: -- but we did not differentiate whether they were in the beginning or the end. They could have been in the middle, and that's another analysis we could do.

DR. KRAMER: So I just want to --

DR. WINCHELL: We'd be happy to that one.

DR. KRAMER: -- reflecting the committee's comments, the people who have commented, I think I've heard more people say they were concerned about throughout the treatment period, and they might expect some use shortly after initiation.

DR. WINCHELL: Right. Great. We've got that. We'll do that one next.

DR. KRAMER: All right. Anyone else?

(No response.)

DR. KRAMER: Okay. Next question.

I'm being told that the speakers should remember to speak directly into the mic so we can record it correctly.

Number 3, customarily in opioid addiction treatment trials, there are many missing urine samples due to relapse and dropout from treatment. Because relapse is the most common reason for dropout, missing urine samples are assumed to be positive.

However, in this study, the patients were stably abstinent from illicit drugs, and they were asked to provide only 10 samples over 6 months.

Therefore, it was expected that there would be few missing samples, and that these could be missing for reasons other than relapse. Therefore, the strategy for imputation of missing data did not assume that all missing samples were positive. However, some situations arose in which it might be appropriate to assume that missed samples are indicators of illicit use.

Discuss how missing or incomplete urine toxicology results should be considered when defining a responder. Consider the following: patients who were completely lost to follow-up immediately after receiving the Probuphine implant; samples that were not collected due to 1) a missed scheduled visit, 2) a missed random sample visit, and 3) refused by the patient. And C) samples that were collected on schedule but were not analyzed in a timely fashion, out of the stability window for the test. Dr. Troendle?

DR. TROENDLE: So this is one that's hard to differentiate between the actual outcome or question 4. They're related. One thing is that

you can start out by making an arbitrary assumption about responders being 2 times 2 months or more having some kind of evidence of opioid use.

I think another way to do it would be to take your actual outcome that you really have, which is opioid use at each individual time point, and that makes things probably easier to work with, which avoids kind of an arbitrary definition to begin with.

You still have missing data, of course, issues with that outcome, but I think it would be easier with that outcome also. It simplifies the modeling, which apparently was not done, to find out what predicts missingness and use imputation models to do this.

It could either be you would have a repeated measures regression, could either implicitly do this, or you could have also still use imputation models separately to impute for missing values. It wouldn't address these issues here on this question of part B, the different types of missing.

I think the FDA actually did a pretty good

job. That being said, I'm wondering why more was not done about developing missing data models for this data. But given the way the analysis was defined, the FDA did a pretty thorough job of investigating, I think, the different worst case scenarios pretty much, so it's pretty well --

The imputation models wouldn't address the different types of missingness. They wouldn't be able to take that into account anyway. So that is one -- and the way the FDA did it was basically to enforce different rules based on the type of missingness, I think.

So there is something to doing it both ways I suppose, even the way the FDA did, but I would also like to see imputation models because they're a lot more informative in general and would reduce the impact on missingness.

DR. KRAMER: Thank you. Dr. Kotz? No? Dr. Bickel?

DR. BICKEL: So there's another way in addiction science that people have analyzed urine samples, which is documented abstinence. And

that's the number of urine samples that don't contain the substance that you have in your hand, and that way you're not making any inferences about what the missing data are. I think that's been used in other trials and is certainly an appropriate one to consider here.

DR. KRAMER: Dr. Dodd?

DR. HERTZ: I'm sorry. This is Sharon Hertz, over here, FDA. I'm not sure I completely caught your point, Dr. Bickel.

DR. BICKEL: So among the urine samples that were actually collected, what is the documented abstinence among those samples?

DR. DODD: So I want to comment on point A because I feel it's very problematic to throw out those 3 patients who were immediately lost after they were randomized to get the Probuphine. We just wouldn't do that.

We'd call it a modified intent-to-treat analysis, but I mean there was a reason we used intent-to-treat analysis as the primary analysis. And I feel quite strongly that we don't know what

happened to those patients, and it could have very well -- it could have been that just getting the Probuphine sent them off, and that's why they were lost to follow-up. So I feel quite strongly that the 87 denominator is the correct denominator in that.

The other thing, in reference to the question about analyzing what you have in hand, the problem is getting it in hand is in itself informative. So when we have missing samples, that's going to be more likely correlated with a positive sample.

I don't know how to really handle that. I agree that some imputation approaches would be useful to see. I did find the other analysis that you did, and I think that one of the problems you have to struggle with now is -- I mean, it's clearly not superior based on my interpretation of the data, but where do you draw that line? I think some people could even make an argument that it's not non-inferior as well.

So there's a big gray zone here, which is

obviously why we're here. But I would like to see more analysis of the missing data and what are predictors of missingness, and if there's any patterns there that would further inform us about how to handle the data and how you will write the label.

DR. KRAMER: Dr. Pickar?

DR. PICKAR: This does overlap to number 4, which we'll get to in a second. But personally I agree with the way you took the conservative approach and the way you re-analyzed the data. I thought it got to the heart that the drug was not inferior, and to call it superior just wouldn't fly. There was just too much missing stuff without considering it as you did.

So I thought you did the right thing on that score. Not that I would ever doubt the FDA, but in this case I thought you did the right thing. And I thought it told the story that we're here to look at, whether this was a non-inferior study, a noninferiority study.

DR. KRAMER: We'll go on to question 4. The

protocol specified responder definition did not take rescue use into account and employed an optimistic imputation strategy for missing urine toxicology results, yielding a responder rate of 96 percent versus 88 percent for Probuphine and sublingual buprenorphine, respectively.

As you have seen, there are many different possible responder rates once these factors are taken into account. Discuss which of the various approaches to expressing a responder rate you think is most appropriate.

So we've heard from Dr. Dodd. No? Yes, Dr. Dodd, that she does not think that we should throw out the 3 patients who got the drug and disappeared. So going from there, other people want to comment?

DR. PICKAR: When the FDA did the analysis, you didn't throw out those folks.

DR. KRAMER: No.

DR. PICKAR: You considered them non-responders. Is that correct? Yes.

DR. KRAMER: Dr. Troendle?

DR. TROENDLE: Well, it's similar to what I said about 3 is very similar. This is related. So I think really having a definition of response that's at each different month -- which is really what you have anyway. It's not coming up with anything new. But using that in an actual model would be preferable with using imputation.

All of those missingness, like Lori says, certainly those would be in this analysis as well. They would be all missing, but you would be imputing for those values if you had an imputation, if they developed an imputation model.

The other thing I didn't mention before, which this would simplify or could get more information, is in the cases where they had some labs available and some not. So I think that was one of the issues the FDA looked at different ways of dealing with that. But an imputation model actually could take that into account in the cases where you did have some labs available, but you weren't able to determine toxicity on the basis of what was available.

So that could still inform you in these models to determine a better probability for whether you were positive at that month.

DR. DODD: Does the FDA statistical group want to comment for the committee to what Dr. Troendle's proposing, or just take that into consideration?

MR. PETULLO: We'll take your advice and your comment, and we'll explore the data further in our review.

DR. HERTZ: Hi, this is Sharon Hertz. I'm seeing a paucity of vertical cards, and I would like to just -- any additional comments that haven't been captured by individual comments for the earlier questions in terms of answering this specific one, which is really just our attempt at putting it all together in terms of if you have any additional thoughts on how to define a responder.

It's useful now, but because this was a novel design, and because we may see more -- the sponsor mentioned they have a product under development as well that's a Depo, so this may come

up more and more. So if you have any other comments on how you would recommend defining prospectively the responder, we would like to hear that.

DR. KRAMER: So I'll actually take a stab at this. I'm not a statistician. I'm not going to attempt to say what the analysis should be. What I've been struggling with here as I've read all the materials and listened to the open public hearing is that we have this terrible problem in our society of addiction, and all of us want a solution.

Yet, I think that we do need to have clarity and rigor in the studies that we do. And I was very disturbed about calling something intent to treat that was not intent to treat, and representing -- I felt that in submitting an application to the FDA, which clearly is the organization that's going to be most skeptical about the analysis, the sponsor was overly optimistic about the results in terms of claiming the most rosy picture in terms of response rate and

superiority.

So I just want to say that I think that, mostly -- because as you look forward, we have to distinguish between the promise of a subcutaneous therapy that could reduce diversion and reduce pediatric overdose versus what we actually have here in terms of data. And we have something that -- there's a fair amount of additional use, and some of the whole purpose of this isn't really clear in the long term.

You know, what are we trying to do? Are we talking about two years if other sites -- if implantation at the original site can't be repeated? Are we talking about a shorter term thing that after being on Probuphine for a couple of years you're going to have to go back on sublingual? I don't think a strategy was put forward, and it wasn't clear to me when I started reading this what the overall strategy was.

So I would just encourage some rigor so that we have a precedent upon which we're comfortable with the decisions we make, and that we have

something to follow on when other companies and other products come along for consideration. I know that's kind of general, but specifically this whole issue about throwing out the 3 patients I felt very strongly about.

DR. WINCHELL: Well, to follow on that, these aren't really necessarily statistical questions. Some of these are questions we really love the input of the addiction medicine clinicians here to tell us what assumptions you think would be clinically appropriate to make about a patient, for example, who receives an implant of a study drug and is never heard from again, this being a patient who's already been in treatment for at least 6 months, well known to somebody who referred him and disappears, or whether someone being incarcerated.

In our analysis, we thought, well, these aren't good outcomes, and we described those patients as non-responders. We'd like to know from your clinical judgment if you think that was the right way to go. And similarly, we thought if a

patient wasn't able to come to the clinic to give a requested random sample that that kind of boded ill, or even a scheduled visit. We discussed that internally, whether scheduled visits and random visits would be different.

On the other hand, if they were able and willing to give a sample, that could not be completely analyzed due to sample handling issues at the site or something happened in the lab, would it be fair to say that that could be construed as a negative sample.

So these are the assumptions that we made in our doing our analyses that were based on our hunches and -- sorry, we have seven addiction medicine specialists here. We would really love to hear if we went the right direction with those assumptions.

DR. KRAMER: Dr. Grieger?

DR. GRIEGER: I completely agree with the intent-to-treat approach, that if you started somebody in a protocol, they get counted in the protocol. I have no problem with that.

I'd go back to the use of rescue medication, supplemental doses, whatever. I mean it's a noninferiority study, right, so you're putting half the people in essentially standard care, and you're putting the other half in another type of care. Why would you say it's okay to give additional oral to the people that are in the oral category but not in the people that are in the other category, if what you're looking at is how the two do together?

It doesn't seem logical to me that you would allow it one arm but not in the other. I've never seen that. I understand the theory that you shouldn't need anything because you've got a long-acting Depo, but in the noninferiority thing, both sides are getting additional doses, so why treat them differently statistically.

DR. KRAMER: Dr. Ionescu?

DR. IONESCU: I think as far as to answer your question from the FDA about from a clinical perspective how do we like to think about this, I definitely think, yes, of course we have to include those 3 patients without a doubt in a new

medication that's not -- sorry, a new indication for a medication, certainly a new dosing route.

Just one thing I've been kind of thinking about as we're talking about these patients, especially the three that were just lost to follow-up, I spend about 90 percent of my time seeing patients in clinical research, and one thing that we've done for studies that has helped is we have these external raters that talk to the study patients before we enroll them into the study. And they do SCID questions, double check to make sure they meet criteria for depression.

Maybe moving forward -- and I know of course we can't go back in time to do this. But maybe moving forward, having patients also interviewed by an external rater that they never meet, we can maybe rule out some patients that might be lost to follow-up. I think certainly in this type of study we have to assume the most rigorous case, and we have to say that the medication didn't work or that they were non-responders or something like that.

But I know as a clinical researcher that's

not always the case. Sometimes people are lost to follow-up not because of that reason. And by using these external raters, we can eliminate some of that so the quality of the study is better. I know these things are relatively new, but I don't want to see medication that could potentially work not be approved because of maybe patient selection.

DR. KRAMER: Dr. Conley?

DR. CONLEY: Yes, thanks again. Rob Conley. To address what you were saying before, Dr. Hertz, about other studies that you're talking about as opposed to this one, for this one, I certainly also think that the ITT design makes sense, and that's what you should do. But again, going back to other Depo medications, we certainly have defined in the field non-responder criteria in advance.

To me, I think you're right. There are some things here that you worry about, like the missed urine samples. In many situations, in many living situations, that would get someone kicked out of their housing or some other problem. It could actually lead to real sequela besides the obvious

sequela of abusing.

I think that makes some sense, but I do think you have to be very careful with that because there are some times when labs lose samples or do tests wrong. So that's one where I do think that -- what I was surprised here, and again I came into this kind of late reading it, is that there wasn't a lot of pre-specification about stuff like that.

I understand there was an assumption that this wasn't going to happen very much. I get that. But it seems to me like if there's a learning for the next time, it really is kind of like in advance, what do we really think response is going to be. Because one last thing I'll say is I feel like something in this study that surprised me, and I don't know if it surprised you all or not, was that the completion rate was really, really high, but for both groups.

So there was something about the care situation that was leading to a high completion rate. That's a good thing, but at the same time

then it raises all the other questions of how else do we define stuff. Because the only thing you could have easily -- what I would have expected in a study like this is you were hearing there's so much churn in buprenorphine use in the regular clinic is that the people on oral buprenorphine weren't going to make it to the end of this, and they did.

So that was the other kind of unusual, I don't know if you want to call it a good thing, but something interesting about this study like the high completion rate. And I'd like to give an agent credit for that if it deserves the credit because to a degree whatever the care situation was here in this study, it must have been pretty good to get that high completion rate. And then to be able to kind of figure out what it means underneath that, I think the urines are important.

DR. KRAMER: Dr. Campopiano?

DR. CAMPOPIANO: I had my name sign sitting up, and then I thought, oh I'm going to be repeating myself, so I put it back down. So I'll

keep my mouth shut for a while longer.

DR. KRAMER: Okay.

DR. CAMPOPIANO: Thank you.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: No.

DR. KRAMER: Same thing. Dr. Carroll? Dr. Carroll on the phone.

DR. CARROLL: Can you hear me now?

DR. KRAMER: Yes.

DR. CARROLL: Oh, good. Yes. I do think the criteria for a responder was far too loose and had some concerns about it being accepted here because it's [inaudible].

DR. KRAMER: Dr. Carroll, we're not hearing you.

DR. CARROLL: It seems like [inaudible].

DR. KRAMER: We're not hearing you.

DR. CARROLL: Okay. Yes, I'll just try to do it by email.

DR. KRAMER: Okay, and then we'll read it. Thank you.

Dr. McNicholas, while we're waiting. Okay.

DR. McNICHOLAS: First of all, I'm not going to beat a dead horse intent to treat is intent to treat. You don't get to say we're not going to count it because we don't like it.

I think though when you're defining responder, you do have to look at a number of things. I would not necessarily think that initial supplementation with buprenorphine is a problem.

I kind of disagree a little bit, Dr. Grieger, on the difference between the two arms because if I have a patient that I'm treating and they come in and they say XYZ isn't going well, I'm feeling in this way, I'm going to change their dose, which effectively is what happened with some of these patients in the sublingual arm, is effectively they changed their dose, they increased their dose. I do it all the time. My patients go up and down depending on what's going on. That's called treatment.

But if you're doing a study, you have limits over which you can't go. And it's not fair sometimes to the patients, and sometimes I tell

patients to withdraw from the study because I need to treat them appropriately. And maybe that should have happened with some of these patients, that you don't just keep supplementing and say that they're a responder when in fact they should have been withdrawn as a non-responder and treated appropriately. And there's where I think some of the question about what is a responder versus a non-responder does need to be looked at.

In terms of the urines, frankly, I can't see why a scheduled urine would be missed. Any addicted person worth his or her salt can figure out to not use for 3 days. A random test being missed would be a flag for me. A refusal to give would be a major flag for me. If my people didn't send it out during the appropriate timeframe, that's not on patients, so I don't think that should be charged against the patient at all. But I don't think that a random sample or a refusal should be tolerated. That doesn't even require imputation on my part. That's an assumed positive.

But I do think that the whole question of

responder versus non-responder maybe needs to be looked at and the data reanalyzed, see if we can get a better picture of what's actually going on here.

DR. KRAMER: Dr. Gordon?

DR. GORDON: So putting on my health service research hat, I think I was pretty impressed how the FDA went through and looked at the different response non-responders, and I just want to give kudos. I think they did a good job.

I'm very concerned about the stability of these patients who were supposedly very stable, and all of sudden the doses are going everywhere or supplemental things are going, and 3 people dropped out pretty quickly after randomization, which doesn't indicate stability.

So as a clinician, I'm a little bit worried about that, but I just want to give kudos to the FDA. I think they did a good job. For a noninferiority trial, model that we use, and using a conservative estimate the FDA did, still showed noninferiority, which is the intent.

Now, we could talk about the limits, and I totally agree with the comment earlier that a 20 percent noninferiority study is kind of odd. So if you want to be really critical, I would potentially consider reducing that 20 percent down to 10 percent or 5 percent. Thanks.

DR. KRAMER: Dr. Brady?

DR. BRADY: Yes. I just want to echo that I thought the analysis done by the FDA was really thorough. And generally, when we look at data like this, as Dr. McNicholas said, we take a very conservative approach. And a missed scheduled visit, missed random sample, or a refuse by patient, it would all be considered positive. And as was just pointed out, even doing the analysis in that most conservative way, that there was still noninferiority, so I think that says a lot.

My main question in terms of responder definition for here really does have to do with the supplemental dosage. If one of the large -- one of the bigger rationales is that this is going to prevent having medications around for diversion,

and it's clear that for -- it wasn't a whole lot of them, but it was for that 8 or 10, this dose -- well maybe not even 8 or 10, but the few that required dosing almost every day, this dose was not sufficient, so they were non-responders.

So I think that I would hope that in a future study, and maybe even in looking back at this data, I think some threshold around supplemental dosing should be considered in the definition of a responder, that there would be some threshold beyond which you can't go and still be called a responder. I think one or two doses should be fine.

DR. KRAMER: Dr. Preston?

DR. PRESTON: Yes. I wanted to think about this as a double-blind study, and presumably it was truly blind. I think we are making an assumption about stable patients and that they did not miss urine collections prior to being in the study. I don't know how good that assumption is, or even that they truly did not get any extra buprenorphine prior to joining the study. And as a person who's

done these kinds of study for more than 20 years, it doesn't surprise me that a few participants drop our immediately after enrollment.

It doesn't surprise me that people don't come in when they're supposed to. And I assume when my dentist calls me the day before, that everybody misses these kinds of visits, not just our patients. So I was really convinced by the thorough and various ways that the FDA reanalyzed things and tried different responder evaluations. So I found that very convincing.

DR. KRAMER: Thank you. Dr. Dodd?

DR. DODD: Yeah, I just want to come back to this comment about the noninferiority margin and the fact that we seem to be satisfied that all the analysis point to noninferiority. Because in my view, a lot of the noninferiority, the sensitivity analyses, actually make the two groups look more similar than more different.

So we're making assumptions that -- I mean if everybody had missing data and we imputed all the values as failures or as responders, they'd be

identical, and we'd hit the noninferiority boundary. So we have to keep that in mind.

This is a very different beast. Noninferiority trials are not superiority trials. So I always get confused. We have to ask ourselves, what is the null hypothesis here? The null hypothesis here is that this is an inferior drug, right, and that means we're in a different realm. It's very different to think about these trials.

So I think as we go through this, and this will be precedent setting. I get the feeling that this idea of using a noninferiority design is new to this specific field.

And a 20 percent margin, I tell you everybody's going to report that, oh they did it with a 20 percent margin, and that will become the standard.

So I just encourage you -- and I struggle with this. My main area is tuberculosis, and I struggle with this because people want to do these wide margins, and it drives me crazy. So I would

love to hear your opinions about what's a reasonable margin here because as this field moves forward, you're going to hear this question again and again.

DR. KRAMER: Dr. Bickel?

DR. BICKEL: So I just wanted to echo Dr. Brady's comment and say that the frequency by which there is supplemental buprenorphine should be considered as part of the failure. But a couple times, regardless of where it's located, early, middle or late, is probably not that big a deal because these people's lives sometimes can be very chaotic. And sometimes a brief modification of dose is a necessary way to deal with their stresses and challenges.

DR. KRAMER: Dr. Grieger, you had a second?

DR. GRIEGER: Just a quick clarification. I wouldn't consider the people that needed supplemental buprenorphine who are on the implant as responders. But I also wouldn't consider the people who need supplemental buprenorphine on the oral or buccal formulation to be responders either.

I think they should just be treated the same. I don't know if I was clear about that before.

DR. KRAMER: So I just seems -- I'm probably one of the few who's a non-addiction specialist, but back to Dr. Dodd's comment, we're facing both a very difficult patient population to study, and we're facing the whole issue of noninferiority studies where the sloppier you are, the better chance you have of being successful. And frankly, I need some advice from people who can put those two together.

We have two more people with their hands up. Dr. Narendran?

DR. NARENDRAN: I do want to -- because you asked about future studies, I think something to keep in mind is, like the noninferiority margin Dr. Dodd mentioned, you also want to make sure that it's not like an inferior dose is being shown in a noninferiority margin, which is something like when you give this much sublingual buprenorphine to augment both arms, it really raises the question of did they just pick an inferior dose to show a

noninferiority margin, which was pretty large, and that's why it happened. So I think that's something to be more, because it's a precedent setting study, to think about for you guys going forward.

DR. KRAMER: We're going to move on. Question number 5, patients managed with buprenorphine may require dose adjustment over time. However, in clinical practice, unlike patients on sublingual buprenorphine, Probuphine treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments.

Discuss how the need for occasional supplemental doses will translate into clinical practice for patients treated with Probuphine. If patients need to have sublingual buprenorphine on hand in addition to Probuphine, discuss how these prescriptions will impact the product's ability to mitigate misuse, abuse, and accidental pediatric exposure.

Some patients on Probuphine required supplemental sublingual buprenorphine only briefly

after insertion, while others required it only at the end of the dosing period when plasma levels could have been falling. In contrast, some patients required ongoing supplemental dosing throughout the 6-month treatment period.

Discuss whether the pattern of supplemental sublingual buprenorphine should be taken into consideration when deciding if Probuphine is effective and should be continued for a given patient in clinical practice, and the "in clinical practice" is emphasized.

Discuss whether there is a pattern of sublingual buprenorphine use that would result in the discontinuation of Probuphine.

So we've obviously already discussed aspects of this, and does the FDA feel we've fully discussed, or do you want to hear some comments from the clinicians about when they would consider discontinuation, for instance.

DR. HERTZ: Right. I think really at this point -- I mean, we've heard a lot I think already about this -- if people would care to discuss or

recommend instructions for clinicians about what they think would be appropriate use of rescue or patient discontinuation, just kind of focus on that.

DR. KRAMER: In the setting of patients who wouldn't be anticipated to be seen that frequently.

DR. HERTZ: Yes.

DR. KRAMER: Okay. Dr. Bickel, do you really have your card up to speak or is that from before? Dr. McNicholas?

DR. McNICHOLAS: I'll get the ball rolling.

DR. KRAMER: Okay.

DR. McNICHOLAS: If I have to supplement throughout the course of an implant, I'm not going to implant again. The patient is clearly not being maintained on the dose in the implant or the blood levels that he or she can attain from that implant. So I'm going to put the patient on an appropriate dose and go from there.

Unless they want it out, I would probably simply put them back on a regularly scheduled clinic visit, and they would get 2 weeks, or a

month, or whatever was appropriate for their level of stability in terms of ongoing care while the implant is in. But would I put another implant in? In all probability, not. I don't see any reason to put in one and then supplement with 4 or 8 more milligrams a day.

If you do need a lot, I think that it really begs the question of are we doing anything to decrease potential diversion. And some of my patients -- and I think anybody around this table who treats these patients knows that one of the things we deal with on a day-to-day basis is my partner needed some. I sold half of it. If I got a 24 milligram a day dose, they know they can get by on 12.

So do I want to put out any more than I have to? No, I don't. So that's one of the reasons I don't think they can be called responders in this thing.

But the other thing is, if they need medication, they need to be seen. I for one am not going to give patients a bottle full of

buprenorphine and say take it when you need it. That to me is not good clinical care, and it's not something you do even with a stable patient who has an addiction issue because that's how they treat ups and downs in their lives.

If their lives are going up and down , then they need more counseling. They need to be seen more frequently. So they would not have a supply to stick in the closet. And if you think you need it, go ahead and take it. No, they would need to be seen and get an appropriate prescription for the period of time that was needed.

DR. KRAMER: Dr. Gordon?

DR. GORDON: Speaking as a clinician, I think I'm kind of reflecting what I do with my chronic, stable patients on buprenorphine. Currently, I'm seeing them on a monthly basis. Maybe my staff are seeing them on a monthly basis, and I see them every other month. But the most part, I want to make sure that they're attentive to all their addiction related needs, whether that be pharmacotherapy, but also non-pharmacological

approaches to treatment.

I'm kind of reflecting and trying to think out, how, if I had buprenorphine in my clinical practice, would I change that at all. But I still want to see them on a monthly basis, and I think I would.

So I think that dosage adjustments can occur, even with this medication or without it in current practice. And I also think that addiction is not something like we give a medication for 4 months or 6 months and say goodbye. It's just not that type of modality of a disease.

So I think one of the things that we may want to consider if this is approved and an indication goes out, that there are special attention to regular visits or regular attention to addiction related needs, I think something that might be in the instructions for providers to make sure that those regular needs are taken care of. Thanks.

DR. KRAMER: Dr. Campopiano?

DR. CAMPOPIANO: I haven't heard anything

today that makes me think that this statement in question 5, Probuphine treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments to be a true statement. I would want to see this person regularly, and I would not want to create the expectation you can just implant this and say bye-bye.

One of the things that happens presently is the tendency of prescribers to medicate cravings, which are complex psychosocial phenomena that can't be treated necessarily or completely eliminated with medication. So to send somebody home with a bottle and say titrate yourself to comfort is bad clinical practice, and not something that this product -- there's any reason to think we can do with this product as opposed to a sublingual product.

So there's a risk that if we create this expectation that, oh, once in a while you're going to need a little bit more, and you might need it more often and during the beginning, or you might

need it more often, or maybe during the middle and at the end, it just kind of absolves the prescriber of responsibility for figuring out what's going on here with this person and gives them license to say see you in 6 months when you're ready for your next implant.

I'll time travel back to 2003 when buprenorphine was first approved and hit the market, and we had very little of anything, guidance, on how to use it or anything other than the FDA label to go on. And I can kind of strategize with myself, okay, what would I do? I'd expect somebody might need additional medication the first month while they're stabilizing, while their blood levels are coming up, while they're transitioning from their oral product to their new product.

If I'm seeing persistent need for more medication after that period, I'm probably going to trigger a restabilize and titrate. I'm going to restabilize you on a dose that works for you every day on top of your implant, and then we're going to

talk about whether it makes sense to titrate down to just the implant. And if we get there and you're stable, and you're not using other substances, and it's time for a new implant, then we make a decision about whether we continue with the implant or we go back to a sublingual transmucosal that gives us the flexibility of titrating back up if we need to.

I don't see a lot of medical, legally, psychosocially, and any other, ethically, to be gained in creating a population of people that are on both an implant and receiving sublingual transmucosal. That sounds like medically wasteful. It sounds like a recipe for diversion. It sounds like a recipe for disappointing the public expectation that somehow this is going to both increase access and reduce diversion in some magic way.

So I think it's going to be really important to take standard medical thinking and apply it to what you do with this person now that you have to manage them in the context of a 6-month implant and

just kind of compartmentalize it into -- and give specific strategies.

DR. KRAMER: Could you comment on the frequency that you would see a patient like that?

DR. CAMPOPIANO: I wouldn't see somebody less than once a month without extenuating circumstances, or I might share their care with a colleague. But they would be seen by somebody qualified to evaluate them at least once a month.

I had people on buprenorphine for 10 years, and I never saw them for less than once a month without needing to change their dose. I don't see doing any differently with this product.

DR. KRAMER: Dr. Winchell?

DR. WINCHELL: I'd like to ask anyone who's familiar with the population, the rural population, the other populations that were referred to in the open public hearing and in other venues, the population for whom access to -- coming to monthly visits is a logistical hurdle, and this medication was posited as potentially being an option for patients who have a long distance or significant

logistical difficulties.

Do you think this is not the medication for those patients?

DR. CAMPOPIANO: I'll just continue. I think that it's a lot to put on this medication to fix that problem because we need to use other resources, telehealth, a physician extender, so-called providers to help improve access.

To say that you don't need to be evaluated further because of this product, I think is shortchanging that rural person. And based on what was submitted, the expectation is that the standards for behavioral interventions and professional behavioral support, counseling and so on, is unchanged for this population. And the reality is they don't have good access to that in the rural areas either.

So saving them a provider visit is great, but you could do that with telehealth. This isn't going to fix the fact that we don't have treatment programs and counselors and stuff in rural areas. So we have to be realistic about what we expect

this can accomplish.

DR. GRIEGER: I would agree for what you're saying with this, but I know in the system I've worked in for a while and the VA system that was in rural northeast Maryland, we've used telehealth and a number of other things.

I could see an agent like this, a depot agent being useful, you know because you don't need to have a person physically come in to see a physician necessarily. There could be another type of a check that the person would have.

I agree with all my colleagues that I have never felt comfortable in a group like this seeing them less than once a month, and I don't think this is going to change anything. But I would say this could give an option because it goes back to how many pills, or how much am I willing for someone to leave my office with. That's often an issue in very rural subjects when it is an issue for them to get in to get a physical refill and this could help that but not the contact.

In fact, I worry about this and any depot,

is that somehow this opens the way to see the patient less. Now I don't think that should be a reason for not approving this particular substance, but I think it's a tension we just have to be aware of in the medical system that I would hope this wouldn't lead to a loss of support for continuing to see people on a routine basis because I think that's really needed.

DR. KRAMER: Dr. Brady?

DR. BRADY: Yes. I just wanted to reiterate and emphasize something that Laura said, just about if the expectation is that maybe particularly early on in the treatment, people may need some supplemental dosage or when stressful times come up.

I think however though, it should be emphasized. And I'd say just about any medication I give substance using patients, but in particular if it's a medication with abuse potential, I would never say PRN, just take it as you need it.

So I think the emphasis should be this may happen occasionally, may be particularly when

they're titrated with the initial titration, if extra supplemental dosing is needed, the patient needs to be seen frequently during that time.

I think that would have to be emphasized when it comes to the supplemental dosing, that that is an indicator that something is going on that means the patient needs to be seen.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: I do want to say although patients probably -- I do agree they have to be seen every month, but there's also the added benefit of like, quite often, patients call their and their medication was stolen, and they're hustling to get in, and they can't get an appointment, and they go use outside and relapse.

So it could prevent that kind of -- when they feel like all of a sudden they don’t have their medication and they've got to go use, and if this person's in rural West Virginia or something, it's a possibility by the time they can get to Pittsburgh, at least they don't have to freak out over -- so there are definitely some benefits,

although it may not reduce the frequency per se.

DR. KRAMER: Dr. Gordon, did you have another comment?

DR. GORDON: Yeah, just quick. I'll agree with everything Dr. Conley and Dr. Campopiano have indicated to the FDA's question. I actually think the fear that I had with this medication is that there would be less frequent visits with providers. And I don't agree with the FDA that this is a reason to help rural communities. There are so many other things that we could be doing. A medication that's a Depo injection is not the answer.

DR. KRAMER: I don't think the FDA -- I didn't interpret them as saying they thought that, but we heard that comment from the public hearing that people were hoping for something that could.

So we have a comment from Kathleen Carroll, first on question -- well, she has one on question 4. I'll read her question 5 response first, since we're on that.

She agrees strongly that ongoing monitoring

monthly telehealth and urine checks, even with dropping off at a lab, is needed.

"So the FDA has asked that we kind of summarize where we are on each question. So am I correct in saying that it sounded to me like everyone who spoke was in favor of these patients need to be seen; that you can't just put it in and think that that's going to mean goodbye. At least once a month I heard.

"I heard, at least Dr. McNicholas say that she would not reimplant someone who was needing this throughout the treatment period. Is that a general feeling? I don't want to put words in anyone's mouth. Is that a fair summary of what we've heard?"

Okay. If I could just go back and read Dr. Carroll's thoughtful comments on question 4, she commented that intent to treat means all patients randomized. The responder criteria, the current definition is not appropriate. She was particularly concerned with that chosen by the sponsor as it may be some sort of precedent for

future studies.

The overly optimistic case presented by the sponsor is of concern, because of the high demand/expectations as voiced in the public comments. The worst case scenario done by FDA is closer to what actual outcomes look like. I'm not clear why definitions used in other large buprenorphine trials were not used.

I would suggest something like, No rescue doses after one month; no missed random urines; no missed/positive urines in the last 2 months. This is more in line with that of Weiss, et al., in 2011.

Okay. We'll move on to question 6. The sponsor has provided information on a training and certification program to ensure that practitioners can safely insert Probuphine. However, the procedure of removing Probuphine after 6 months of implantation is not readily modeled for the purposes of training because there is development of fibrotic tissue around the implants.

Discuss the steps the sponsor should take

to ensure that removals, including complicated removals, are performed appropriately.

Dr. Grieger?

DR. GRIEGER: This was my biggest concern about this whole proposal, is that I think that practicing on a pork loin just doesn't get it for me. I mean that's not the way I learned to be a doctor. If you're going to do procedures, I think you have to do them on humans with a preceptor watching you do them, unless it's something so close to what you already do.

But you're talking about to get to the outer rods, you're doing one dissection underneath the skin and trying not to cause any problems. I don't even think most anesthesiologists are used to doing that. Probably ICU docs are used to doing that because they're putting in mainlines and stuff like that. But I think that, really, there needs to be something more than practicing on a pig loin. It just doesn't make it.

I'm curious about the -- we had some people from that, what is it, DBRUP's group, in here

earlier. What does the Nexplanon certification program require? I tried to get that from them, but you have to sign up and go to the course. They won't just tell you over the phone what it is they do.

But I mean, I don't know. Other physicians in here, would you feel comfortable doing that? Would you feel comfortable with having it done to you by somebody that doesn't routinely do that?

DR. PICKAR: By you, Tom, any time.

DR. GRIEGER: No. I wouldn't feel comfortable doing it. That's my concern is that it would require some different type of training.

DR. KRAMER: Someone from FDA's going to help us out here.

DR. CHANG: My name is Christina Chang. I'm the clinical team leader in DBRUP, the Division of Bone Reproductive and Urologic Products. So as you know, the Norplant was the first iteration. And in the history of contraceptive implants, there have been many, many iterations until Nexplanon.

So our experience with these implants really

have evolved, and Norplant was marketed quickly, and the launch was very wide. Then within a few years or so, marketing was discontinued; I think it was back in 2002.

Right now, the use of Nexplanon, it's coming back, but it hasn't certainly reached the promise that was held out for Norplant back then. At first, when Norplant was approved, there was no certification program. So we may be regretting that at this moment, but there's nothing we could have done.

There was no REMS program back then, and by the time Nexplanon was approved, we felt like the OB/GYN experience, or the community, is experienced enough that we didn't need a certification program. So that's the sentiment that we have right now because everyone's fairly familiar with the risks of the procedures.

DR. GRIEGER: Well, I'm a little confused, because if you go on to their website, they've got a thing to sign up to get the certification training, and they've got the same REMS thing where

you can put in your zip code and it will tell you within 50 miles, 100 miles, 150 miles, who is certified to do that. And it's a wide variety of people. There are physician's assistants who are certified. There are nurse practitioners who are certified. OB/GYN that are certified, and surgeons that are certified. So I don't think it takes a physician to do it, but they have some type of certification program that they require in order to be able to do the implants.

MS. CHANG: Well, the certification program is implemented voluntarily by the applicant for Nexplanon.

DR. KRAMER: Dr. Ionescu?

DR. IONESCU: I think in the grand scheme of procedures from many of our surgical colleagues, ICU colleagues, this is probably not a big deal. However, I do think that because this is something new, as far as the removals go, I think there has to be a really strict program in place if this were to get passed.

For example, there are some super users that

have done this many, many times who are experts. Maybe if they for the first few years could be kind of on call and maybe they could do like Facetime or something with the physicians that have already certified and kind of on demand -- it might be something that they kind of have to be on call and can answer at any time if someone needs help, or maybe have super users set up in certain urban areas as indicated by zip code, where patients and providers, if they're having issues, they have someone that they can go to.

Because ultimately, at the end of the day, procedures are all about volume, and the more a provider does it, the better they're going to be at it. However, those first few years might be a little bit tricky as people get their volumes. So I think it's doable; it's just having something in place.

MS. SHELDON: I just want to confirm, both of your suggestions are actually part of our plan. They're not part of the required REMS, but we will be making our master trainers available at any time

in order to Facetime, or get any other kind of consultation, and the map will be available for location of clinicians who are kind of super users and centers of excellence.

DR. KRAMER: I'd hate to be the patient sitting there when the doctor picked up the phone and tried to do Facetime to find out what they're doing wrong. Sorry. It's getting late.

Dr. Higgins?

DR. HIGGINS: I just wanted to raise the point that the Norplant experience is completely different when we're talking about a completely different population. I imagine this would be used in people with thinner tissue, lack of musculature structures that would be present in a younger population.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: Yes. I just think for the non-proceduralist, for psychiatrists, general practitioners who don't really do routinely surgical procedures, it's probably good to have like a live person and maybe like observe them for

the first three or five -- like that's what they do if we have do arterial lines in our studies. The anesthesiologist kind of sees how we do it, so they give us -- like after five, they credential us.

So maybe for them, it must be a different. And probably for an anesthesiologist doing it on a pork tenderloin, probably not a big deal. I'm sure it's not necessary.

DR. KRAMER: Dr. Kotz?

DR. KOTZ: I just wanted to clarify. My understanding is that when the person that implants, the proceduralist, that they have to be waivered; is that right? Is that what one of the slides said?

So if that's the answer, then when you just said, Tom, that when you go on the website there is nurse practitioners and other people besides physicians that are being trained. I'm not sure why that is.

DR. KRAMER: Okay. Are you asking a question of the sponsor, Dr. Kotz?

DR. KOTZ: Pardon me?

DR. HERTZ: I think that website that was referred to by Dr. Grieger was for Norplant or for the contraceptive, not for this.

DR. KOTZ: Oh, okay. Thank you.

DR. KRAMER: Well if we have a question, I'll call you. Dr. Campopiano? Okay. All right.

So what's a fair summary of this? There are some people that are uncomfortable with the explantation procedure and the blunt dissection. A suggestion of actual observed implantation with a mentor prior to -- but we don't have any --

DR. GRIEGER: Unless you're in practice and especially where you do something very similar to that. Yes, if you're doing arterial venous grafting, you're going to know how to do this.

DR. KRAMER: And what's the mechanism, though? Are you proposing that this be --

DR. GRIEGER: I don't know what a clear mechanism would be other than what's kind of traditional, is that you would go to a center that routinely does a bunch of these and hang out for a morning and watch five of them get removed. The

problem is when it first starts out and you don't have a lot of centers --

DR. KRAMER: And are people going to do this?

DR. GRIEGER: Who's going to be doing it?

DR. KRAMER: Do they have the time to do this?

DR. GRIEGER: Right. But I think if you then want to do it three years from now, as a psychiatrist, I might be interested in doing it. But I think I'd have to go watch two of them be done, and I'd have to do one under direct supervision and make sure I'm going through the checklist, just like they do with the pork tenderloin, but with real skin.

DR. KRAMER: Real skin, real person.

DR. GRIEGER: And real bleeders, and what do you do if you hit an arteriole that's pulsing out a little bit blood? Do you just put pressure on it and let it ooze and turn into a hematoma? Or do you -- what do you do with it?

DR. KRAMER: Dr. McNicholas?

DR. McNICHOLAS: I agree with what Tom has said, but I think that there's a larger problem here, and I don't know how it can be addressed by the sponsor. And that is, you send a bunch of practicing psychiatrists to even practice on a pork tenderloin, half of them aren't going to be able to do it.

How many psychiatrists in this room have put sutures in, in the past 10 years? I think if you have a bunch of psychiatrists and probably even internists who don't do it and stuff like that, you take them and you start to train them, and they're going to go, "This is too much trouble. I'm not going to do it."

I don't know how that gets addressed, but I think that's a major concern, that you have got to figure out how to make this palatable to the clinical population that needs to be able to use it.

DR. KRAMER: I think we need a clarification from the sponsor. I thought the sponsor said that they originally considered just using surgically

trained individuals, and then changed their mind, or something happened. Could you clarify that?

MS. SHELDON: Right. So to start, psychiatrists are clearly very critical to this field and to the adoption of any product, but you guys are 24 percent of the people who prescribe buprenorphine right now and the vast majority of other clinicians who prescribe buprenorphine have some sort of surgical specialty background that allows them to do so.

We've actually also had a number of psychiatrists who said that this is a second specialty and they feel that they can actually do the procedure.

In our original estimation, we suggested that people with procedural specialty or folks who have done -- they've just kind of gotten into doing some procedures and have done one at least in the last three months, should be the ones that are allowed to take the training in the first place.

The Division of Risk Management pointed out that restricting access by virtue of someone's

specialty or training may not be appropriate. And we, ourselves, did see in the human factor study that this wasn't something that was generalizable. There were some psychiatrists, especially if they were pretty new, they were pretty early in their career and had just been out of training a couple of years, who did fantastically well.

So it seemed more reasonable to let people self-select, and if psychiatrists think that they can learn the procedure, they're welcome to come to training and pass the competency. If they don't pass the competency, then they will not be certified to implant.

If somebody needs to go to another clinic, at least to refer out to another clinician, the other clinician will need to be data waived.

DR. KRAMER: Thank you for the clarification. Dr. Pickar?

DR. PICKAR: Yes. I don't think there's necessarily a danger. They psychiatrists who want to train will be able to do it just fine. The bigger issue for you folks is can you get into

enough people? It's just simply the mechanics of getting this important drug out and getting it into people, and that's a strategy. I don't know if that's for us. But boy, that's going to be a strategy for you folks, and I'm sure you're thinking about it all the way. But that's critical, whether it's the family practice guys or the shrinks.

I don't think you'll get incompetent guys doing that, or gals. I don't think that's what will happen. You just might not find that many frequent psychiatrists doing it.

DR. KRAMER: Dr. Campopiano?

DR. CAMPOPIANO: I think it makes sense to train anybody who's willing to come and be trained and certify those who can pass the training, and then perhaps have something in place like the -- I can't your name sign, but the doctor from Pittsburgh over there -- that if you don't have a certain -- if you can't report a certain number of procedures in the last reasonable period of time, then perhaps you need to do this, your first case,

under supervision.

That may sound burdensome, but I think it may actually promote adoption, because that person who's just a little, like, yes, I really want to do this and I think I can do it, but I'm never going to do that first case, because I'm just not quite comfortable enough -- but if somebody's coming out and is going to stand over my shoulder, and talk me through it, or just be there, maybe then I will adopt that technology.

So it's a fine line between making it burdensome versus promoting adoption. But I think that there's probably -- maybe it needs to be a fairly solid rule that if you don't have X number of procedures of a certain type in your background in the last certain window of time, you will have somebody watch you do your first one, sort of the way they require your records when you want to get procedure privileges in the hospital or something, just to make it very clear.

DR. KRAMER: Okay. All right. Go ahead.

DR. IONESCU: It's kind of like ECT a little

bit. No psychiatrist ever does ECT without being trained. I think this is kind of equivalent to that.

DR. PICKAR: That's a good analogy.

DR. KRAMER: Okay. Number 7. The sponsor has proposed a risk evaluation and mitigation strategy, which consists of restricted distribution and a training/certification program for healthcare professionals who will insert and remove the product.

Discuss whether the REMS is adequate to address the risk of potential complications associated with the insertion and removal and abuse, misuse, and accidental overdose.

I think the discussion we just had is absolutely relevant to this question. I think I heard a summary that there should be actual hands-on training on people, and that we realize that you probably can't specify by specialty, but the training should be required. And I thought Dr. Campopiano's way of expressing that that actually could promote the use because people

wouldn't have to feel there's something wrong with them because they are uncomfortable; they might get over that.

So is there anything else the FDA is looking for on that question? No? Is it possible that we're on to the voting question? Okay. Yes?

DR. McNICHOLAS: On that question, they have stuff on not just the insertion and removal, but abuse, misuse, and accidental overdose. Did I miss part of that on what is included in the REMS on that?

DR. KRAMER: Yes, yes. Okay, we'll open it up to comments on that. Oh, I'm being told I have to read that into the record. I thought I did read it. Discuss whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

DR. McNICHOLAS: Does the REMS address the last three: the abuse, misuse, and accidental overdose, because I don't think that we got a lot

of information on that.

DR. KRAMER: Of the implant or of sublingual buprenorphine?

DR. PICKAR: It's just the way the question's worded.

DR. KRAMER: Yes. Would you like me to expand on it?

DR. LEHRFELD: Hi. This is Kim Lehrfeld, Division of Risk Management at the FDA. The accidental overdose, misuse, and abuse, it's really related to if the device is somehow expelled from the patient. Therefore, the education is just how a patient should adequately handle if a device starts to protrude or actually falls out.

So it has more to do with what happens in those rare cases that we saw, but very important cases. So it really has to do with patient counseling, the med guide, being reviewed by the inserter as well as the prescriber, as well as the patient counseling tool available to prescriber who may not be the one inserting it, but needs to talk about if those complications occur. And making

sure the end disposal of the product appropriately when it's removed.

Also, since the prescriber may not be the one inserting it, we do want them to be aware if that patient has to be managed 3 months after it's inserted and there's a complication. We want them to be aware to how to counsel their patient if it does protrude

DR. KRAMER: Dr. Grieger?

DR. GRIEGER: We got the general layout of the thing, which basically had a big circle, and the patient was in one part and the dispensing person was in another part of the circle. I guess the question is have they provided the details of exactly how they're going to monitor that? If this event occurs, who does what, what's the time frame of getting these things done?

A REMS program is complicated. Like the clozapine REMS program. Literally you've got designees that are sending stuff up and you have to accept new patients into your thing. It's a very systematic way of doing the REMS. I don't know if

they've given that same amount of detail at this point, and maybe they don't have to. I mean they've laid out what they plan to do. Maybe the specifics can follow later.

DR. LEHRFELD: We have some details. I will say because all of the training has to be live, it's a little easier for them to set this up, as long as they have the training session set up. That's where everyone will be enrolled. There's not an online component to this where there's training or any aspect of that. At this point in time, everything's going to be live. So the prescribers and the implanters will both have to go to that session. That's where they'll become enrolled.

So we do have some of those details, and we also have details of the distribution process. But, as with all REMS, there will be growing pains when it first gets approved. We do everything we can to get as much detail as we can so we understand the process so that doesn't happen, but --

DR. KRAMER: Okay. Dr. McNicholas?

DR. McNICHOLAS: Yes, when I look at this distribution system, the physician has to order the medication. Is that going to have to go through DEA forms? And when it's received, does it have to be logged in and logged out and et cetera, et cetera. Is this going to be a paperwork nightmare for the office.

DR. LEHRFELD: I'll honestly say I'm not the expert in that. This is a C3 as opposed to a C2. C2's have a lot more controls, but there are specific outlines for how buprenorphine is managed when prescribers right now order it. So the recording and logging would be the same for anyone else who keeps any buprenorphine in their office for initiating Subutex on patients if anyone's doing that.

DR. KRAMER: And is there a DEA -- can anyone answer it more?

DR. McNICHOLAS: I mean, most people don't keep it in their office, because it's so burdensome. There's a difference between writing a

prescription for a patient and ordering from a supplier.

DR. LEHRFELD: I completely agree, and like I said, I don't know what the CSA requires of recording for people who order buprenorphine in their office. I don't know if anyone here has any experience with that.

DR. KRAMER: It sounds like this is an implication of a decision, but it's not the basis for our considerations here today, but it's a very good question.

DR. LEHRFELD: No, it would not be within the REMS. We would expect that the prescribers would understand how to order it.

DR. KRAMER: Dr. Hertz?

DR. HERTZ: I would like to see if the sponsor would care to address some of the mechanics of the practicalities here.

MS. SHELDON: Probuphine would have to be ordered through a single distributor, through a buy and bill process, and the same controlled substances regulations would apply in terms of

storing in a locked and secure cabinet and disposing as pharmaceutical biohazard waste.

We have provided a log-in sheet, and depending on how the office is used to keeping records -- because while many clinicians don't currently keep buprenorphine in their offices, some do, and some actually keep other kinds of controlled substances. So they may have their own systems for logging in and logging out.

We have a receipt form where you would record receiving it, and then afterwards, when it's been, of course, disposed, so that everything is properly documented. This again is not considered part of REMS at this point, but as it may be of assistance to people in following what is required by the Controlled Substances Act, it will be made available.

DR. KRAMER: Okay. The next question is a voting question and I'm going to read you instructions about the voting, but first I'll read question 8. Based on the data presented and discussed today, do the efficacy, safety, and

risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine, as defined during prior discussion?

Then in discussion after that, we're going to discuss, comment, on further developments or explorations, higher doses the sponsor should undertake. Any questions?

DR. DODD: With regard to this question, we say efficacy, what are we talking about? Noninferiority? Are we talking about superiority? Are we talking about the 20 percent margin? Are we talking about -- which analysis are we referring to? Could I get some clarification?

DR. HERTZ: It's always interesting to find how our incredibly worked on, thought up, discussed and edited questions can come out less than crystal clear.

So I think the fairest way to say that the efficacy question would be, within what you've heard today, do you think there's efficacy and

safety such that the overall profile supports approval?

I think that opens you up to decide on the analysis you consider appropriate and the safety that you consider appropriate. And then, perhaps, when we go around to ask folks to say their vote for the record, if you'd like to comment on any aspect of what you took into account to support your vote, that might be an opportunity to explain a little more.

DR. KRAMER: We will be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the

vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want. We will continue in the same manner until all questions have been answered or discussed.

Does anyone have any questions, clarifications? Is everyone ready to vote? Okay.

(Vote taken.)

LCDR SHEPHERD: For the record, the vote is 12 yes, 5 no.

DR. KRAMER: Now, the vote is complete, we'll go around the table and have everyone who voted, state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. Dr. Campopiano, would you mind starting off the record?

DR. CAMPOPIANO: I'm supposed to say my name? Okay. Melinda Campopiano. My vote is yes. I'm satisfied that the product is not inferior and offers a benefit not currently available in other

products.

My, I guess, modifications or stipulations would be that the patients be behaviorally stable and that clear clinical guidance about who's appropriate for this medication, how to manage breakthrough, withdrawal, relapse, polysubstance use, et cetera, while on the medication be provided and that supervision of the medication and behavioral interventions be on par with other formulations.

DR. BICKEL: Warren Bickel, I voted yes. I'll second all your supplementary material, but I found that the FDA's very conservative analysis that rendered a noninferiority analysis was very important in my determination.

DR. DODD: Lori Dodd, and I voted no, largely because I wasn't sure what I was voting for, so I didn't want to vote yes. I think it depends a lot on what the noninferiority margin is. And furthermore, it depends on some yet to be seen analyses of the missing data, which I think have been described through the panel. So if you call

me back in a month, I might change my vote.

DR. TROENDLE: James Troendle. I voted yes. Although I think the sponsor's analysis was pretty much incomplete, I do think the FDA's analysis was pretty thorough and gave what I would consider to be pretty conservative assumptions that still being able to pass a fairly small noninferiority margin. So I was convinced by that.

MR. YESENKO: Michael Yesenko. I voted no based on the way the question was written. The sponsor was able to provide an analysis, but I voted according to the way the question was written, rather than the way FDA interpreted it at the end.

DR. HIGGINS: Jennifer Higgins. I voted no.

DR. PRESTON: Kenzie Preston. I voted yes. I think the FDA did a very thorough evaluation. I do want to say that I think the labeling needs to be very clear about the patient population on whom it was tested, that people on low doses of buprenorphine who've been shown to be stable.

DR. McNICHOLAS: Laura McNicholas. I voted

yes. I also agree with the FDA's analysis of the data more so than the sponsor's. And I also second the issue of the way that the label needs to be worded in terms of behavioral stability, as well as the dose of buprenorphine. I also think there needs to be something in the label about how to manage supplemental doses and what the implications of supplemental doses are.

DR. GRIEGER: Tom Grieger. I voted yes. I think that overall the data did have some problems in the analysis. As the FDA put their input into it, it was improved. I think clearly there was not evidence of significant risk using this agent, and there is evidence of significant benefit and hopefully great promise once it's actually out there.

DR. PICKAR: I voted yes. I think the FDA did a very nice, fair job in sort of reanalyzing it as it was. And I think the issue of efficacy in this case, in noninferiority was demonstrated. I think this will save some folks lives, and we heard from the public on how intense and awful these

experiences are for everybody involved.

So from a safety point of view I think you're in good shape and I think it's noninferior, and I vote to approve it.

DR. KRAMER: Could you state your name, Dr. Pickar, into the record?

DR. PICKAR: My name is Dave Pickar, and I'll stand by that.

(Laughter.)

DR. KRAMER: And you voted yes.

DR. PICKAR: And I voted yes.

DR. KRAMER: My name is Dr. Judith Kramer, and I voted no, and I was very conflicted about this. It seemed to me, starting with the review of the materials in advance and listening to the discussions today in the open public hearing, quite a blurring between the fundamental problem we've got of the epidemic, which is truly a public health crisis. And I think all of us, everyone in the room, the sponsor, the panel, and all the people in the open public hearing desperately want something to be available to us to use.

I realize this is a very -- I mostly focused on clinical trials in my career, and I realize this is a very challenging clinical trial population. I fully understand that. But I was dismayed by what I thought met all the criteria for not a very rigorous approach on the part of the sponsor in terms of things like deciding to leave out 3 patients and then claiming that it is really superior, and repeatedly using that as the line.

So I felt that there was already an inflation going on. And when I started to hear the statisticians talk about the lack of conservativeness of the margin, of the noninferiority margin, I realized I'm very concerned about the precedent this sets about what we're going to do for this epidemic.

The bigger picture, the whole time I've been thinking to myself, this was presented like it was a 6-month treatment or a year treatment. But wait a minute, these people have been on for 10 years? And we're not sure about the training and we're not sure about what's going to happen, but after it's

on the market, we'll look into it?

We don't have a strategy. There were some things in the material that didn't come out in the discussion today about opioid use being a surrogate endpoint for lack -- we're talking about treating opioid addiction, so what is the goal? What are we actually doing?

It doesn't appear we're trying to withdraw people because the specialists who say that these patients at this level, if they come off 75 to 80 percent of them will be using.

So we are talking about long-term treatment, maintenance treatment, but we haven't studied that. And we're claiming it's superior to something that we know has done well and has saved many lives. And the biggest elephant in the room is that we have an access problem. People aren't getting treatments that are available because of a law that limits the number of patients a practitioner, who would be willing to treat more, could treat.

So I don't think with our desire to do something, we should be careless about what we

address. Somebody needs to get active and change the law and get more people able to treat and use the drugs that are approved, and we need to be rigorous about the precedence we set. And I'll see what Dr. Dodd thinks in a few weeks.

DR. IONESCU: Dawn Ionescu. I voted yes, primarily thanks to the FDA's very thorough analysis, showing that this did, indeed, pass the noninferiority margin that was set at the outset. Whether or not that margin is right, it was set, and therefore beat that.

Just as an aside, I think that this represents somewhat of an exciting thing beyond the statistics, beyond the numbers, and that this is an example of psychiatry breaking through the status quo that we currently have, thinking outside the box, thinking for future, potential future treatment. So thank you for that.

DR. NARENDRAN: Raj Narendran. I voted yes. I thought the FDA's sensitivity analysis, even with all the conservative assumptions, seem to demonstrate noninferiority, and I think there's a

need. Although, I do feel that the labeling has to be crystal clear and offer a very narrow indication, which should really mimic the population they recruited and their sample. I think that's very important.

DR. BRADY: Kathleen Brady. I voted yes, and I really don't think I have anything to add to all the reasons people have already given.

DR. KRAMER: Dr. Carroll, would you like me to read your response into the record?

DR. CARROLL: Yes, if you can.

DR. KRAMER: Okay. If I say anything incorrect, please speak up. For the record, Kathleen Carroll voted yes, but with mixed feelings and with multiple caveats and concerns, including: a clearer definition of what constitutes a stable patient; clear language with labeling covering some of the concerns raised in the discussion regarding regular monitoring; re-analysis of sponsor trial data with corrections as noted in the discussion including ITT, handling of missing data; consider other definitions of response, clarity, and REMS

regarding training of physicians for implantation and removal.

Dr. Gordon?

DR. GORDON: Adam Gordon. I voted yes. I actually had a difficult time on this one simply because of several caveats I'll mention briefly. I do think that the FDA did a great job in re-analyzing the data and being very conservative in their analysis. And I think the noninferiority issue really swayed me.

Certainly, I think that there's more benefit than risk at this point for this approval, and that's what really swayed me. However, I do want to point out two or three things that I thought were really concerning.

I think the issue of stability is not well-defined. And based on that lack of a clear definition of what a stable patient is, I really worry, postmarketing, whether we're going to have a lot of aberrant behaviors, aberrant use of this medication in this very vulnerable population.

I think in general, reflecting on my patient

population, I think you're going to have a lot of people on supplemental doses of this medication. And particularly if people, practitioners, who we can't regulate right now with normal buprenorphine practices, are doing untoward things, I really worry that we may insight a harm with this implantable device, implantable medication in this population.

So with those caveats, I was a little bit concerned, but overall, based on the evidence presented today, not the implications down the road, but the evidence presented today, I voted yes.

DR. KOTZ: Margaret Kotz. And it's with mixed feelings I voted no. The reasons for my voting no were really spelled out well by Dr. Kathy Carroll. And the main things were the supplemental medication, and in terms that does have increased risk for diversion I feel. And the other thing was, is what do you do after two years? That still is a huge question for me.

DR. KRAMER: Okay. So we've read into the

record everyone's response, and we still have question 9, which is to comment on any suggestions regarding further development or explorations that the sponsor should undertake. For instance, higher doses or anything else you want to suggest.

Jennifer Higgins?

DR. HIGGINS: I'd like to see more -- a diverse population studied if possible.

DR. KRAMER: Dr. Bickel?

DR. BICKEL: I'd like to see different doses explored. I'd like to see better characterization of who responds well to this treatment. I'd like to see exploration into how it could be extended beyond two years.

DR. KRAMER: Dr. McNicholas?

DR. McNICHOLAS: I would like to see data on need for supplemental doses. I think that needs to be followed as this drug is rolled out, as to whether or not patients require supplemental doses, and also how often they're being seen; are they being seen on a regular basis as clinically appropriate?

DR. KRAMER: You mean surveillance of that or a study?

DR. McNICHOLAS: Yes.

DR. KRAMER: Dr. Campopiano?

DR. CAMPOPIANO: I agree, all of that, plus I think there's a unique potential for this type of implantable or Depo product, because it doesn't go to zero immediately. So I think there's a potential for a role for this type of technology in long-term slow titration off of medication for people for whom it's appropriate. And I think that would be worth studying.

That said, future products should be analyzed much more rigorously by the sponsor and much more conservatively, because despite the fact that people are dying, we have the privilege of providing this medication through an act of Congress. And that can be taken away from us if we are irresponsible with this medication or we screw it up because we're too glib.

So that's just a word of caution, because I understand more products are in development, and

they need to come forward absolutely crisp and conservative in their analysis.

DR. KRAMER: Dr. Narendran?

DR. NARENDRAN: My recommendation is we really do a PET occupancy study. Get the appropriate dose, 80 percent occupancy, and test it, because I feel like anything else is like sub-therapeutic. It's sort of an inferior dose.

There's a good literature. I didn't quote that, but a meta-analysis was on 21 clinical trials in buprenorphine, that showed that patients 16 milligrams or higher have a higher retention in 21 clinical trials. I know your trial, you felt very high retention rate.

So it's clear evidence that with methadone and buprenorphine, you have to be at a much higher dose. So an 80 percent occupancy dose to shoot for would have saved you a lot of trouble.

DR. KRAMER: Dr. Ionescu?

DR. IONESCU: As far as recruiting patients, maybe considering one of those external reader strategies to really have a nice, as clean as we

can get, currently population.

DR. KRAMER: Dr. Brady?

DR. BRADY: Yes, I think it would be good to have a study that would help determine what's the best way for induction or getting people started on it, how supplemental doses should be used and how many and for what period of time?

DR. KRAMER: Dr. Pickar?

DR. PICKAR: I think this might be an opportunity to really utilize postmarketing data of any new drug that I think about. I'm just fascinated to see how it goes. In my judgment, the risk-reward was on the basis of moving it along. But this is just an interesting opportunity, so all the questions are pertaining to that. But what we have a little more uniquely now is to see data coming in. So however you can keep track of these guys and see what we see, I think will be very helpful for their future development.

In terms of their not so conservative analysis, that's why the FDA is here. Everybody's got a role.

DR. KRAMER: Dr. Dodd?

DR. DODD: Yes, from a design perspective, I'd like to see a little more exploration of the frequency of the urine measurements because I don't want the message to be sent that -- because in the previous studies, they did much more frequent measurement, well we can back it off and then we get a non-inferior result.

So I'd like to see more of that explored. Maybe that's a plea to the statisticians to explore this.

DR. KRAMER: Actually, on that point, I remember reading in the packet that when they did the survey, that the response was that every -- I think that every 2 weeks would have been considered reasonable; 2 weeks and a month was the longest, and yet the sponsor chose the month instead of the every 2 weeks. It looks like it would have been within the realm of practice for these patients that are maintained.

Dr. Preston?

DR. PRESTON: So obviously having doses that

would be higher would be a good thing. It also occurs to me that one of the frequent causes of relapse is missed doses. So if we can possibly think of this as sort of the baseline medication administration under sublingual dosing, and that this would, perhaps if people miss doses, keep them from having a relapse. And that would be a totally different paradigm from what's planned now. But it seems like a potential use of this dose administration.

DR. KRAMER: And it takes away the advantage of avoiding diversion and pediatric overdose --

DR. PRESTON: Yes, that's true.

DR. KRAMER: -- and the marketing.

DR. McNICHOLAS: One last thing, and it just occurred to me, because I know coming from Philadelphia, we had this problem with something called a naltrexone implant. We have got to keep track of any ER visits, et cetera, if patients try and take the implants out themselves. That has got to be followed, because that's danger that we need to know about.

DR. KRAMER: Do you know of ways to do that?

DR. McNICHOLAS: Actually, the ERs in the tri-state area set up a computer base that they could all plug into and say the patient came in and somebody had dug it out of his or her back or, and now they're in with an infection, et cetera.

DR. KRAMER: Somebody would have to organize that. There's no system that would currently surveil this.

DR. McNICHOLAS: No, the sponsor can set up a surveillance on that.

DR. KRAMER: Is the devices group involved in looking at this with you or not? Because I know they've gotten into surveillance of -

DR. HERTZ: Only to the extent that they're evaluating the trochar, the implantation device.

DR. KRAMER: Could they help in surveillance of explants?

DR. HERTZ: We will certainly ask them what they have available. We'll take this topic up for further discussion and see what resources might be available or might need to be requested.

DR. KRAMER: Any other comments?

(No response).

Adjournment

DR. KRAMER: The FDA got their questions answered? Thank you all for staying until the bitter end and being so forthright.

DR. HERTZ: Yes, thank you all. Greatly appreciate all the input.

(Whereupon, at 4:55 p.m., the meeting was adjourned.)