FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC
DRUG PRODUCTS (AADPAC) AND THE
DRUG SAFETY AND RISK MANAGEMENT (DSaRM)
ADVISORY COMMITTEES

Tuesday, May 22, 2018
8:00 a.m. to 2:57 p.m.

College Park Marriott Hotel and Conference Center
3501 University Boulevard
Hyattsville, Maryland

A Matter of Record
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Meeting Roster

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DR. WINTERSTEIN: Good morning, everybody.

Let's get ready. I would like for us to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so.

I would also like to identify the FDA press contact, Michael Felberbaum. If you are present -- doesn't look like he is yet. Michael, sorry, Michael Felberbaum. Doesn't work, either.

My name is Almut Winterstein. I'm the chairperson of the Drug Safety and Risk Management Advisory Committee and I will be chairing this meeting. I will now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introduce ourselves. We will start with the FDA to
my left and go around the table. Sharon?

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

DR. FIELDS: Ellen Fields, deputy director in the same division.

DR. MEYER: Tamra Meyer. I'm the team lead for the Prescription Drug Abuse Team in the Office of Surveillance and Epidemiology.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen, professor of statistics at Wharton School at UPenn.

DR. KAYE: Alan Kaye, professor, program director, and chairman at LSU School of Medicine in New Orleans.

DR. FLICK: Randall Flick, anesthesia, critical care, Mayo Clinic.

DR. ZELTZER: Lonnie Zeltzer, head of pediatric pain and palliative care at UCLA.

DR. MCCANN: Mary Ellen McCann, associate professor of anesthesiology at Harvard Medical School and staff anesthesiologist at Boston
Children's Hospital.

DR. LITMAN: Good morning. I'm Ron Litman. I'm a pediatric anesthesiologist at the Children's Hospital Philadelphia and the medical director of the Institute of Safe Medication Practice.

DR. ZACHAROFF: Good morning. I'm Kevin Zacharoff. My expertise is in anesthesiology and pain medicine. I am at the State University of New York Stony Brook School of Medicine.

DR. GOUDRA: Good morning. I am Basavana Goudra, associate professor of anesthesiology at Penn Medicine in Philadelphia.

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

DR. WINTERSTEIN: Almut Winterstein, professor and chair of pharmaceutical outcomes and policy at the University of Florida.

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

DR. WARHOLAK: I'm Terry Warholak and I'm
professor and assistant dean at the University of Arizona College of Pharmacy Arizona.

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

DR. BOUDREAU: Good morning, Denise Boudreau. I'm a pharmacoepidemiologist from Kaiser Permanente, Washington in Seattle, Washington and affiliate professor at the University of Washington.

DR. BEYRER: Good morning, Chris Beyrer. I'm a medical epidemiologist and professor at Johns Hopkins Bloomberg School of Public Health in Baltimore.

DR. COFFIN: Hi, Phillip Coffin, infectious disease and substance use research at San Francisco Department of Public Health and UCSF.

DR. DASGUPTA: Good morning. I'm Nabarun Dasgupta. I'm a pharmacoepidemiologist and drug abuse epidemiologist at the University of North Carolina in Chapel Hill.

MS. ROBOTTI: Hello, I'm Suzanne Robotti,
founder of MedShadow Foundation and executive
director of DES Action.

DR. JONIAK-GRANT: Hi. I'm Elizabeth
Joniak-Grant. I am the patient representative
today. I'm also a sociologist with the National
Coalition of Independent Scholars. The areas I
tend to represent surround chronic pain, including
chronic migraine, arthritis, and neuralgias.

DR. HERRING: Hello, good morning. I'm Joe
Herring, a neurologist, a scientific associate vice
president in clinical neuroscience at Merck, and
industry representative to the AADPAC committee.

DR. WINTERSTEIN: For topics such as those
being discussed at today's meeting, there are often
many varied 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 general 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 topics 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 will pass it to Moon Hee Choi, who will read the conflict of interest statement.

**Conflict of Interest Statement**

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

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

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

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

Related to the discussions at today's
meetings, members and temporary voting members of
the committees have been screened for potential
financial conflicts of interest of their own, as
well as those imputed to them, including those of
their spouses and minor children, and for purposes
of 18 U.S.C. Section 208, their employers.

These interests may include investments,
consulting, expert witness testimony, contracts,
grants, CRADAs, teaching, speaking, writing,
patents and royalties, and primary employment.

Today's agenda involves discussion of new
drug application NDA 209588 or buprenorphine
sublingual spray, submitted by Insys Development
Company, for the treatment of moderate to severe
acute pain where the use of an opioid analgesic is
appropriate. The committees will also be asked to
discuss whether this product should be approved.

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

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

With respect to FDA's invited industry representatives, we would like to disclose that Dr. W. Joseph Herring is participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck and Co.

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

FDA encourages all other participants to
advise the committee of any financial relationships
that they may have with the firm at issue. Thank
you.

DR. WINTERSTEIN: We will now proceed with
the FDA's introductory remarks. Dr. Sharon Hertz?

FDA Opening Remarks – Sharon Hertz

DR. Hertz: Good morning. To our chair,
Almut Winterstein, our members of the Anesthetic
and Analgesic Drug Products Advisory Committee,
Drug Safety and Risk Management Advisory Committee,
and invited guests, welcome.

We're going to be discussing today a new
drug application from Insys Development Company for
Buvaya, a sublingual spray formulation of
buprenorphine with the proposed indication of the
management of acute pain severe enough to require
an opioid analgesic and for which alternative
treatments are inadequate.

Buvaya was not formulated to include
properties intended to deter abuse, nor is the
applicant requesting such claims. Buprenorphine is
a partial mu agonist and a kappa antagonist, and is
under Schedule III of the Controlled Substances
Act.

It's the active ingredient in an injectable
formulation for acute pain in sublingual and
transdermal formulations for chronic pain and in
several combinations alone and in combination with
naloxone as medication-assistant therapy for opioid
addiction.

The applicant has relied in part on the
agency's prior findings of safety and efficacy for
Buprenex, which is a buprenorphine injection, for
the management of pain, and Subutex, which is a
buprenorphine sublingual tablet indicated for
treatment of opioid dependence.

So I'm going to go over what is the
505(b)(2) pathway because it tends to create a little confusion, rightly so. It's a little confusing. So a 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Yes, I quoted the regs, which is why it sounded that way. So in other words, this regulation permits reliance on the literature or on our prior findings for something relevant to the product at hand. A 505(b)(2) can be submitted for a new indication, a formulation change.

There's several situations in which we can accept the 505(b)(2) application. It's not for a failed generic. Sometimes there's a little confusion there, but there are some times 505(b)(2) applications that are bioequivalent to the reference product, but have sufficient differences to not be eligible to be generic product or 505(j).
If the applicant seeks to rely on our prior findings of safety of efficacy for a listed drug, the sponsor has to identify which products these are. And then even if the application is only based on referring to the literature, that can be a 505(b)(2) if it's talking about a specific drug substance.

So the number and type of studies that we require of an application for a (b)(2) application depends on how the product under development is similar and how it's dissimilar to the reference products. And here, we have two products because the company is planning to rely on our findings for different elements from each approved product.

So when there's a new indication compared to the reference products, we require a demonstration of efficacy in clinical trials because it's not the prior finding, but there may be enough safety information from the prior application to reduce the safety requirement for the new product depending on the similarity of dosing, patient populations, and risks.
Or the company may just choose to rely on non-clinical information. So there's many different pieces that can be relied on. In general, we'll require some additional safety information for the new product because it's presumably going to behave differently than the reference products.

So Buprenex, the parenteral that is being referenced, has a different route of administration, dosing regimen, and pharmacokinetic profile than the product under discussion today. So the studies that we required are not intended to demonstrate that buprenorphine is an analgesic.

That's our prior finding relating to the injectable, but it's to show whether buprenorphine, when delivered by this new formulation under the proposed dosing regimen and, two, the proposed population was suitable to manage pain in that intended population.

Similarly, Subutex has a completely different indication. It's got a different population and it's generally higher doses used in
MAT, medicated assisted treatment, then for pain. But there are elements of the application that may be suitable for the applicant to rely on so they don't have to repeat studies that have already been done and reviewed.

There are limitations on when one can rely on other products. I don't think we need to go into that today. We'll take care of that behind the scenes during our review.

So I just also want to note that, as an immediate-release, opioid analgesic which is expected to be used, we have already determined that the product, if approved, will need to have a REMS, risk evaluation and mitigation strategy, similar to what we're planning for the other immediate-release opioids.

So we're going to present a variety of data today, including some efficacy and safety data, some PK, drug utilization trends for buprenorphine products, and some epi data on misuse and abuse of buprenorphine.

We're going to highlight particular areas in
our presentations where we have some questions that
we're going to ask you to address later that day.
So we request that you provide your expertise, your
experience, and your best insights in order to help
us find a reasonable and responsible path forward.

We review the advice that we get during this
meetings, not just the votes, but all of the
discussion quite extensively. I rely on them quite
a bit. I refer to them over the years when we have
similar situations arise.

So I want to just say how grateful we are
that you've agreed to come take time from your busy
schedules again, and thank you all.

DR. WINTERSTEIN: Thank you, Dr. Hertz. We
just had Dr. Rich join us. Do you want to
introduce yourself real quick?

DR. RICH: I'm Jody Rich, professor at
Brown, infectious disease and work with the opiate
epidemic a bit lately.

DR. WINTERSTEIN: Like all of us voluntarily
or involuntarily. Thank you. Welcome. So we will
proceed with the applicant's 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, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the 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 presentation, it will not preclude you from speaking. We will now proceed with Insys
Development Company's presentations.

DR. MEISEL: Before we get started, just technically, there is some echoing in this room. I don't know if the AV people can do something with that. For anybody who's speaking from sort of this part of the room that way, the echo is quite loud.

The folks who are speaking from their desks over there, it was not, so just to point that out for the AV people in the room if there's something you can do.

**Applicant Presentation – Stephen Sherman**

MR. SHERMAN: Good morning. While there are numerous options for the treatment of chronic pain, the therapeutic landscape for the management of moderate to severe acute pain is somewhat limited.

The only approved Schedule III products are IV buprenorphine and oral codeine. Codeine is often used in combination products that include acetaminophen that may not be well tolerated and cannot be used in a number of patients.

Schedule II opioids are further limited by a greater risk of abuse, misuse, and diversion, and
non-opioid alternatives are usually inadequate and also burdened by their own risk and limitations.

Good morning. I'm Steve Sherman. I'm senior vice president of regulatory affairs and clinical development at Insys Therapeutics. We are an Arizona-based company, developing and commercializing innovative drugs and novel delivery systems for unmet medical needs. First, I would like to thank the FDA and the advisory committee for allowing us to discuss Buvaya with you, our newest drug product.

We're excited to work with this committee in bringing forward a new Schedule III treatment option for acute pain patients. Buvaya is a novel formulation of buprenorphine that is a single-use gray device for around-the-clock management of acute to moderate pain, moderate to severe pain.

Despite its proven clinical utility, buprenorphine has only been used widely for the treatment of acute -- has not been used widely in the treatment of acute pain because it's really only available in an IV form.
However, today, there is a growing need to make buprenorphine more accessible in the acute pain study. Buprenorphine is, as Dr. Hertz mentioned, a partial mu agonist that has unique attributes that make it particularly useful for the treatment of pain.

The inherent properties of the molecule diminish its appeal as a drug of abuse and give it potential safety advantages over full mu agonist. It really has a slower onset of effect, reducing its appeal to abusers, plus multiple publications suggest that it has a ceiling effect for respiratory depression, but not for analgesia.

As a result, it is a Schedule III opioid with a lower abuse potential than Schedule II opioids. This is reflected not only in its scheduling, but also it is ranked relatively low in the RADARS reporting structure and in other multiple systems that track abuse, misuse, and diversion.

The primary diversion of buprenorphine is for self-medication to prevent opioid withdrawal,
really not to get high. Currently, it is only available for acute pain as an injectable therapy which is in part due to a very high first-pass effect that limits its oral bioavailability.

With these concerns in mind, we developed a sublingual spray. With products intended to treat acute pain, there is an expectation that meaningful pain relief will be experienced soon after taking the first dose, generally within the first hour.

However, we will demonstrate that there are currently approved opioids that would have similar times to meaningful pain relief as our product, Buvaya. Additionally, the use of an opioid in patients who are naïve can result in a high level of nausea and vomiting.

According to the consensus, guidelines for the management of post-operative nausea and vomiting, the incidence of nausea in a high-risk patient population like those that we study can be as high as 88 percent, which is about what we she wants in our clinical trials.

Most of these events occurred at the
beginning of therapy and, in a subsequent trial, with prophylactic antiemetic treatment, actually, the rate that was reported was about 50 percent. These data suggest that a prophylactic antiemetic medication should be recommended with the use of Buvaya.

Another risk associated with the use of opioids is respiratory depression. Hypoxia or oxygen saturation decrease were reported in our studies and we’ll discuss those. This is a common problem associated with the use of opioids.

Our prescribing information and our medication guide will educate both the prescribers and patients on how to recognize this event and then what to do when they see it.

Because most of these concerns were associated with initiating therapy, we are recommending that the initiation of treatment occur in a medically supervised setting for a duration of up to 12 hours. That will generally cover the first two doses and the majority of adverse events. This should also reduce the potential risk of re-
dosing for patients who do not achieve meaningful
pain relief as rapidly as anticipated.

Buvaya avoids the first pass effects that
limit its oral bioavailability. It was developed
to be administered every 8 hours in the treatment
of acute pain with a proposed treatment duration of
up to 7 days. The spray is delivered in a single-
use device that delivers 1 dose only of medication.

The spray system is easy to use and has
undergone human factor testing. And we actually
have 6 years of commercial use for the product in
an already-approved Schedule II opioid. The spray
requires little or no training. The patient holds
the device, points it under their tongue, and
pushes the purple plunger to administer the dose.

The patient then needs to hold the liquid
under the tongue for 30 seconds to receive the full
dose. We've developed the spray formulation as
buprenorphine under 505(b)(2) pathway, using both
IV formulation of Buprenex and the sublingual
tablet of Subutex as the listed reference compounds
for safety and efficacy along with established
safety data in the public domain for other buprenorphine products.

As Dr. Hertz mentioned, at the end of our phase 2 meeting, the agency agreed that the efficacy of this product could be demonstrated in the single adequate, well-controlled trial, which is our pivotal trial, study 062. Our overall clinical program actually consists of 10 studies, including 7 PK studies, 1 phase 2 open-label safety study, 1 dose-ranging study, and our pivotal trial.

These data, the data from these trials support the proposed indication for the treatment of moderate to severe acute pain when an opioid is needed and alternative treatments are inadequate. The agenda for the remainder of our presentation will be Dr. Joseph Pergolizzi, who's senior partner and director of research at Naples Anesthesia and Pain Associates.

We'll introduce you to the medical landscape and unmet medical need that this product addresses. Dr. Dean Mariano, who's our senior director of clinical development and medical affairs, will
discuss the product development rationale, the
pharmacokinetics of it, and the efficacy and
safety.

I will come back and introduce you to our
risk management program because, as Dr. Hertz
mentioned, we will have a REMS for this program.
And then Dr. Pergolizzi will come back and present
to you that benefit-risk that we did. Thank you,
and I am honored to introduce Dr. Pergolizzi.

**Applicant Presentation – Joseph Pergolizzi**

DR. PERGOLIZZI: Thank you, Steve. I'm Joe
Pergolizzi and I have been compensated for my
attendance at this meeting and I have no financial
interest in the outcome of this meeting.

I do, however, have a long-standing
professional interest in finding new alternatives
for effective pain relief with less abuse, so I am
especially appreciative of the opportunity to speak
with you today.

I spent over 20 years of my life researching
and developing analgesics, including several
formulations of buprenorphine with multiple
different routes of administration and have global experience with its use of buprenorphine, including the treatment of acute pain.

Acute pain takes on many forms and can be severe enough to require opioid analgesics. Pain is the number one reason why people seek medical care. Not all pain is the same and there are many ways to classify pain. It is important to distinguish acute pain from chronic pain.

Acute pain is generally caused by direct tissue trauma. Its duration is typically considered to be the normal healing period for the specific insult. Acute pain can last for hours to days such as with acute phase dental pain procedures or days to weeks for pain after orthopedic procedures.

There is a wide range of examples of moderate to severe acute pain which are managed in the inpatient and outpatient settings. It should be noted that cancer patients with chronic pain can also experience acute pain for various reasons, for example those associated with the treatment such as
the following surgical biopsy procedures or
invasive testing.

Though not exhaustive, this list highlights some types of moderate to severe pain for which patients need an effective therapy for the duration of their pain. Adequately and appropriately managing acute pain with analgesics shortens hospital stays, avoids readmissions, enables us to treat these patients as outpatients.

This is consistent with ARAS, Advanced Recovery After Surgery, a paradigm shift in perioperative care resulting in substantial improvements in clinical outcomes, earlier hospital discharges, and cost savings.

We need a range of options for patients with moderate to severe acute pain and its variety of causes and their trajectories. For these reasons, non-opioid analgesics are inadequate to manage intense pain in certain patients.

While non-opioid analgesics are specific to manage mild to moderate pain, these drugs do have side effects and dose-limiting toxicities,
especially in at-risk patients, including GI irritation, cardiovascular side effects, renal and hepatotoxicity, and bleeding.

For these reasons, various regulatory agencies recognized the risks of NSAIDs and APAP, especially at high doses, and recommend that they be prescribed at the lowest effective dose for the shortest duration possible.

Because of these risks, these drugs are not routinely recommended for extended use, especially in at-risk patients. Patients with more severe pain will commonly benefit from opioid analgesics.

Opioids are effective for moderate to severe pain. They act centrally to reduce pain awareness in the brain. They're all controlled substances. Most are either Schedule II or Schedule III. They're commonly used as mono-analgesic therapy or part of a multi-mechanistic analgesic plan.

Opioids have class side effects, including nausea and vomiting, constipation, androgen deficiency, sedation, respiratory depression, and rash.
They also carry the risk of physical dependence, tolerance, abuse, and addiction. Once a patient has developed physical dependence, they can experience withdrawal symptoms upon discontinuation or dose reduction.

Most of the available opioids for acute pain are Schedule II. There are two Schedule III opioids indicated for acute pain, IM or IV buprenorphine in the form of Buprenex, and all codeine with acetaminophen or APAP. They have limited utility. In the case of Buprenex, it's only available as an injection for PRN use, but it is effective for moderate to severe acute pain.

Codeine with APAP is indicated for mild to moderate pain. Codeine is constipating, plus not all patients can metabolize it to the active morphine and therefore its clinical utility is low.

Plus, combination products with APAP must be used cautiously in the elderly and patients with hepatic impairment. There are more Schedule II IR opioids for acute pain use. These all come with a higher potential for risk, abuse, and diversion.
Currently, there is only one approved opioid for acute pain management that, in Section 9.2 of its label, is administered in an around-the-clock manner. This is Xartemis XR.

This dose is divided orally, is an oral dose that is divided every 12 hours and it is not approved for PRN use. There is a long list of Schedule II opioids approved for PRN use, the most common of the immediate-release formulations of oxycodone, hydromorphone, and hydrocodone with their respective fixed combinations with APAP.

These currently available opioids all have challenges. The Schedule II opioids all have high risk for addiction, overdose, and death. Only one IR formulation is currently approved with labeling in Section 9.2 of the package insert for acute pain that has abuse-deterrent properties and is a C2.

The chief hazardous and greatest safety concern related to opioids is opioid-induced respiratory depression, which can lead to apnea and death. Additionally, many of the commonly prescribed formulations contained fixed doses of
APAP, limiting their use in the elderly.

Several of these drugs have limitations based on the pathways of elimination that limit their utility in patients with hepatic renal failure and require dose adjustment.

All formulations can be problematic in patients who are NPO, cannot take oral medications or have swallowing difficulties. Vomiting and nausea are common side effects and vomiting may cause a patient to lose their oral dose.

Finally, I would be very concerned about using some of these drugs in patients with a history of substance use disorder or even those I judge at risk. Unfortunately, the commonly prescribed Schedule II opioids for acute pain are highly abused.

As shown here in 2011 data, oxycodone, hydromorphone, and morphine were the acute medications that caused the most drug-related emergency department visits for misuse and abuse. Together, they were linked with over 300,000 visits during this time period.
During the same period, buprenorphine-containing products were linked to just over 25,500 visits, of which the combination project with naloxone used for medication-assisted therapy of opioid use disorder account for the majority.

Several publications suggest that most drug abusers do not use buprenorphine to get high and its value on the street is primarily to treat the symptoms of opioid withdrawal. Buprenorphine pain medications are not a significant contributor to opioid abuse, misuse, addiction, overdose, and death.

Buprenorphine does not appear to be on the list of the top 10 drugs involved in drug overdose death in this 2014 review, while other opioid medications, including oxycodone, methadone, Ms. Steward, hydrocodone, and fentanyl, real-world experience shows limited number of ER visits in overdose deaths related to any formulation of buprenorphine despite 11.5 million prescriptions dispensed at the same time.

The biggest driver for opioid overdose
deaths is respiratory depression. Opioid's reduced respiratory drive, which can result in respiratory depression by decreasing the rate and effectiveness of breathing. This in turn causes plasma oxygen levels to drop and carbon dioxide levels to rise.

The serious complications that can result include respiratory acidosis, apnea or respiratory arrest, decreased cardiac heart rate and cardiac arrest, coma, brain damage, and death. Patients with serious life-threatening respiratory depression require medical attention.

Even when opioids are prescribed appropriately, there is a risk of opioid-induced life-threatening respiratory depression. Class labeling advises that patients are to be monitored closely for respiratory depression. It should be noted that the vast majority of these prescriptions are dispensed in an outpatient setting and patients may take their first dose while at home.

It becomes a question of how we actually monitor. Typically, the only way we know there is respiratory depression in the outpatient setting is
if the patient presents to the emergency department. In most if not all studies, the respiratory effects of opioids are quantified by the observed changes in breathing frequency and/or oxygen saturation, SpO2.

Studies have defined post-operative hypoxemia as SpO2, 94 percent, with moderate hypoxemia as SpO2 of 90 percent, and severe hypoxemia as SpO2 of 85 percent for more than 6 minutes per hour.

With respect to breathing frequency, severe respiratory depression is considered at breathing rates of less than 8 to 10 breaths per minute. It is important to understand that oxygen saturation and breathing frequency are surrogate indicators for ventilatory drive and provide only information that's limited on the effects of a drug on the ventilatory control system and an example is that oxygen saturation is the measure of gas exchanged in the lung rather than a direct indicator of ventilatory efficacy.

Inspired minute ventilation and arterial
carbon dioxide concentration in clinical settings and the hypocapnic ventilatory response in experimental settings are direct measures of ventilation and ventilatory drive, but are often difficult to assess in a continuous base.

However, SpO2 is a simple measurement used commonly to indicate a serious opioid-induced ventilatory event, perhaps together, even looser indicators of respiratory depression such as sedation and bradypnea or low breathing frequency.

While encouraging a patient to breathe more often and more deeply or supplemental oxygen via the use of a nasal canular may be sufficient to overcome mild respiratory depression. Serious events may require positive airway pressure, reversal with naloxone, fluid therapy for respiratory acidosis, mechanical ventilation, or CPR.

Life-threatening respiratory depression is a drive for opioid-related deaths. We need new treatment options for acute pain with lower risks of addiction, overdose, and death.
From a public health perspective, the need for Schedule III opioids couldn't be clearer. Until we develop an armamentarium of non-opioid treatment options that can manage moderate to severe pain safely and conveniently, there will be a growing need for opioid analgesics with a lower-risk profile.

By definition, Schedule III opioids have a lower risk of abuse and physical dependence, which can result in lower rates of addiction, overdose, and death. However, there are very few Schedule III opioids available for acute pain. This is a compelling need for new Schedule III opioid treatments options for acute pain.

Buprenorphine possesses unique pharmacological properties as a partial mu opioid receptor agonist that make it a good option. Buprenorphine has a prolonged receptor occupancy and is an activity at multiple opioid receptors. It is a potent opioid that is a Schedule III with a large therapeutic index of about 12,000.

Studies have shown that buprenorphine has a
ceiling effect on pCO₂. In my clinical experience, buprenorphine has a lower rate of constipation than other opioids. Both attributes may be due to its partial agonism at the mu receptor.

Perhaps more importantly in the context of the opioid epidemic that it is a C3, it has a lower potential for abuse and physical dependence as determined by the DEA.

Lower rates of abuse have been reported on multiple tracking systems, including the raters. Studies have shown that opioid abusers have a low preference for buprenorphine and it seems to have lower or slower euphoric effects compared to other opioids. And it has been suggested that this is a reflection of its longer time-to-peak effect and that is what Dr. Lynn Webster has described as a low abuse quotient or AQ.

For this reason, it may be an option for patients who have opioid use disorder. One of the noted side effects of buprenorphine is that it does have a high rate of nausea and vomiting, especially in opioid-naïve patients. However, these side
effects are manageable with common mitigation strategies and the use of antiemetics when necessary.

The ceiling effect on respiratory depression may account for lower rates of overdose deaths with buprenorphine. In 2006, Dr. Dahan demonstrated that there was a ceiling effect on respiratory depression.

He looked at healthy volunteers, doubling the IV dose of buprenorphine from .2 to .4 milligrams, and showed that it resulted in a tripling of the analgesic effect and less than one-tenth increase in respiratory depression, which was within the range of standard deviation that's measured by inspired minute ventilation.

While respiratory rates were depressed on buprenorphine, the extent of depression was limited and similar at both doses. There was no change in entitled pCO2 levels at either dose. Another study published in 2005, Dahan compared the effect of buprenorphine on respiratory depression to the Schedule II opioid fentanyl in opioid-naïve
subjects.

He was able to show that subjects who received fentanyl had larger drops in ventilation, plus several developed respiratory instability and apnea. The subject at the highest dose of 7.1 micrograms per kilogram was immediately unblinded due to severe respiratory depression with apnea 8 minutes in duration and oxygen saturation of 68 percent.

The subject was instructed to take regular breaths and was given oxygen by face mask at 100 percent O2. After this event, the dose was no longer used in the study. These can be serious and life-threatening changes and we have already seen that fentanyl accounts for many ER visits and overdose deaths.

In contrast, buprenorphine subjects in this study had a smaller decrease in ventilation that plateaued even as they increased the IV dose above 8 micrograms per kilogram or greater than 560 micrograms in an average male.

While the subject experienced nausea, her
minute ventilation fell to 10, similar to that observed at one-half or one-quarter of that dose. This was not considered life threatening and there was no respiratory instability or apnea noted.

Again, this is consistent with lower rates of ER visits and overdose deaths for buprenorphine despite the fact that it is dispensed as a sublingual dose as large as 8-milligram tablets for medication-assisted therapy of opioid use disorder.

Currently, buprenorphine is extensively used in medication-assisted therapy for opioid use disorder. At doses of 2 to 24 milligrams per day in a variety of formulations including sublingual tablets and planted pellets and injectables. The majority of this treatment is done as outpatient, including the induction phase of MAT.

For 12 months ending in March 2017, there were 12.5 million prescriptions for buprenorphine products used in medication-assisted therapy. In the same period, there were 1 million buprenorphine prescriptions for chronic pain at much lower doses anywhere between 75 micrograms to 1.8 milligrams.
The only available formulation for acute pain of buprenorphine is an injectable at the dose of 300 to 600 micrograms per day and there were 1.4 million prescriptions in that period.

There is a need for more buprenorphine treatment options for acute pain. We need more Schedule III treatment options for the management of moderate to severe pain. And there are patients whose pain is not measured adequately or managed adequately by non-opioid alternatives and therefore are prescribed Schedule IIIs, which have a higher potential for abuse and physical dependence.

There are only two Schedule III options currently available for acute pain and they're not widely used because of their limitations. Buprenorphine is an excellent candidate for treating acute moderate to severe pain because of its unique properties, including a ceiling effect on serious life-threatening respiratory depression.

There is a clear need for non-parenteral formulations of buprenorphine for acute pain. I am
now pleased to introduce Dr. Dean Mariano, a pain specialist who will describe how sublingual buprenorphine spray meets these needs.

**Applicant Presentation - Dean Mariano**

**DR. MARIANO:** Thank you, Dr. Pergolizzi. I am Dean Mariano, senior director of clinical development and medical affairs at Insys. I'm an anesthesiologist, board certified in pain management as well as addiction medicine.

Until last year, I was in private practice, treating patients with pain and addiction disorders in West Harvard, Connecticut. I'm the immediate past president of the Connecticut Pain Society and the former chairman of the Connecticut State Medical Society's task force on opioids.

Insys developed buprenorphine sublingual spray to give patients a non-parenteral injectable buprenorphine option to treat acute pain around the clock for up to 7 days.

The goal is to develop a new Schedule III treatment option, a non-parenteral formulation for moderate to severe acute pain. By definition,
Schedule III opioid pain medications have lower risks of addiction, overdose, and death compared to the Schedule II opioids.

It's important in this context in the opioid epidemic. Buprenorphine sublingual spray was developed under the 505(b)(2) pathway. It meets the requirements for bioavailability compared to the reference compounds. The development program showed that the efficacy is similar to approved buprenorphine medications and the safety program revealed no new or unexpected events.

Buprenorphine is a unique agent and, in spite of its opioid status is not popular as a recreational drug of abuse. A study investigating the reasons for illicit buprenorphine use among untreated intravenous opioid addicts demonstrated that a majority, approximately 77 percent of respondents, reported using buprenorphine as self-medication to prevent opioid withdrawal rather than obtain a high.

Ten to 12 percent of the patients reported euphoria or pleasure as the reason for their misuse.
or abuse of buprenorphine. In Susan Comer's study, inherent dependent individuals, buprenorphine was the only drug that had increases in rings of I feel a "bad drug effect". It was not taken more than placebo.

Most important to this program, a new route of administration did not change the abuse potential. Insys conducted an eight-factor analysis for this product. The analysis demonstrated that buprenorphine sublingual spray had a low abuse potential similar to Buprenex and other Schedule III buprenorphine and buprenorphine-naloxone combination products.

Buprenorphine sublingual spray was developed for continuous use every hour for up to 7 days. The approach of dosing around the clock every 8 hours has advantages over PRN or as-needed dosing. Around-the-clock dosing is recommended when pain discontinues or present for at least 12 hours a day. It has the potential to improve adherence and pain relief and also tends to improve the patient's mood.
It is preferable for elderly patients, who may have more challenges with adherence to effective as-needed dosing. Around-the-clock dosing is also associated with greater compliance.

In contrast, as-needed dosing is more appropriate for breakthrough or intermittent pain. It requires the patient to stay on top of the pain and ensure dosing before the pain becomes severe and out of control.

If the patient waits too long, they are faced with a time lag with the onset of action and can end up with higher pain intensities. If patients are compliant with around-the-clock pain regimen, they should have continuous pain relief without overshooting or undershooting the targeted blood levels for analgesia.

Even if patients are compliant with optimal PRN dosing, they will still wait until they feel pain for each dose. This can result in blood levels that end up falling below target range prior to dosing and exceeded with each dose. If patients are not optimally compliant, they can have a worse
experience.

If patients wait too long between as-needed dosing, they can end up with a high pain intensity. In this example, the pain at the 12-hour time point is too high. As a result, the patient took an earlier additional dose outside the recommended dosing schedule to get the pain back under control.

This unintentional misuse can result in overdose and complications such as respiratory depression. The buprenorphine clinical development program supports around-the-clock dosing.

The clinical development program comprised 10 studies, 7 phase 1, 1 phase 2, and 2 phase 3 studies. The 7 PK studies thoroughly characterize the behavior in the product in healthy volunteers who wore naltrexone block.

The phase 2 and phase 3 studies demonstrate the safety and efficacy of the formulation. The PK studies supported dosing every 8 hours. The dosing provided levels in the desired range and did not exceed levels observed with the comparator compounds. The metabolite, norbuprenorphine, had a
lower level than the comparator, Subutex, 8 milligrams, sublingual tablets.

This is an expected and desired outcome. The sublingual spray reached study site by day 3. The Tmax was approximately 2 hours and the elimination half-life is up to 2 days for a parent and metabolite. It's important to keep in mind that this is not a PRN or as-needed therapy, but instead is an around-the-clock every-8-hour alternative that can be taken safely for up to 7 days. Plasma concentrations observed with a single dose provided predicted linear pharmacokinetics and exposures are dose proportional.

Buprenorphine is metabolized by the cytochrome P50 3A4 and does not inhibit or induce the isoenzymes at therapeutic levels. However, levels of buprenorphine can be affected by drugs that inhibit or induce the cytochrome 3A4, so they should be used with caution if co-administered with buprenorphine.

In addition to relying on the established efficacy of the reference compound, IV Buprenex,
the clinical program provided additional efficacy
data for the sublingual spray in 2 phase 3 studies,
026 and 062.

These studies demonstrated pain relief and
satisfaction with treatment in the post-
bunionectomy patient. Both phase 3 studies were of
similar design. They both assessed buprenorphine
sublingual spray versus placebo in the relief of
moderate to severe post-surgical pain with baseline
pain intensity scores of at least 4.

Each had a SPID 48 as the primary outcome
measure. The studies included men and women, 18 to
65, with an ASA physical status of P1 or P2, a body
weight of at least 45 kilograms, and no BMI more
than 40.

The key inclusion criteria were unstable
conditions, long QT syndrome, the use of certain
antiarrhythmic medications, the history of
intolerance of buprenorphine or opioid tolerance,
and the history of substance abuse or dependence.

In the 026 study, 40 patients were
randomized to 1 of 3 doses of sublingual
buprenorphine or matching placebo. The treatment pair was for 48 hours. The patients received blinded study drug 3 times a day. Patients were admitted to the study site on the morning of the scheduled surgery on day 0.

They remained at the site until post-op day 3 for a total of 3 nights at the study site. They return for a follow-up visit, days 5 through 9, after surgery. Baseline patient characteristics were well balanced across all arms.

As expected in bunionectomy, a majority of the patients were female. Approximately two-thirds were white, one-third were African-American, and the mean age was 45. Of the 40 patients randomized, 33 completed the study. The other 7 patients discontinued for adverse events or subject request.

Even though 7 patients discontinued and the overall enrollment was lower than planned, the study still showed a statistically significant effect favoring the sublingual buprenorphine spray. Buprenorphine sublingual spray resulted in
statistically significantly greater relief of pain compared to placebo on this BID 48 for the 0.5-milligram TID and the 1-milligram BID dose.

The 1-milligram TID dose did not achieve statistical significance. Doses above the 0.5-milligram TID dose were not more effective and were associated with 2 cases of discontinuation for somnolence, 1 with a decreased respiratory rate.

For this reason, the 0.5-milligram TID dose was selected as the highest dose for subsequent studies. Because the higher doses were associated with events of somnolence in decreased respiratory rate, the study was discontinued early. In spite of this, the 0.5-milligram TID dose still demonstrated statistically significant differences from placebo in substantial clinical benefit.

The subsequent pivotal trial, study 062, included this dose and evaluated lower doses using a similar design of the study 026. The pivotal trial, study 062, evaluated doses of 0.125, 0.25, and 0.5 milligrams TID against matching placebo. Aside from the differences in doses, the design was
identical to that used in study 062. Those studies had the same rules of rescue medication.

For breakthrough pain prior to administration of study drug, patients could receive oral ibuprofen. If ibuprofen was insufficient or not tolerated, they received parenteral ketorolac. After administration of the first dose of study drug, patients were encouraged to wait at least 1 hour before receiving the first dose of rescue medication.

If local block and supplemental analgesia was insufficient, the subject was discontinued. Patients who were not discontinued were evaluated for efficacy. Both studies had the same endpoints.

The primary efficacy endpoint was the summed pain intensity difference over 48 hours between buprenorphine sublingual spray and placebo. Statistical testing of the primary variable was done sequentially for each dose to preserve the overall alpha and there was no adjustment for multiplicity in the secondary endpoints.

Therefore, all secondary endpoints are
The secondary endpoints that directly support this BID 48 were SPID 4, 8, 24, the pain intensity difference at each time point, and the total pain relief or TOTPAR at 4, 8, 24, and 48.

Additional secondary endpoints further evaluated pain relief. The other secondary endpoints evaluated pain relief, time to pain relief as well as the use of rescue medication, the time to use of rescue medication, and finally the subject's global evaluation of study drug.

Baseline characteristics were balanced between all treatment arms. The demographics were similar to those observed in 026, both more women than men. A majority of the subjects were white with about one-quarter African-American. The mean age was 46. The baseline pain intensity was about 6.5 and the study had an overall 90 percent completion rate.

A total of 322 patients signed informed consent and were randomized. 298 patients or 92.5 percent completed the study. There was a low-rated discontinuation due to adverse events with 16
patients or 3.7 percent overall, half in the
highest dose. 9 patients withdrew for lack of
efficacy, mostly on the lowest dose or on placebo.

All the doses in the study demonstrated a
statistically significant difference from placebo
for the primary endpoint. For this BID 48, the
0.5-milligram group had the highest score and
achieved a p value of less than 0.001 versus
placebo.

The 0.25-milligram and 0.125-milligram doses
all showed, achieved statistically significant
differences from placebo and were virtually
indistinguishable from each other for this time
endpoint, with similar point estimates and
confidence intervals.

The secondary endpoints also demonstrated
benefit for all three doses. All the secondary
pain endpoints support the efficacy demonstrated by
the primary endpoint, this BID 48, which is
included in this forest plot for reference.

The secondary endpoints of SPID 4, 8, and 24
all favor buprenorphine sublingual spray and have
nominal p values of less than 0.05 for each dose comparison to placebo. Similarly, the total pain relief for 4, 8, 24, and 48 all favor buprenorphine sublingual spray and have nominal p values of less than 0.05 for each DoE comparison to placebo.

The magnitude of benefit was largely dose dependent, as was also reflected in the patient's global satisfaction scores. The majority of patients on buprenorphine sublingual spray rated their global evaluation was good, very good, or excellent with percentages increasing in a dose-dependent manner.

This endpoint conveys the patient's perception of overall clinical benefit. Another secondary endpoint assessed the onset of analgesia. Most patients on buprenorphine experienced the onset of analgesia within 90 minutes of their first dose, with half experience at onset within the first 45 minutes and one-third within the first 15 minutes.

It's important to keep in mind that patients will be on buprenorphine sublingual spray for up to
7 days and they will reach steady state by day 3. After the initial onset of analgesia, the time to meaningful pain relief occurred within the range expected with other opioid pain medications.

Time to meaningful pain relief was dose dependent with patients on the 0.5-milligram TID dose experienced as shortest durations to meaningful pain relief. Looking at the median values provides a snapshot of the results.

The median time to meaningful pain relief in the intended-at-treat population was dose dependent with the highest dose to the 0.5-milligram TID having the shortest time of 92 minutes and the lowest dose, the longest, at 166 minutes.

These results are similar to what is published for multiple other medications you use to treat acute pain. While there may be expectations that medications for acute pain will generally show meaningful pain relief within 1 hour, published data on approved therapies for acute pain mostly have reported times in excess of 90 minutes in bunionectomy studies with Tmax values as high as 3
hours.

All of these medications except Xartemis XR are indicated for as-needed use while Xartemis, like buprenorphine sublingual spray, is indicated for around-the-clock use.

There is some concern about the onset of action of buprenorphine sublingual spray. It's important to note that the indication is for use every 8 hours and not PRN, so the concern with time to meaningful pain relief will be primarily related to the first dose unlike PRN medications, where the onset of action could be an issue for every dose if patients are not taking it on a recommended interval dosing schedule.

So if there is a concern that patient with acute pain might take additional dose of an opioid pain medication if the onset of action is greater than 60 minutes, this would be a concern for a majority of the approved products that are routinely used to treat acute pain.

Further, with PRN dosing, this potential could apply not just to the first dose, but to
possibly every dose that the patient administers in an as-needed fashion. With the first dose in mind, we look closely at the first 2 hours of treatment.

We see the treatment hours begin to separate in terms of pain relief as early as 60 minutes. The separation begins between the treatment arms and continues to go over time through the first 4 hours. Looking through 12 hours, we see even greater separation with the impact of the second dose.

The mean SPID over the first 12 hours gives us a more granular look at the initial treatment period, showing that all doses have changes from baseline that increased through the first 12 hours with the addition of the second dose at the 8-hour time point, illustrating graphically that concerns about the onset of action would be primarily applied to the first dose.

Note that, in this graph, for the first 12 hours, the 0.125 and 0.25 doses are superimposed. Focusing them on the first 8 hours is also important to look at the use of rescue medication.
In the first 8 hours, there was an inverse dose relationship with regard to the use of ketorolac rescue medication, with the highest use on placebo and less with the increasing doses of buprenorphine sublingual spray.

Despite the higher rates of rescue on the placebo arm, there was still separation from placebo at the clinically important measure of at least 30 and 50 percent improvement in pain scores. At 8 hours, there was a consistent dose-response relationship with a higher percentage of patients achieving a 30 or 50 percent improvement in pain intensity.

Literature supports the clinical meaningfulness of a 30 percent improvement which correlates to a clinically relevant improvement in patients' global impression of change. This demonstrates that the pain reduction is associated with the first dose.

The clinical program demonstrates the efficacy of all 3 doses for the primary and secondary endpoints, with the highest dose showing
the greatest efficacy. The global evaluations show that a majority of patients in all 3 doses rated buprenorphine sublingual spray good or higher, reflecting the patient's perception of clinical benefit.

The complete rate of 92.5 percent also suggests the patients were satisfied with treatment. The safety of buprenorphine sublingual spray is consistent with established safety of approved buprenorphine products in other opioid pain medications. There were no new safety findings associated with the spray formulation.

The rates of nausea, vomiting, dizziness, and decreased oxygen saturation required further discussion and will be addressed in the safety section. Vomiting and respiratory depression will be further addressed in the risk management section. The exposure of the product is adequate to characterize the formulation.

Four-hundred and ninety subjects have been exposed to buprenorphine sublingual spray. The majorities were in the phase 2, 3 studies with 273
of the phase 3. Most of them participated in the pivotal trial, study 062.

The majority of patients received the highest proposed dose of 0.5 milligrams TID. 217 patients have been exposed to the 0.5-milligram TID dose. The exposure to the other two doses were 112 and 110 for the 0.125 and 0.25-milligram doses respectively.

A smaller number of patients were exposed to the higher and lower doses that are not being considered for further development, a preponderance of data for the 0.5-milligram dose which reflects the design of this clinical program.

All three studies included the 0.5-milligram TID dose. The two phase 3 studies were placebo-controlled, double-blinded, randomized trials. The early study was 026, which included higher doses of 1 milligram, both BID and TID. These higher doses were not tolerable, so the study terminated prior to full enrollment.

The 1-milligram doses were no longer pursued. In the subsequent trial, study 062, the
doses were 0.125, 0.25, in able to the 0.5-milligram all-TID dosing. After completion of studies 026 and 062, Study 111 was added to explore the potential for prophylactic antiemetic therapy for the reduction of vomiting and nausea.

The study also assessed the safety of the highest proposed dose for treatment of acute pain around the clock every 8 hours for up to 7 days. The only dose in the 111 study was a 0.5-milligram TID dose with an active comparator of standard opioid therapy.

These studies yielded data that support safety and tolerability of buprenorphine sublingual spray from several perspectives. To examine the most common adverse events, including dizziness, we looked at the pooled phase 3 studies, 026 and 062. Study 111 provided further insight into the vomiting and decrease oxygen saturations on its own and in comparison with study 062.

Study 111 also showed differences in the rate and severity of nausea and vomiting with prophylaxis. Finally, we used all three studies to
examine the events of decreased oxygen saturation and hypoxia.

Using the pooled data from the two phase 3 studies, 026 and 062, we see that the most notable adverse events are nausea, vomiting, and dizziness. It's important to keep in mind that these two studies did not allow prophylactic use of antiemetics and also limited the types and doses of antiemetics permitted.

While there were some events of nausea and vomiting, there were no events that were considered serious. Across all three studies, there were a total of three serious adverse events. There was one serious adverse event in each trial, all in the 0.5-milligram TID dose, 1 of atrial fibrillation in a 56-year-old woman with a history of cardiac disorder and rhythm abnormalities.

There was 1 case of angioedema in a 65-year-old woman after her last dose of study medication. This may have been an allergic reaction to Zofran that was treated in the emergency department and resolved.
Finally, the third patient had an incisional site hematoma. This was a 32-year-old woman who developed a hematoma 24 hours after discontinuing buprenorphine spray due to nausea and vomiting. The hematoma was treated and resolved the same day.

There was a low rate of discontinuation due to adverse events. Most of the events leading to discontinuation were GI events of nausea and vomiting. There were 6 events of hypoxia that led to discontinuation of buprenorphine sublingual spray in Study 111.

We thoroughly assessed events of nausea and vomiting and also examined the impact of prophylactic antiemetics. The analysis begins with the temporal relationship to treatment. A majority of events occur within the first 16 hours after initiation of study drug, suggesting that the first and second doses are associated with the highest number of events.

There were still some events at subsequent doses, but rates much lower by the third dose and down to 5 percent by the 5th. The rates may also
be a consequence of the limitations on the use of antiemetics.

In studies 026 and 062, the sites were not allowed to use prophylactic antiemetics in these surgical patients who were predominantly female and all had received general anesthesia. The only antiemetic was ondansetron. It was only allowed as an initial dose of 4 milligrams IV. It can only be followed by an additional 4-milligram dose.

The maximum dosing frequency allowed was every 4 hours and the maximum dose allowed was 8 milligrams. No other antiemetics were permitted, so patients who are not adequately managed by this protocol would have to be discontinued from the study.

The rules of antiemetics were very different in Study 111. Study 111 was a phase 2 randomized open-label safety and tolerability study of the 0.5-milligram TID dose compared to standard of care opioid therapy for the treatment of post-operative pain. The patient had undergone bunionectomy, breast augmentation, or abdominoplasty.
One-hundred patients were randomized to either buprenorphine sublingual spray, 0.5 milligrams TID, or 4 milligrams IV morphine q6 hours for the first 24 hours followed by immediate-release oral oxycodone, 10 milligrams, 3 times a day.

Patients received study medications for up to 7 days. The primary objective was to evaluate the safety and tolerability for up to 7 days. The secondary objective was to evaluate the impact of prophylactic use of antiemetics.

The treatment phase was divided into 2 sections. The first portion was inpatient for 72 hours. The second portion was outpatient for 4 days, for a total of 7 days. Patients had a follow-up visit between day 8 and 10 inclusive.

The study methodology allowed evaluation of the impact of prophylactic antiemetic treatment. Patients were stratified by their baseline risk of nausea and vomiting as well as by surgical procedure. All patients receive intravenous prophylactic antiemetic therapy, starting with
induction with dexamethasone, 10 milligrams,
followed by ondansetron, 8 milligrams, near the end
of surgery.

During the period between the end of the
surgery and prior to randomization of study drug,
patient could receive rescue analgesia in the form
of IV morphine and/or fentanyl dosed based on the
investigator's discretion.

Within 4 hours after completion of surgery,
patients were randomized and received their first
dose of study drug. After randomization, the rules
of rescue medication were different from those from
those from the prior study.

Rescue medication for pain during the
inpatient phase was oral acetaminophen, 1,000
milligrams every 6 hours, and/or ketorolac,
30 milligrams IV or IM every 6 to 8 hours as needed
with a maximum daily dose of 90 milligrams.
Outpatients were allowed only on oral
acetaminophen, 1,000 milligrams every 6 hours.

Rescue medication for nausea during the
inpatient period was only ondansetron, 4 milligram
IV, and outpatient was only ondansetron, 4 milligrams, orally disintegrating tablets. The randomization resulted in baseline characteristics that were very evenly balanced between arms.

As expected for these surgical patients, most of the subjects were female, the mean age was in the mid-30s, approximately one-third of subjects were African-American, and one-third were of Latino ethnicity. 85 percent of the patients were at high risk for post-op nausea and vomiting.

The Apfel scale classifies patients as low risk if their score is 0 to 2 and high risk if their scores are 3 and 4. The scores translate to the probability of post-op nausea and vomiting such that the high score of 4 translates to a 79 percent probability of an event.

Eighty-five percent of the patients in Study 111 were in the high-risk category. Additionally, Gan, et al. in 2014 found that another independent risk factor is age below 50. Most of the patients of Study 111 were also below the age of 50.

Despite the high risk of vomiting, the rate
and severity of the events were lower with prophylactic antiemetics compared to the prior studies. In contrast to the prior studies, in Study 111 there were no severe events of nausea or vomiting, plus the overall rate of vomiting declined.

The rates of nausea, vomiting, and hypoxia were higher on buprenorphine than those observed on morphine. As in the prior studies, the majority of events occurred within the first 16 hours after the first dose of study drug.

Twenty-eight percent of the patients experienced related events of vomiting within the first 16 hours after the first dose of study drug with the largest proportion, 20 percent, occurring within the first 8 hours.

The frequency and timing events compared favorably with the occurrence on the comparable 0.5-milligram TID arm of study 062, supporting the use of prophylactic antiemetics. Compared to study 062, both the rate and severity of vomiting events observed in Study 111 were lower. Also, there were
no severe events of nausea and vomiting in Study 111.

Study 111 showed that buprenorphine sublingual spray at the highest proposed dose of 0.5 milligrams TID was generally safe and well tolerated for up to 7 days. Compared to prior studies, the use of prophylactic antiemetics resulted in lower incidence and severity of events of vomiting as well as a lower severity of events of nausea.

The recommendation to initiate therapy in a medically supervised setting should assure that the administration of prophylactic antiemetics will occur and that medical personnel will be available to manage any events for the first 12 hours.

Adverse events of dizziness were also predominantly associated with the initial dose of buprenorphine sublingual spray. Dizziness was observed in all three studies. The highest proportion of events occurred in the first 8 hours after the first dose. In study 026 and 062, the rates as high as 42 percent for the 0.5-milligram
dose was in this time period.

However, the rates were substantially lower in subsequent time periods. Additionally, the rate observed in Study 111 was 6 percent, which was still limited to the first 8 hours of treatment.

There was no immediate explanation for this lower rate, but it's possible that the vomiting prophylaxis may have reduced not only the rate of vomiting, but also the rate of dizziness.

Because the majority of the events occurred within the first 8 hours of treatment, the recommendation of initiating in a medically supervised setting for the first 12 hours should assure appropriate management of this event.

Other events were also analyzed across the program as it related to reduced oxygen saturation. The studies had different definitions and thresholds for these events. Events were either defined as hypoxia or oxygen saturation decreased.

In 026, hypoxia was defined as oxygen saturation less than 90 percent of room air, oxygen saturation decrease defined as greater than 92
percent and less than or equal to 95 percent on room air in study 026.

In study 062, hypoxia was defined as oxygen saturation less than or equal to 92 percent on room air and oxygen saturation decrease was defined as less than or equal to 95 percent and greater than 92 percent on room air.

In Study 111, hypoxia defined as oxygen saturation less than 90 percent on room air. Oxygen saturation decrease was not defined or reported. The rates of these events varied across studies. The highest rates of events were observed in Study 111, most at a single site.

This may be due to part of the range of surgeries included. In addition to bunionectomy, Study 111 included patients who had undergone breast augmentation and abdominoplasty. Both of these procedures make breathing difficult and the rates were highest in these two groups.

That said, the rate of hypoxia in the bunionectomy population was 19 percent, still higher than observed in the larger 0 to 62 study,
which was 3.7 percent in the 0.5-milligram TID dose, while no patients in the smaller 026 study had events of hypoxia on the 0.5-milligram TID dose or on either of the higher doses.

For the patients who had reported events of hypoxia on buprenorphine, the lowest oxygen saturation reflected a wide range of pulse oximetry values. As expected, the lowest values were observed in Study 111, which had patients who had undergone and breast augmentation in addition to bunionectomy.

These two procedures had the potential to impair respiratory mechanics. The lowest values observed in Study 111 was 86 percent in a patient who had undergone abdominoplasty. 7 patients had values as low as 87 percent. 1 of these was in a bunionectomy patient. All the rest have undergone either breast augmentation or abdominoplasty.

In study 062, which only included bunionectomy surgery patients, the lowest value was 91 in 1 patient and now they have the lowest value of 92 percent. The other two had lowest values of
94 or 95 percent, so they actually did not qualify for the study definition of hypoxia, though the investigator still reported the adverse event.

Looking at all patients with an event reported in study 062, the oxygen saturation ranged from 89 to 95 percent in patients with events of decreased oxygen saturation and hypoxia. It's notable that the two lowest oxygen saturations, 89 and 90 percent, were not included on the prior slide as they occurred in patients with reports of decreased oxygen saturation, not hypoxia.

So this table is a more complete representation. It also shows that there were 4 events in the placebo patients in the 90 to 92 percent range. In Study 111, both arms had oxygen saturation less than or equal to 95 percent.

To look at reduced oxygen saturation more comprehensively, we assessed all patients for any oxygen saturation value at or below 95 percent regardless of any reported adverse event. The lowest values were observed on the buprenorphine arm in Study 111, with patients at 86 and 87
percent.

The lowest value observed on the morphine arm was 88 percent. The morphine had a total of 40 patients at or below 95 percent while the buprenorphine arm had a total of 39 patients. Buprenorphine sublingual spray was generally safe and well tolerated for up to 7 days.

Events of vomiting were lower in number and severity in the study with prophylactic antiemetic therapy compared to the prior studies. And there were no reports of dehydration in the study while there were observed in study 062.

There were oxygen saturations at or below 95 percent in all study arms. The lowest observed saturation on buprenorphine was 86 percent, the lowest observed on morphine at 88 percent. The rates of these events were consistent with those observed in most commonly used opiates in the outpatient setting.

No subjects on the proposed doses were part of naloxone. 2 patients at the higher dose of 1 milligram BID and 1 milligram TID doses that are
not recommended did require naloxone. No subjects at any dose required any resuscitative measures.

Now, I'd like to reintroduce Steve Sherman, who will present the risk management program.

**Applicant Presentation – Stephen Sherman**

MR. SHERMAN: Thank you. The risk management program for Buvaya is designed to address the established safety profile and risk associated with both Buvaya and opioids in general. The goals of the risk management program are to reduce and mitigate the risk of vomiting, mitigate the risk of respiratory depression, mitigate the risk of misuse, abuse, diversion, overdose, and death, and reduce the risk of unintentional exposure.

Vomiting is a known risk with opioids and has been identified as a risk with Buvaya. In the clinical development program, the highest rates of vomiting were generally associated with the first 2 doses and the rates were dose related.

The literature shows the opioid-naïve patients, women, patients under 50, and post-
surgical patients who receive opioids are at the highest risk of vomiting, which were exactly the types of subjects we enrolled in our safety and efficacy trials.

In Study 111, that included many patients who were at risk. Prophylactic antiemetic therapy was administered. There was a lower rate of vomiting reported than was reported in our previous study that did not use prophylactic antiemetic therapy.

Additionally, the severity of vomiting was reduced compared to prior studies with the use of prophylactic antiemetics. Thus, Insys will be recommending prophylactic antiemetic therapy. Education materials will be provided to both patients and providers to discuss the risk of vomiting. Similar to other opioids, the use of Buvaya can be associated with serious life-threatening or fatal respiratory depression, even when used as recommended.

The risks will be managed by administering the drug in a monitored setting and using the same
tools as those for other opioids such as the
prescribing information, a medication guide, and
the education of prescribers and patients as
described in the proposed REMS program.

The prescribing information and the
medication guide describe the risk of hypoxia
respiratory depression and guide prescribers and
patients on how to recognize and deal with
respiratory depression.

We are recommending that patients should
initiate Buvaya in a medically supervised setting.
The warning included in the box warning and the
medication guide prosed for Buvaya are presented on
this slide and are consistent with those approved
for other buprenorphine products and opioids in
general.

Additionally, the sponsor will provide
education for prescribers, healthcare providers,
and pharmacists on the management of this risk and,
more particularly, on patient education when
prescribed for outpatient use.

The sponsor is recommending the use of a
patient education tool that consists of a patient counseling document, which is intended for distribution to the patient with the prescription of the product or when the product is dismissed.

One of the tools Insys is proposing is the patient counseling document that you see here. It contains a quick guide on how to recognize and management of respiratory depression. The document will be tested for its literacy and comprehension prior to dissemination.

As previously stated, this document is intended to be taken home by the patient. Patients should initiate buprenorphine therapy in a medically supervised setting that will allow the healthcare provider to monitor the patient's respiratory status for the first 12 hours to determine if therapy with Buvaya can continue to be administered for up to a total of 7 days.

The duration of medical supervision will assure that the first 2 doses are administered appropriately without a risk of redosing. Patients may also receive supplemental analgesia in the form
of ketorolac or ibuprofen, as was demonstrated to be safe in our clinical trials.

Medical supervision will also ensure that patients receive anti-medicine for vomiting, prophylaxis to mitigate the risk of vomiting.

Insys will participate in the opioid analgesic REMS that is currently under development by the FDA.

Until that REMS program is available, our proposed REMS program will be designed to educate both physicians and patients on the risks associated with the use of Buvaya, starting with the recommending prophylactic antiemetic therapy.

The program will also reinforce the physicians to initiate therapy in a medically supervised setting for the first 12 hours. Insys will also educate physicians about prescribing the drug product to appropriate patients, the risk of misuse, abuse, diversion, addiction, the overdose, and the safe use, storage, and disposal of the product.

An additional factor to consider concerning abuse of the drug product is that, compared to
other currently available buprenorphine products, Buvaya contains a very small amount of buprenorphine.

Moreover, of the various opioids available, buprenorphine is not a drug that abusers use frequently to achieve a euphoric effect or get high. Insys is committed to reducing the risk of unintentional exposure. We have a storage system to assure safe disposal and patient education on the safe use, storage, and disposal of the product.

We are proposing a packaging and disposal system similar to our Schedule II fentanyl. Our proposed packaging is child resistant and requires scissors to open it. There are warnings in and on the packaging concerning the use of the product.

The proposed packaging and disposal configuration were demonstrated to be safe and effective for our fentanyl Schedule II product based on the data we collected during its development and more than 6 years of post-marketing experience.

Upon activation of the device, it delivers 1
dose of the product. Once actuated, the spray cannot be reused when less than 0.02 milliliters of the product remain in the vial. The vial is contained in a child-resistant secondary package. The unit dose spray device are packed in individually sealed child-resistant opaque blister packages that must be cut with scissors to remove the device for use.

The instructions for use direct the user to dispose of the use device by placing it in a single child-resistant disposal bag provided in the carton and sealing it. Once sealed, the package is again child resistant and requires scissors to access the use device. The efficacy of the proposed REMS program will be assessed and submitted to the FDA at post-approval month 6 and post-approval month 12 and annually thereafter. In case of identification of a pattern or diversion or any additional risk, we will work with the agency to appropriately mitigate them.

Insys will educate healthcare providers on the appropriate use of opioids and proper patient
selection. Additionally, providers will receive patient and caregiver education materials so that they can provide education to the patients as well. These materials will focus on adverse events associated with the use of Buvaya and the selection of appropriate patients as well as monitoring for possible misuse, abuse, and diversion.

Healthcare providers will be instructed to alert patients to potential adverse events, including vomiting and decreased oxygen saturation. They will also be instructed to educate patients on the safe use, storage, and disposal of the buprenorphine product.

The patient education materials will include a medication guide and the patient counseling document we discussed earlier. The medication guide will be tested for literacy and comprehension. Additionally, patients will receive additional education materials on the possible adverse events associated with opioids, including vomiting and decreased oxygen saturation.

They will also receive instructions on the
use of the spray device and for the safe use,

disposal of the information of the product and
information on the risk of abuse, misuse, and
diversion. Healthcare providers will use these
materials to educate patients on the safe use of
Buvaya.

Patients will also have access to the
product website and all patient education materials
will be provided there as well. The
pharmacovigilance program includes gathering
spontaneous reports of adverse events, reviewing
them, and reporting those assessments of serious
adverse events.

There will be a quarterly review of
aggregated spontaneous adverse event information,
monitoring for trends, and signals related to
Buvaya or the active moiety, including the review
of scientific literature to identify any safety
issues associated with buprenorphine.

Insys will also evaluate individual
spontaneous adverse event case assessments for
possible product quality issues that could impact
patient safety. Additionally, Insys has an employee training program that assures all spontaneous events are recorded and evaluated in a timely manner.

Insys will conduct post-marketing surveillance to assess the potential abuse, misuse, and diversion of Buvaya using established tracking programs such as IQ, IQVA, prescription data, and we will work with the RADARS reporting system to understand patterns of abuse.

Insys is committed to responsible sales and marketing of its products. We have implemented a rigorous compliance program for our marketed fentanyl spray. We will follow similar practices for Buvaya. We will monitor prescription patterns to identify suspicious office and develop a no-call list and monitor that.

We will monitor the supply chain by working with both retail and especially pharmacies and our warehouses to identify suspicious orders. We will obtain data to confirm drug shipped from the warehouse to pharmacies to ensure compliance with
the pharmacies' SOPs on suspicious orders.

We will train and monitor all external facing employees to identify any suspicious activities concerning our employees. And our field-based compensation is actually based on a number of different factors, but one of them includes compliance with all applicable laws and regulations as determined by field monitoring, both from internal and external sources.

Insys has developed a comprehensive risk management program that builds on its experience with our transmucosal or immediate-release fentanyl spray. To address the risk of nausea and vomiting, respiratory depression, and misuse of the product, Insys is recommending initiation of treatment in a monitoring setting for the first 12 hours.

To address the risk of nausea and vomiting specifically, Insys is also recommending prophylactic antiemetic therapy prior to dose. The program includes adherence to a product REMS, patient and healthcare provider education, special use, unit sprays, and child-resistant packaging.
that includes warnings on the packaging, a safe disposal system for disposing of used product, ongoing pharmacovigilance systems of adverse events, including events of vomiting and decreased oxygen saturation, surveillance for events of abuse, misuse, and diversion.

These proposals, we believe, effectively help to mitigate the risk associated with the use of Buvaya. And now, I'd like to reintroduce Dr. Pergolizzi to review benefit-risk.

** Applicant Presentation – Joseph Pergolizzi**

DR. PERGOLIZZI: Again, thank you very much. The benefit-risk assessment for buprenorphine sublingual spray is favorable. It fills an important unmet need for a Schedule III immediate-release medication for the management of acute moderate to severe pain.

Buprenorphine is a well-established clinical profile with an inherently lower abuse profile than other opioids and a safety profile that has a ceiling for respiratory depression. No golden analgesic bullet exists that works in 100 percent
of the patients 10 percent of the time without any side effects.

We need options. Buprenorphine sublingual spray could potentially fill an important gap in our acute pain management options by offering a lower schedule product to treat moderate to severe acute pain. This is no small accomplishment.

The only approved formulations of buprenorphine for acute pain is injectable Buprenex. While other buprenorphine formulations are available for the treatment of chronic pain or chronic treatment of opioid use disorder, this is the first easy-to-use option for the management of acute pain.

Buprenorphine sublingual spray is a reasonably safe and efficacious drug for the around-the-clock treatment of moderate to severe acute pain. The potential for abuse and physical dependence has been well characterized for buprenorphine.

Buprenorphine was initially classified as a C2 drug during its clinical development in the
1970s. In 1981, the parenteral form of buprenorphine, Buprenex IV/IM, was approved at a 0.3-milligram dose as a C2. Four years after real-world experience that showed a low rate of abuse and physical dependence, Buprenex IV/IM, 0.3 milligrams, was moved to a C5.

In the earlier years, again, it maintains C5. Then in the early 2000s, in anticipation of approval of higher doses of buprenorphine products like Subutex and suboxone for medication-assisted therapy at doses ranging from 2 milligrams to 24 milligrams a day.

The HHS conducted a vigorous review of numerous scientific studies and years of human experience, which included a review of higher doses used for the management of opioid addiction outside of the United States.

The DEA also conducted an independent, 8-factor analysis in accordance with Title 21 of the United States Code of Controlled substances Act, 21 U.S.C. 811(c), which concluded that buprenorphine products should be Schedule III.
It is important to look at buprenorphine sublingual spray in this context and acknowledge the dosing of 0.5 milligrams, which equates to an exposure of 0.24 milligrams based on absolute bioavailability. It should be noted that the sponsor conducted an independent 8-factor analysis in accordance with 21 U.S.C. 811(c) for buprenorphine sublingual spray that showed alignment with current DEA scheduling.

Buprenorphine possesses several characteristics that make it preferable to other opioids currently available. A spray is more convenient than an IV formulation, as it did not require IV access and does not require swallowing, which is important, particularly for patients with swallowing difficulties or those who cannot take medications orally.

The spray avoids the first pass effect that limits bioavailability of oral buprenorphine formulations. The molecule itself has inherent properties that make it favorable for the use for the treatment of pain.
It's a lower potential for abuse and physical dependence. And this seems to correlate with lower rates of abuse, as published by the RADARS system. It has a ceiling respiratory effect and, in my clinical impression, a lower rate of constipation than full mu opioid agonists.

This product is particularly well-suited for elderly, as it has no restrictions on age, dosing, or renal impairment and is not combined with acetaminophen.

It also has a minimal drug-to-drug exposure and interaction which may help patients who were on a rational polypharmacy.

The clinical trials demonstrated that buprenorphine sublingual spray has proven efficacy for pain relief, consistent with what was already known about Buprenex. The studies demonstrated statistically significant superiority over placebo for all three doses.

The secondary endpoints also supported the efficacy and, importantly, the majority of the patients rated their overall satisfaction with
treatment as good, very good, and excellent. And this was also reflected in the high rate of completion in the pivotal trials.

The spray was generally well tolerated and the rate of discontinuation for adverse events in the pivotal trial was 3.7 percent. This is important to keep in mind as we assess the impacts of adverse events.

While many patients experience nausea and vomiting, particularly with the first dose, by far the majority stayed on therapy. There were no new safety risks associated with the formulation or the route of administration.

But the product cures risks of the opioid class. And several of these risks were observed in the clinical trial. Of note, there were events of vomiting and reduced oxygen saturation.

While none of the patients on the proposed doses required positive pressure ventilation, naloxone, or resuscitation, there were patients who received oxygen by nasal canula.

The sponsor's inclusion of the
recommendation to initiate therapy in a medically supervised setting is intended to address and mitigate several of these risks. The 12-hour period covers the administration of the first 2 doses.

This approach can assure that patients receive vomiting prophylaxis and any necessary treatment as they begin therapy. It also enables the use of supplemental analgesics and mitigates the risk of misuse in the form of redosing for patients who may have a longer initial time to meaningful pain relief.

Finally, clinicians will be able to identify any early events of respiratory depression and determine whether or not patients should continue on therapy. There are no new product-specific risks identified in these trials and that is to be expected as buprenorphine is a well-characterized compound and there are no inherent risks associated with the spray formulations or the route of administration.

My assessment is that the benefit of this
drug outweigh the risks. The risks are well characterized and manageable. Importantly, buprenorphine has safety advantages over other opioids due to its partial mu agonism. This is a product that I am comfortable using in a wide range of patients, including elderly patients, those with renal impairment, patients on a polypharmacy, and those with swallowing difficulties.

I would even consider this as an option for patients who have a history of substance abuse or maybe a medication-assisted therapy that experience acute type of pain in, let's say, a trauma-type setting as well as for the potential that it has lower euphoric effects.

We know buprenorphine. It's well characterized and has established and well published safety and efficacy. The formulation represents an important step forward. The clinical program established the efficacy of all three doses as well as the overall satisfaction with treatment, both from the survey and reflected as low discontinuation rates.
Given the tremendous need for treatment options for acute pain that have a lower abuse profile, it is clear that the benefits outweigh the risk and that this represents an important new treatment option for patients suffering from moderate to severe pain. Thank you.

Clarifying Questions

DR. WINTERSTEIN: Are there any clarifying questions for Insys? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. First one is Dr. Litman?

DR. LITMAN: Can you come back to me? I'm just looking for the page where I had the questions. Thanks.

DR. WINTERSTEIN: No questions? Dr. Zacharoff?

DR. ZACHAROFF: Hi, Kevin Zacharoff. And, Ms. Sherman, since you're up there, I'll start with you. One of the things you mentioned in your introductory statements was the ceiling effect for respiratory depression and I'm wondering, since
there are many different phrases used along the
course of your presentations this morning, if
respiratory depression is intended to mean hypoxia
or a decreased respiratory rate, decreased O2
saturation, or what.

So I'm not 100 percent clear on what you
were referring to when you mentioned ceiling effect
for respiratory depression.

MR. SHERMAN: When I mentioned it, it was
for respiratory depression and I think, when
Dr. Pergolizzi and Dr. Mariano addressed it, they
talked about the ceiling effect that we saw in
Dahan's article.

Slide number 1, please; to me, this is what
we're discussing, the ceiling effect, where you see
a doubling of the dose, but you don't see an
increase in any respiratory depression.

DR. ZACHAROFF: Thank you. Next question is
for Dr. Pergolizzi. Dr. Pergolizzi, when we talk
about the clinical utility of this medication, but
yet we mention that it's possible for the first
dose, the onset of action can be as long as 90
minutes or even longer.

Is that a practical utility for treating in your mind acute post-operative pain?

DR. PERGOLIZZI: Thank you, Dr. Zacharoff. If we look at the other agents that have an immediate-release indication for the use of acute post-operative moderate to severe pain, we find that, particularly the .5 dose falls within common range for expectations.

It's not uncommon that, because of pain's individuality and personal aspects that we will have to use supplemental rescue medication in the real-world setting. And I think that was exemplified with the use of ketorolac in this particular case. Actually, in a recent review of a database, we saw that 79 percent of the individuals in an institutional setting will receive or be exposed to a perioperative dose of an injectable opioid analgesic.

Approximately 17 to 20 percent of those patients will get a rescue medication during that initial dosing of the medication as well. So
because of the individuality of pain and the real-world experience, it's not uncommon to have to give supplemental analgesia. And this also allows for a multi-mechanistic analgesic approach for these patients.

DR. ZACHAROFF: Also, Dr. Pergolizzi, in slide CC-25 and CC-26, you referenced respiratory response, analgesia, and I'm wondering what is the Y axis measuring in these slides.

DR. PERGOLIZZI: Yes. We looked here at pCO2. The response is not that you cannot have respiratory depression. What we find in Albert Dahan's study is that, by doubling the dose, you actually had a 3.5 increase in analgesia. And you did not have a linear decrease in the pCO2 levels.

So it leveled out, as opposed to what we'd see with a pure mu opioid agonist like fentanyl.

DR. ZACHAROFF: Then just a couple of questions for Dr. Mariano; Dr. Mariano, in study 026, am I correct in that those were bunionectomy patients?

DR. MARIANO: Yes, they were.
DR. ZACHAROFF: Is there anywhere where it was described what type of anesthetic the patient received in the determination of high-risk stratification for PONB?

DR. MARIANO: They all received the general anesthetic along with a sciatic block for the post-bunionectomy patient and standard anesthesia care and monitor setting.

DR. ZACHAROFF: In slide CC-47 that you presented, if we could just take a look at that slide, I'm wondering if decreased respiratory rate was used as the definition for respiratory depression as compared to increased PCO2 or decreased oxygen saturation?

DR. MARIANO: I do not have the information on that. This was actually identified in the ER as a decreased respiratory rate as part of the somnolence.

DR. ZACHAROFF: Lastly, when we talk about the utility of this medication for 7 days, in any of the studies presented, was there a rationale as to why 7 days? Were there any patients studied
where patients were administered this therapy beyond 7 days and, if they needed pain medication beyond 7 days, what were they given?

DR. MARIANO: Actually, the last study in Study 111, the safety study, was only up to 7 days, which we were looking to be in line with some of the legislative guidelines for some of the state legislation as being inactive. And about 26 of the states currently, where a majority of them are up to 7 days, some are at 3 days. Some are at 5 days for acute pain, post-operative setting, so we limit it to 7-day use without initiation it'll be reevaluated by the healthcare provider in conjunction with the legislation that's being proposed in multiple states.

DR. ZACHAROFF: During that 7 days, did the patient self-administer the medication or was it administered to them?

DR. MARIANO: Actually, in the inpatient period, it was administered to them. In the outpatient arena, when they were at home, day 4 through day 7, they did it themselves.
DR. ZACHAROFF: Thank you.

DR. WINTERSTEIN: Let's move on to Dr. Coffin.

DR. COFFIN: Phillip Coffin, and I'm going to follow up on that 7 days question. And this can be for any of the speakers. So post-operative pain can often be quite short or longer, but last exposure to opioids is probably optimal in terms of the data showing that longer exposure to opioids can oftentimes lead to higher rates of chronic use.

So how is the patient supposed to determine when to stop if this is an around-the-clock administration as opposed to a standard PRN?

DR. MARIANO: The reason for the around-the-clock use was to maintain even consistency of pain, education, and control during the period of the perioperative setting, when they needed the actual pain control with an opiate medication.

As pain decreases over time, as the surgical incisions heal and as the pain improves, especially as you saw in the post-bunionectomy patients, patients will then make the decisions that they
don't really require an opioid medication to manage your pain.

If it does decrease down to a mild to moderate, they should be then able to discontinue the use of an opioid and start another medication such as ibuprofen or an acetaminophen that is more indicated for a mild to moderate pain type scenario.

DR. COFFIN: Did that happen in these studies in terms of how long people actually took the medication?

MR. SHERMAN: Actually, I was going to point out that one of the reasons for continuation was the patients no longer needed analgesia, so yes. Some patients identified that, after 3 or 4 days, they no longer needed analgesic medications and they discontinued the trial.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you, Ron Litman. So Dr. Mariano, I have a question, please, about Study 111. So one of the most concerning things is the incidence of hypoxia compared to the morphine group
and you had mentioned in your presentation that you thought one of the reasons might have been because of the procedures, the abdominoplasty. Maybe the patients weren't taking deep enough breaths.

But I did have a couple questions about the methodology to try and tease it out a little bit that I wanted to ask about, so if you could bring up slide CC-81, please, I had a couple questions about this. So in point number 2, there was rescue before randomization, but what about after randomization? I'm trying to get an idea of why these patients that had received the Buvaya had so much more hypoxia in this study.

MR. SHERMAN: Dr. Mariano?

DR. MARIANO: As you stated, before randomization, they are allowed IV morphine and/or fentanyl based on the investigator's discretion. Once they were randomized, they were allowed only acetaminophen, 1,000 milligrams, q6 hours, and/or ketorolac in the inpatient setting. In the outpatient arena in 111, they were only allowed 1,000 milligrams of Tylenol every 6 hours for
rescue.

DR. LITMAN: So randomization occurred at what point?

DR. MARIANO: Four hours.

DR. LITMAN: Four hours post-op?

DR. MARIANO: After discontinuation of the block or 4 hours after the breast augmentation or abdominoplasty.

DR. LITMAN: So then what happens if patients had pain that was not responsive to the acetaminophen or the ketorolac?

DR. MARIANO: You mean before randomization?

DR. LITMAN: No, afterwards, when they weren't allowed a rescue medication.

DR. MARIANO: Well, they were allowed rescue after getting the first spray times 0. They were still allowed ibuprofen or ketorolac. If they weren't able to be tolerated on those, they were discontinued.

DR. LITMAN: So if they needed rescue medication, they were discontinued from the study?

DR. MARIANO: No, sir.
DR. LITMAN: So I'm missing that.

DR. MARIANO: I'm sorry. They were allowed rescue medications before randomization, either IV morphine or fentanyl. Once they received the buprenorphine supplemental spray times 0, that's when they were allowed rescue medication of either Tylenol and/or IV or IM ketorolac.

DR. LITMAN: Right. So my question is, I mean, those of us who have had surgery know that sometimes after the first few hours Tylenol and ketorolac are not sufficient. What were they rescued with then?

DR. MARIANO: Well, they also were receiving the buprenorphine supplement spray or they were also receiving the standard of care opioid therapy.

DR. LITMAN: Right. But if they were randomized to the Buvaya group, they weren't receiving any other opioids or they were?

DR. MARIANO: No.

DR. LITMAN: So to me, that clarifies it. So one of the reasons I wanted to make sure that they weren't having more hypoxia because they
weren't getting additional opioids, so they weren't --

DR. MARIANO: No. Once they went on either standard of care narcotic therapy or buprenorphine supplemental spray, they were only allowed the acetaminophen or ketorolac. The additional opioids was prior to randomization.

DR. LITMAN: So let's take a couple days later now. So they went home. They were monitored by pulse oximetry?

DR. MARIANO: No. They weren't at home.

DR. LITMAN: So how do you know who was hypoxic once they went home?

DR. MARIANO: Just like we looked at with people going home from surgery with standard PO medications as needed. We used in our risk mitigation the signs and symptoms of respiratory depression such as somnolence, confusion, blueness in lips. Can you pull up the slide with our mitigation strategy?

DR. LITMAN: Who monitored that on these patients at home?
DR. MARIANO: Well, the caregivers, the patients like we do when we actually prescribe medications to outpatients from surgery or in chronic pain.

DR. LITMAN: You also showed a slide that talked about the different levels of hypoxia, the oxygen saturations. I presume that, once a patient got below 90, they were aroused. Was that part of the protocol?

DR. MARIANO: Protocol varied between sites. We had a protocol for hypoxia where they were supposed to be set up, encouraged to take deep breaths, cough, do all these maneuvers, reposition in the pulse oximetry to make sure that you had a good way for them, assess them for sedation, respiratory rates, and then if need be, the study says automatically put 2 liters of O2 nasal canula down anybody who went below 90 percent.

DR. LITMAN: Below 90, so it makes sense that, once a patient starts downtrending, they're going to be aroused. And with an opioid, once you arouse them, that will come up. So it's no
surprise that you didn't find stats lower than 86, but what concerns me is, once they went home, you didn't really know that and that interventions weren't really implemented at home.

DR. MARIANO: Correct. Could I see slide 3, please? Some of the things, and even our mitigation for respiratory depression at home; how do they know to recognize respiratory depression? Shortness of breath, slow or shallow breathing. These were instructions given to patients on discharge to be monitored at home like we would in any outpatient clinic when we're prescribing opioids in an outpatient setting.

So we did instruct them to look for signs and symptoms and to seek emergency care if needed, if any of these things do occur.

DR. LITMAN: Thank you. One quick for Mr. Sherman, please. At the end of your presentation, you mentioned that Insys will monitor how well your REMS program is working. How do you do that?

MR. SHERMAN: We currently subscribe to RADARS. We also look for literature surveys. So
the RADARS looks at a myriad of different things on misuse, abuse, and diversion, ER visits for overdoses with our drug. So we were kind of plugged in. We also monitor -- I forget the name of the site which shows you. I don't go there very often, but our pharmacovigilance people do.

DR. LITMAN: Bluelight.

MR. SHERMAN: Bluelight, thank you, where they talk about drugs for abuse.

DR. LITMAN: Yes. We know on the committee we review it a lot.

MR. SHERMAN: Then you guys know. So we tried to find almost all ways that we know to monitor for misuse, abuse, and diversion.

DR. LITMAN: Thank you very much.

DR. WINTERSTEIN: I have a follow-up to Dr. Litman, I think, that fits very well in here. So slide 85, if you could bring that up one more time, please, from the sponsor. So just to clarify, so basically the standard opioid therapy is a post-op 4-milligram morphine dose at investigator discretion, provider discretion, and
then after 4 hours we are starting either the
buprenorphine regimen or an oxycodone regimen.
Right?

So what we are looking at here are reported
rates either in the inpatient or the outpatient
setting. And we see a roughly 3 times higher rate
of nausea, 4 times higher rate of vomiting, 4 times
higher rate of hypoxia, 2 times higher rate of
dizziness, 2 times higher rate of pruritis
somewhat.

So the hypoxia in here corresponds to the
same data that's reported in slide 94. There, we
also have the 6 to 26 percent, so since we have
here received oxygen, that's more the inpatient
data I would imagine.

So for all the other events, nausea and so
on, there was some type of diary for patients or
they reported what happened to them at home or how
exactly did that work? Can you quantify what
happened at home versus what happened in the
inpatient setting?

MR. SHERMAN: Number one, I wanted to
address your concern about what happened at home with respiratory depression. Actually, none of the patients discontinued due to respiratory depression or reduced oxygen saturation once they went home.

In the study itself, we monitor for AEs and bring patients in on regular visits.

DR. WINTERSTEIN: So basically, what we have here is probably the inpatient observation, but we have a roughly 4 times higher rate of hypoxia on that regimen compared to standard opioid regimen, which is the oxycodone regimen we are looking at. Is that correct?

MR. SHERMAN: That is correct.

DR. WINTERSTEIN: Then one follow-up question to the REMS question again because I think it fits logically well from a flow perspective. You said that, there, the first 12 hours should be monitored in an inpatient setting, so that is that an ETASU?

Are we talking about REMS where that would be a requirement, that the drug can only be initiated under inpatient monitoring or is that a
recommendation?

MR. SHERMAN: Well, that's a recommendation. We haven't really finalized our REMS because we'll be negotiating with the FDA for that. And so whether it's a requirement or recommendation, it's still open for negotiation.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: Michelle Ruha. I can ask Dr. Mariano. Actually, this follows pretty much directly what was just asked. You had mentioned monitoring for 12 hours. However, the episodes of hypoxia, I thought when I read the subject events with the patients who had hypoxia, that some of those episodes occurred well after 12 hours. Is that correct? Can you clarify how far out during observation the episodes of hypoxia were noted?

MR. SHERMAN: Dr. Mariano?

DR. MARIANO: Slide 2, please. As you see on slide 2, these are the phase 2 and phase 3 studies. A percentage of patients experience a hypoxia event from all doses. What we did see from that hypoxia is that they occurred within the first
11 hours the true definitions of the hypoxia cases in these studies.

So they were caught going to clinically supervise recommended period of monitoring for 12 hours. These are all events at all doses, including the standard opioid therapy.

DR. RUHA: So there were some episodes with onset if I can see that, like, over 50 hours?

DR. MARIANO: Correct. In those events, the clinical trials were mild to moderate and at no time were any patients at risk. Neither do they require naloxone on those doses or any resuscitative measures.

The true hypoxia was defined as less than 90. In our studies, we had some of our hypoxia events as low as equal to 92 percent in our 062 study.

DR. RUHA: The blue is Study 111, so it had to be less than 90 percent to be hypoxia. And even though we're saying no resuscitative measures, they did get oxygen and they got stimulation. Correct?

DR. MARIANO: Yes.
DR. WINTERSTEIN: Dr. Meisel?

DR. MEISEL: Thank you. I'm going to change gears just a little bit, a couple different kinds of questions. Bioavailability, I know there's only 36 patients in the bioavailability study, but did you at all attempt to differentiate people who have dry mouths, lots of saliva, different kinds of populations in terms of what actually gets absorbed versus swallowed?

MR. SHERMAN: Unfortunately, we did not. We just did normal, healthy volunteers.

DR. MEISEL: In terms of the disposal system that you've got, I know it copies the fentanyl model, but is there any end user testing? And it's an interesting model you put into this little envelope and so forth, but do people actually follow that? That seems interesting, but maybe difficult to follow and then also interested if you have any data on literacy and its impact on people's ability to follow through on those instructions.

MR. SHERMAN: When we developed SUBSYS, we
did do readability studies, could they read the
instructions, and could they follow them. And
we've got sufficient data to demonstrate to the
agency that they could follow the instructions and
could do so.

DR. MEISEL: But do they follow the
instructions?

MR. SHERMAN: I can't answer that
definitively, but according to all the monitoring
that we do, we haven't had reports of lots of
either used SUBSYS devices or unused SUBSYS devices
out in the general population.

DR. MEISEL: The product is formulated as a
single-dose sublingual thing or spray. Is there
any risk or have you assessed the risk of people
trying to divert it by cracking them open or
spring, instead of under the tongue into a beaker,
a bowl, a glass, or something, and then using that
for diversionary purposes?

MR. SHERMAN: We have not conducted that
study, but if you look at the amount that is in the
device total, it's .5 milligrams. They have to
have tools to take the device apart. And then to get the drug out of the glass vial in the container, they need a very small needle. And so there's a lot of other buprenorphine formulations available that have a lot more drug.

DR. MEISEL: Then lastly, you've referred several times to an 8-factor analysis about this particular spray and being a low abuse potential, but I haven't seen any data that showed the results or exactly what that was all about.

MR. SHERMAN: In the NDA, we submitted the 8-factor analysis and if you'll put up slide number 1, we looked at these factors. It's actual relative potential for abuse, and went through these 8 factors and found that, for the sublingual spray, it's not really different than other buprenorphine formulations.

DR. MEISEL: Then just to follow up briefly on that, if you go to slide 17, using this and there was also some data in the briefing book that referred to the same thing, that buprenorphine seems to be really low here, some of this may be --
and oxycodone is very high -- related to market share and availability.

In other words, there's less fentanyl being used out there. Therefore, there's less in this particular slide. And it compared to oxycodone. I mean, is this really more of a market share and availability slide as opposed to a risk slide?

MR. SHERMAN: Actually, no. If you look at the market share, the number of buprenorphine, the preponderance of the buprenorphine use is either buprenorphine or naloxone and then buprenorphine by itself for chronic pain.

So then as Dr. Pergolizzi mentioned in his presentation the number of prescriptions for buprenorphine and chronic pain was over a million, but we only have 2,200, 2,300 reports of misuse or abuse.

DR. WINTERSTEIN: There certainly is market share reflected here as well. Dr. Rich?

DR. RICH: Hi, Jody Rich. So I heard it mentioned this was easy to use and I look at this as fairly cumbersome to use because, I mean, it's
easy to spray, but requiring the 12 hours of monitoring and also the need to include an antiemetic.

I'm not a surgeon, but I suspect that this is probably going to be most likely used in the perioperative, postoperative setting, and I'm thinking about day surgeries, coming in for a bunionectomy.

Those people probably don't get normally watched for 12 hours post-op. And so I'm kind of a little concerned that, once it gets out there, people are going to go, well, we'll watch it for a few hours and then let them go rather than actually monitoring for 12 hours.

So perhaps you could comment on the likelihood that people will be watched.

MR. SHERMAN: Dr. Pergolizzi, I think, would be the most appropriate person to respond to you.

DR. PERGOLIZZI: Right. So it's not uncommon with patients that have 2 of the 4 Apfel risk factors, a woman who is being exposed to post-operative opioid therapy that they will receive,
routine prophylactic antiemetics.

This has been pretty well established in the 2000s, but it is a concern. And then the suggested monitoring by the sponsor really comes off as their experience in the institutional type of monitored setting. And at that point, you wouldn't be able to make any type of adjustments necessary, including not allowing the patient to have a second dose if it's inadequate or if they've had a severe type of adverse event related to it.

So it's an additional layering approach. Again, when you look at the number of surgeries done in the United States, I think it was about 40 million that were done in the hospital setting, so I think this is the population we'll be looking more towards, which is in alignment again with the reference listed drug, Buprenex. Thank you.

DR. RICH: The second thing, I'm a little concerned about is, it seems like you have a branch point. You're either going to go as buprenorphine or another opiate. You can't really use them both at the same time. Buprenorphine will block the
full agonist.

So it was mentioned that there was supplemental, that because of the slow onset, there will be supplemental pain management at the beginning, but I'm just worried about, you give someone a pure agonist opiate and then you give them the sublingual spray. Isn't that going to block the pure agonist opiate and make the pain management sort of complicated?

MR. SHERMAN: Dr. Pergolizzi?

DR. PERGOLIZZI: So in the clinical trials for the currently approved therapies for chronic pain with buprenorphine, if necessary, you can use both opioid and non-opioid analgesics for the use of supplemental analgesia or rescue medication, particularly during titrating those agents.

It has not been studied for this particular product. I think you can go to the literature and you'll see studies by Richard Langford and others that suggest in a perioperative period that, when patients are exposed to both fentanyl and buprenorphine, there actually was an additive
effect.

But again, this was not studied in this particular setting, so I would assume that you'll have similar labeling that partial mu opioid agonists have in their current label now. The same type of warnings and precautions would be applied here and, again, those that would align with the reference listed drug.

DR. RICH: So the other thing that I hadn't heard measured and similarly is precipitated opiate withdrawal. And you mentioned, Dr. Pergolizzi, that this might be useful in an emergency setting with somebody who has a history of addiction but is on therapy. I would be very concerned if somebody was on methadone, had an acute pain episode, and then got a dose of this, yet you would precipitate acute withdrawal. Perhaps you could comment on that.

DR. PERGOLIZZI: There are a couple questions that I'm always asked as an interested individual or subject matter expert. One is, what if a patient is on a buprenorphine product like a
transdermal buprenorphine patch and they get into a
car accident and they wind up in trauma or in the
emergency room and we're going to have to do
surgery.

What do you treat them with? Do you give a
pure opioid agonist? Will that be problematic?
Well, they need more than another patient.
Unfortunately, we don't have great studies.
There's one I can refer to out of Chile that looks
at orthopedic patients in that procedure.

So now, if we look at the reverse of that
and say, what if you're a chronic pain patient on
50 or more NSEs of morphine? Right? And you come
in and you get an acute exposure to buprenorphine.
I think, from the standpoint of buprenorphine, my
knowledge of buprenorphine is that the
pharmacodynamics of this unique what we call
atypical opioid are very much based on exposure
levels, so here in the United States, we have
exposure, approved exposure levels established in
chronic pain and acute pain anywhere between 75
micrograms up to 1.8 milligrams.
It's during that exposure level that buprenorphine, though it is a partial agonist by definition in comparison in a test tube to maybe morphine. Its pharmacodynamic activities have been described as a full agonist. Once we get beyond the 2-milligram dose, we start to have opioid substitution therapy and pharmacodynamics of the drug seem to change.

So I think, at the dosing that we're giving, the absolute bioavailability would be .24 milligrams' exposure of buprenorphine. And although there may be theoretical concerns, I think, from my personal criminal experience, it should not precipitate withdrawal in those patients.

Now, again, I would defer to the label of the reference listed drug when it comes to how ultimately if this drug is to be approved that will be given in the warnings and precautions. And I think the regulatory agencies will be very keen on this, as they have been with other buprenorphine products.
DR. RICH: Thank you.

DR. WINTERSTEIN: We will break. Sorry.

DR. RICH: Another question over here.

DR. WINTERSTEIN: I know we have way more people on the list who have questions, but we need to stick a little bit with the time scheduled. For the public speaking session, we don't have that many speakers scheduled, so we will be able to make up some time there and go back to questions for the sponsor.

So we will now take -- we have a list that stops with Dr. Flick, so there's still a number of people listed here, so everybody who has a question is on our sheet. We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any members of the audience.

We will resume at 10:30 and continue with the FDA presentations. And as I said, we will go back to the sponsor questions.

(Whereupon, at 10:16 a.m., a recess was
taken.)

DR. WINTERSTEIN: I think almost everybody's back. So we will now proceed with the FDA presentations.

FDA Presentation – Robert Levin

DR. LEVIN: Good morning. My name is Robert Levin. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products.

This morning, I will be talking about the Buvaya clinical development program, study 062, used to support efficacy, study 026, an efficacy study terminated early due to adverse events, the safety of Buvaya, where I will focus on the adverse events of nausea, vomiting, dizziness and hypoxia.

I'll also review results from Study 111 that allow prophylactic use of antiemetic drugs in a study comparing Buvaya to an opioid control. There is a large number of options for drugs that are used to manage acute pain. Some products carry a specific indication of acute pain. Some carry a broad indication that encompasses acute pain and some are used off label for acute pain.
For inpatient use, there are injectable formulations of opioid and NSAID moieties and acetaminophen. There are a wider variety of oral analgesic and NSAID drugs approved for oral use. In the inpatient setting, local anesthetics, usually in the form of a nerve block, are used as part of multimodal analgesia for acute pain.

Gabapentinoids are also used off label with other analgesics in the perioperative period. In the outpatient setting, the armamentarium is normally limited to oral analgesics, although suppository formulations for some analgesics exist.

As you have previously heard, Insys conducted 7 phase 1 studies in naloxone-blocked healthy volunteers. My presentation today will focus on the results of the 2 phase 3 placebo-controlled studies and the phase 2 safety study using an opioid comparator.

I will now discuss efficacy. The applicant has already told you about study 062 that was conducted to demonstrate efficacy of Buvaya in patients with post-operative pain after
bunionectomy. It was a randomized double-blind placebo-controlled study of 3 doses of Buvaya administered every 8 hours for 48 hours.

Study 026 which preceded this study used the same design, but higher doses and was terminated early due to adverse events after 40 patients were enrolled. As you heard, 2 subjects in this study on higher doses than currently proposed developed drowsiness and were administered naloxone.

The primary efficacy endpoint was the Sum of Pain Intensity Difference at 48 hours, referred to as the SPID 48. This represents the change in pain from baseline to each of several time points across 48 hours.

The SPID is similar to the concept of area under the curve. The primary efficacy analysis for the SPID 48 showed statistically significant differences for all 3 treatment groups relative to placebo with the largest treatment effect observed for the 0.5-milligram dose, shown in the box.

For the lower two doses, the treatment effect size is less than half the high dose. The
FDA statistician confirmed that the SPID 48 was statistically significant for all doses.

It is common to rely on a SPID analysis as a primary endpoint. However, it is possible to have a statistically significant SPID that does not represent efficacy over the entire treatment interval. Looking at pain curves can provide additional useful information on the efficacy at different time points.

This graph shows pain intensity scores by time point and treatment group. For the 0.5-milligram dose, the pain intensity curve, bottom line, separates from placebo, top line, throughout the entire 48-hour treatment period.

The lowest two-dose groups do not separate from placebo as clearly as the 0.5-milligram group across the full 48-hour time frame. This is especially noticeable for the 0.125-milligram dose, second line from top, at 8 hours, shown by the arrow, and suggest that the analgesic effect may not last the entire dosing interval for this dose.

Although most of the secondary endpoints
support the primary endpoint, I will now review certain secondary endpoints of special interest. In assessing the onset of analgesia, we do not use sum of pain intensity to determine onset because small differences may not be meaningful to patients.

Rather, we ask the patients when they are failing the analgesic effects of the medication. We prefer to use time to meaningful pain relief which was measured by the double-stopwatch method. Each subject was instructed to stop the first stopwatch when he or she experienced any perceptible pain relief and the second stopwatch when he or she experienced pain relief that was meaningful to them.

Time to meaningful pain relief is summarized in this table. The analyses indicate a long latency to meaningful benefit with a medium time, shown in the second box from the top, of over 2.5 hours for subjects in the 0.125-milligram dose group, over 2 hours for subjects in the 0.25-milligram dose group, and about 1.5 hours for
subjects in the highest dose group.

Also, less than 50 percent of patients treated with the two lower doses stopped the second stopwatch before the next dose of study drug for the use of rescue, shown in the top box. Even for the high-dose group, more than one-third of patients did not experience meaningful pain relief.

This table provides historical controls for the time to meaningful analgesia for other opioids. To construct the table, we searched the database for all drugs approved for acute pain since 2000. Then we limited the list to opioids whose development programs included studies in acute pain patients, usually bunionectomy.

Not all opioids approved for acute pain had studies relevant for inclusion into the table. We limited our table to the pivotal trials for approved drugs because we have validated those data and to protect confidentiality for unapproved drugs.

The time to meaningful pain relief for Buvaya is shown in the bold font for the different
doses. The medians are at the high end of the historical controls. Use of rescue medication is displayed in this table. The top box shows the number of subjects using rescue medication by treatment group.

Nearly the same number of patients treated with the two lower doses of Buvaya, 88 percent, required rescue compared to patients treated with placebo, 98 percent, although active groups used fewer doses of rescue.

The mean number of doses used is shown in the middle box and was 3.9 for the 0.125-milligram dose and 3.7 for the 0.25-milligram dose compared to 5.6 for placebo. For the 0.5-milligram dose, 56 percent of subjects used rescue medication and the mean number of doses was 2.9.

Time to first use of rescue medication, shown in the bottom box, was greater for the Buvaya groups compared to placebo, but the difference was most noticeable for the highest dose with the median time of 937 minutes, over 15 hours, compared to 220 minutes for the 0.25-milligram dose and 193
minutes for the 0.125-milligram dose.

For placebo, the median time to the first
dose of rescue medication was 107 minutes. I will
now review the safety findings and provide a brief
review of Study 111.

To better understand the safety of Buvaya, I
will discuss the importance of Study 111 and also
reluctantly have included historical control data.
Historical controls are problematic for multiple
reasons, including potential dissimilarity of
patient populations, treatment paradigms at the
time a given study was conducted, differences in
outcome measures, and biologic variability.

We also acknowledge there may be other data
in the literature that support a wider range of
values. As I will cover in my presentation, we
think that Buvaya may have unusually high rates of
certain opioid-related adverse events, specifically
nausea, vomiting, dizziness, and hypoxia.

The applicant has mostly submitted placebo-
controlled data that does not aid in the
interpretation of class risks. However,
fortunately, there are some direct head-to-head
data comparing the safety of Buvaya to what the
applicant defined as standard opioid therapy in
Study 111.

While the applicant chose to conduct the
study open label, these data provide the only valid
comparative data for the opioid class risks. The
applicant defined standard opioid therapy as
morphine 4 milligrams IV for 3 doses, followed by
immediate-release oxycodone, 10 milligrams by mL, 3
times a day.

It is unclear whether the 2 dose groups were
comparable for efficacy since the applicant did not
collect efficacy data. Rates of nausea and
vomiting were confounded by the use of prophylactic
antiemetics administered in the perioperative
period.

Exposures to study drug for the Buvaya
development program totaled 490 subjects, of which
223 were in phase 2 and 3 studies. There were no
deaths or SAEs that appeared to be related to
Buvaya. Other findings were consistent with the

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opioid class. There were discontinuations of study drug due to nausea, vomiting, and hypoxia.

There were no major safety findings of adverse events that were unexpected with opioids. In the phase 2 and 3 studies, the most common adverse events that resulted in discontinuing Buvaya were nausea and vomiting. In the standard narcotic therapy group, only 1 subject discontinued due to nausea.

I will now discuss adverse events known to occur with opioids, but which appear to be more frequent than expected. The top table shows the incidence of nausea and vomiting in the combined phase 3 studies.

Both nausea and vomiting appear to be dose dependent with a range for nausea of 44 percent for the 0.125-milligram dose at 83 percent for the 0.5-milligram dose. The higher doses were only studied in the terminated phase 3 study and are not being proposed for use.

Vomiting ranged from 29 percent to 72 percent for the 0.125- to 0.5-milligram doses. For
Study 111, which allowed the prophylactic use of antiemetics, the rates of nausea and vomiting were shown in the bottom table.

Nausea for the 0.5-milligram dose was 78 percent and vomiting at 52 percent, although less than seen in the phase 3 studies, the rates of nausea was still double the rate for standard narcotic therapy and the rate of vomiting was fourfold higher than the standard narcotic therapy.

Antiemetic drugs were permitted in all studies and perioperative antiemetics were administered prophylactically in Study 111. Throughout the program, not only was the rate of nausea and vomiting higher in the Buvaya treatment groups, but the proportion of subjects using rescue antiemetics was such higher.

This table shows the use of antiemetics by study and the maximum number of doses used by an individual. In study 062, the rate ranged from 21 percent for the 0.125-milligram dose to 68 percent for the 0.5-milligram dose.

In Study 111, shown in the bottom two rows,
74 percent of subjects on Buvaya used rescue antiemetics compared to 24 percent in the standard narcotic therapy group.

I have described earlier the limitations of using historical controls and how products were selected for inclusion into these tables. This table provides historical controls for the rates of nausea compared to other opioid in the single concurrent control Study 111, with the results of this study shown in the boxes.

The rates for patients treated with Buvaya are in bold font. The data indicates that the rates of nausea in general are consistently higher for Buvaya than the concurrent control and most historical controls.

This table is similar to the previous table, but provides historical controls for the rates of vomiting. The data indicates that the rates of vomiting in general are higher for Buvaya than other opioids, even when prophylactic antiemetics are used. In Study 111, shown in the boxes, prophylactic antiemetics decreased the rate of
vomiting for Buvaya, but it was still over 50 percent and over 4 times greater than the morphine oxycodone control used in the same study.

This table from the background package shows the rates of nausea and vomiting and pharmacokinetic parameters for approved buprenorphine drugs. The table shows that Buvaya has the highest rate of nausea and vomiting. It should be noted that interpretation of the data is limited due to cross-study comparisons.

However, overall, the PK data do not appear to explain the adverse event profile of Buvaya. I do note an error in the FDA background package for this table. The AUC for Butrans is 27, not 2.7.

The top table shows the rates of dizziness in the phase 2. In the 2 phase 3 studies combined, the incidence appears to be dose dependent from 0.125 to 0.5-milligram doses. The bottom table shows the rates of dizziness in Study 111 and, although the overall incidence of dizziness for the 0.5-milligram dose is less than in the phase 3 studies, the rate of 22 percent is twice that of
the standard narcotic therapy group.

This table provides historical controls for the rates of dizziness for other opioids. The Buvaya rates are shown in bold font. This table shows dizziness appears to be more frequent with Buvaya than other opioids.

Respiratory depression is a well-recognized risk of the opioid class of drugs. However, adverse events of hypoxia were observed much more frequently with Buvaya compared to standard narcotic therapy in Study 111.

In the Buvaya group, hypoxia was reported in 28 percent of patients, more than 4 times the rate in the standard narcotic therapy group. As you can see from this table, the likelihood of developing hypoxia in the Buvaya group appeared to be related to the type of surgery with abdominoplasty resulting in 39 percent of subjects developing hypoxia, compared to no subjects in the standard narcotic therapy group.

In Study 111, 12 percent of subjects in the Buvaya group discontinued study drug due to hypoxia.
compared to 4 percent in the standard narcotic
treatment group. In the phase 2 and 3 studies,
there were no serious adverse events of hypoxia.
The 2 subjects on higher doses, the 0.5 milligrams,
required naloxone. The rate of hypoxia in study
062 for the 0.5-milligram dose was under 4 percent
for Buvaya. No placebo subject in this group
reported having hypoxia.

In the following three slides, I have
summarized the efficacy and safety for each of the
three doses. Most notable, for the 0.5-milligram
dose is the high incidence of adverse events,
especially nausea and vomiting, with rates of
vomiting as high as 72 percent.

Rates of dizziness and hypoxia also appeared
higher than the narcotic comparator used in Study
111. For the 0.25-milligram dose, the treatment
effect size is less than half the high dose. The
median time to meaningful pain relief is over 2
hours.

The rates of nausea and vomiting are less
than with the highest dose, but vomiting still
occurred in over 40 percent of subjects. The
results of the 0.125-milligram dose were similar to
the mid-dose with the rates of opioid-related
events being slightly lower.

I would now like to summarize our findings.
Buvaya met the standard for efficacy for the
primary endpoint and most relevant secondaries.
However, it has a long latency to meaningful
analgesia and the lower doses had high rates of
rescue use. The adverse event profile is notable
for high rates of nausea, vomiting, dizziness, and
hypoxia compared to pertinent concurrent and
historical controls.

This concludes my presentation. Thank you.

FDA Presentation – Cynthia Kornegay

DR. KORNEGAY: Good morning. My name is
Cynthia Kornegay and I am an epidemiologist in the
Office of Surveillance and Epidemiology. I am
going to spend the next few minutes describing two
analyses my office completed to support this
advisory committee meeting, a drug utilization
analysis and an epidemiological assessment of
abuse-related issues for buprenorphine.

First, I will describe the impetus behind and the scope of these analyses. I will then present the drug utilization results, which will help provide context for the subsequent epidemiologic assessment.

At the request of FDA, the National Academies of Sciences, Engineering, and Medicine examined the state of the science for prescription opioid misuse and abuse and reassessed the agency's approach to the opioid approval process.

The report outlines a wider framework for considerations, including assessing the potential for diversion and misuse, the potential risks to family members and society, and the potential effects on the abuse of opioids or other illicit drugs.

We reviewed the epidemiologic data on buprenorphine within this framework with attention to the novel dose form and lack of a mechanism intended to deter abuse. The purpose of the drug utilization analysis is to provide context for the
issues being discussed.

There are currently 3 buprenorphine products on the market indicated for the treatment of pain. First is Butrans or the buprenorphine transdermal delivery system. I will refer to this as BTDS. Second is BELBUCA, a buccal film approved in 2015. Third is Buprenex, an injectable buprenorphine product.

Buprenex is not often used in the outpatient setting and will not be included in this analysis. While there are many epidemiologic studies that focus on the use of buprenorphine and opioid use disorder for medication-assisted therapy or MAT, they were not the focus of this inquiry.

This is because buprenorphine products for analgesia have a lower dosage range than those indicated for MAT and abuse rates and patterns in higher-risk MAT populations may be different compared to the rates of patients receiving analgesic buprenorphine.

So the drug utilization analysis results -- this figure shows the estimated number of
prescriptions dispensed for buprenorphine products, stratified by labeled indications from outpatient retail pharmacies. Of the total buprenorphine products examined during the time period, about 5 percent of dispensed prescriptions were for products indicated for pain management, while the majority of prescriptions dispensed were for products indicated for the treatment of opioid dependence.

Focusing on the buprenorphine incident for pain management, dispensed prescriptions increased from 500,000 in 2013 to 700,000 prescriptions in 2017.

Using an office-based physician survey data source, this figure provides the nationally estimated number of times buprenorphine products were mentioned during an office visit. The word mention indicates that, while buprenorphine was discussed during an office visit, it did not necessarily result in a prescription being written.

In 2017 of the buprenorphine products indicated for the treatment of opioid dependence,
the majority of diagnoses were associated with opioid-related disorders, with approximately 93 percent of drug use mentions, followed by a diagnosis associated with pain at approximately 5 percent.

Using the same data source, this figure shows, of the buprenorphine products indicated for pain management, the majority of mentions were associated with various pain diagnoses at approximately 57 percent of drug use mentions, followed by various opioid-related disease diagnoses at approximately 34 percent.

The following limitations should be kept in mind for the drug utilization analysis. Only outpatient utilization was assessed. No inpatient or mail order data were included. However, this setting accounted for the majority of utilization. Diagnoses data are not linked to dispensed prescription data. Rather, the data presented were mentions of a drug at a physician visit based on a survey of a sample of physicians.

As the diagnosis data were derived from
surveys of office-based physicians, they may not have captured prescribing patterns of physicians who practiced in other settings where buprenorphine may be prescribed such as opioid treatment clinics, pain clinics, and hospitals.

Next, I will describe the epidemiologic assessment. In considering the public health impact of Buvaya, we realized that there were some gaps in our knowledge that, if addressed, might be helpful in understanding the potential for misuse and abuse associated with this product.

The first question related to the dosage form. If we could find literature on how other opioid spray formulations were misused or abused, it might provide insight into what could be expected for this product.

The second question concerned the lack of a mechanism intended to deter abuse. If we knew the extent to which naloxone decreased buprenorphine abuse, that knowledge might help us predict if or how much the absence of naloxone might affect the potential for Buvaya misuse or abuse.
As buprenorphine is already a scheduled opioid, we were aware that it is abused and that injection abuse is a particular concern. However, since the majority of the use in the literature on the abuse focus on buprenorphine MAT products, we sought information on misuse and abuse and particularly injection abuse of buprenorphine analgesic products.

Finally, we wanted to know more about off-label use of buprenorphine products because, if it is substantial, that could increase the availability of and risk of buprenorphine misuse in the community. We were also interested in what patient characteristics might lead providers to preferentially prescribe analgesic buprenorphine instead of other opioids.

A brief word on the methods we used in this assessment -- our primary source of information was a PubMed search for the epidemiologic studies that included analgesic buprenorphine products. Because the field of prescription abuse research changes rapidly, we chose the time period of 2012 to 2018.
Clinical trials and studies that included buprenorphine for MAT exclusively were excluded. However, epidemiologic investigations that included both buprenorphine analgesic and MAT products were included if they addressed one of the questions that we considered.

We also searched the American Association of Poison Control Centers National Poison Data System for Butrans and BELBUCA misuse and misuse and abuse calls to assess the prevalence of abuse in a diverse geographic sample because it is not possible to determine the route of abuse for a single drug.

When multiple substances are listed in a call, only single-substance exposures were categorized when examining the route of exposure.

The literature was very limited with regards to the abuse of opioid sprays. We found a single abstract that examined the misuse of Instanyl, an intranasal fentanyl spray in France. Unfortunately, this was a small study in a non-U.S. population. And there could be important
differences in how the product was used in France versus the U.S.

The definitions of misuse and abuse were unique to the study and there was insufficient detail provided to draw conclusions about the abuse of transmucosal spray delivery systems in general.

We also felt it was important to assess the impact of naloxone on reducing the risk of abuse associated with buprenorphine. This is not an easy question to address since the population that receives buprenorphine combination MAT products likely differs in the risk, patterns, and routes of abuse compared to patients receiving analgesic buprenorphine products.

In a prior review of this question, FDA did not find a clear preference for either single-ingredient or combination buprenorphine formulations, which was also the case in two subsequent studies, both of which used the researched abuse, diversion, and addiction-related surveillance or RADARS surveillance systems.

Of note, while there was not a preference
for single or combination products, the investigations did indicate that the tablet dosage forms had higher abuse rates compared to the film forms.

A third question explored rates of abuse associated with BTDS and BELBUCA. Although they differ in dose and form compared to Buvaya, addressing this issue may provide some insights into how this product could be misused or abused.

Two investigations, one in NPDS and one in RADARS, found that transdermal buprenorphine had a generally lower abuse rate compared to other buprenorphine dosage forms or other opioids. We did not find any studies on BELBUCA misuse or abuse, which is likely due to its recent entry into the U.S. market.

The NPDS study period was between July 2012 and June 2014. When we looked at U.S. Poison Center data between January 2015 and March 2018, we found a total of 25 misuse and abuse calls for BTDS and 6 were BELBUCA. Injection buprenorphine abuse is a widely recognized issue, although it is mostly
associated with products for MAT.

We found 3 studies that included BTDS in their analyses, but the results were not consistent on whether the injection abuse rates for BTDS were different from other buprenorphine dosage forms or other opioids. The U.S. Poison Center data did not capture any calls that mentioned injection abuse of either BTDS or BELBUCA.

Finally, we looked at off-label use of buprenorphine, particularly the use of buprenorphine MAT products. Although the buprenorphine analgesic products have different characteristics than the MAT products, we still believed that exploring this issue could provide some insight into the potential for off-label use of analgesic buprenorphine.

We found studies investigating the use of buprenorphine MAT products in patients with complex chronic pain regimens, depression and related psychiatric issues, and/or suspected substance abuse.

Very often, patient populations fell into
multiple categories, even if they were not specifically included on that criteria. In terms of patient characteristics associated with buprenorphine analgesic prescribing. The patients were opioid experienced with suspected or confirmed substance abuse disorders.

While the data we reviewed have fairly wide geographic coverage and provides some useful information on abuse and misuse of buprenorphine, post-marketing abuse data have many limitations, including that abuse can be difficult to measure, particularly for low-volume products.

None of the U.S. data sources can provide national abuse prevalence estimates for these products. Products may be misidentified in self-reported data and it is unclear how well abuse patterns for marketed products informed potential abuse of new market entrants with different dose and delivery systems.

In conclusion, use of utilization of buprenorphine products for both pain management and opioid dependence has increased in the past five
years. In the overall buprenorphine market, the majority of dispensed prescriptions were for buprenorphine products labeled for the treatment of opioid dependence.

Buprenorphine analgesic products represented only 5 percent of the dispensed products throughout the entire study period. While there is a sizeable literature on buprenorphine MAT products, there is less on the abuse of analgesic buprenorphine. While BTDS is abused, the rates are generally lower compared to buprenorphine MAT products and other opioid analgesics.

Finally, the base study populations were rather difficult to find and may not reflect abuse patterns in the broader population. Overall, the epidemiologic data provides very limited insight into the risks of misuse or abuse associated with buprenorphine sublingual spray compared to other buprenorphine products or other opioid analgesics.

Finally, I would like to acknowledge my colleague Jennie Wong, who provided the drug utilization data for this analysis. Thank you.
Clarifying Questions

DR. WINTERSTEIN: Thank you. So we start now with questions to the FDA and then, depending on time, we go back to the question for the sponsor as well, so are there questions for the FDA or the speaker? Please remember to state your name for the record before you speak.

If you can, please direct questions to a specific presenter. We start with Dr. Zacharoff.

You're establishing a pattern here.

DR. ZACHAROFF: Thank you. Kevin Zacharoff. This question is for Dr. Levin with respect to slide number 27, where you discussed the rate of nausea and vomiting based on surgical procedure type in standard analgesic therapy with narcotics versus study drug. Hypoxia, yes. I just want to make note, in the situations with standard narcotic therapy and breast augmentation and abdominoplasty, there was no difference in treatment with respect to oxygen administration or methodologies to prevent hypoxia in the standard narcotic group to your knowledge as compared to the study group?
DR. LEVIN: I'm not aware of that. I believe they were treated the same.

DR. ZACHAROFF: Thank you.

DR. WINTERSTEIN: Dr. Dasgupta?

DR. DASGUPTA: Thank you. Dr. Kornegay, two questions for you -- so first is, did you consider any abuse data for Stadol butorphanol nasal spray in your lit review? And was there any findings from that or was there a reason to not include that in the comparison?

DR. KORNEGAY: I did look for any type of abuse related to nasal sprays or nasal opioid sprays. I could not find any articles that specifically address butorphanol abuse and, when I looked at the aggregated data, the rates were so low that it was included with the other opioids and there was no way to disentangle that.

DR. DASGUPTA: Great. Thank you. And the second question is, we heard from the sponsor this morning that the non-medical use of abuse of buprenorphine is largely related to people self-medicating for withdrawal and addiction and
addiction scenarios. That's not been my experience from looking at the surveillance data.

Did you see any in your review any indication how true that statement was?

DR. KORNEGAY: I did not find that in my review, either.

DR. HERTZ: I would like to address that. This is Sharon Hertz. This is something we follow in our division pretty closely, because we have the buprenorphine products that are used for pain management as well as to manage opioid dependence.

We're aware that that's a belief among some, but we don't have data to support that. In fact, there are data to the contrary that affirm the use of buprenorphine for its euphoric effects. A simple review article, 2011, by Yokel, et al, describes that.

To this point, in comparing the abuse of the products approved for MAT, it's important to recognize that most of the sublingual products are formulated in combination with naloxone because of problems with abuse for the euphoric effects. And
whether or not that's effective is another discussion, but it's worth noting.

DR. WINTERSTEIN: Thank you. Dr. Beyrer?

DR. BEYRER: Thank you. This is a question for Dr. Levin. I wonder if you could share with us if you have more details on historical controls because, particularly relating to both hypoxia and dizziness in these rather high rates in the sublingual buprenorphine compared to the historical controls, the question I have is really in light of the issue of the potential utility of these as the sponsor has put forward for elderly populations.

The median age, at least in this study, on the buprenorphine side is not elderly. It's very much middle age. So do we have an age breakdown in those historical controls? Does that shed any light on potential adverse events?

DR. LEVIN: No, I don't have any age information related to those rates.

DR. MARIANO: Then I have a different question for Dr. Kornegay, which is just, following on these questions, my understanding is that
there's more data from some international settings, where buprenorphine is widely used, like, India and France, so this is really more of a process question for you in terms of the epidemiology, which is really how much do international studies inform that kind of search. Is it limited to U.S. populations?

DR. KORNEGAY: So I did not limit the specific search to the U.S. I actually started with international. The biggest limitation came with trying to specifically target buprenorphine analgesic products.

Most of the international literature actually had to do with MAT products. And so it told its own story, but it was a very limited use in this specific setting.

DR. WINTERSTEIN: Dr. Flick?

DR. FLICK: Dr. Levin. I apologize. I may have missed this, but on slide 8, pain intensity scores by time point, can you tell me at what point or whether the .5 dose differs from placebo across the time range? I don't see that there and I don't
recall hearing it. Is there a significant
difference in pain intensity scores between the .5
dose and placebo across that time range?

DR. LEVIN: The two curves clearly show
their separation is greater for those two doses.
There was, like, a SPID 8, and a SPID 24, and a
SPID 48. And they were all statistically
significant, I believe. But I believe there's a
statistical issue in taking a specific point and
then doing an analysis on that.

DR. FLICK: I think those are different
questions, aren't they?

DR. HERTZ: Yes. This is Sharon Hertz.
Randy, we don't have a blow-up of that first hour
to see if those pain intensity curves were
separating.

DR. FLICK: I guess I would be looking more
toward the later time period. So these are not
SPID.

DR. HERTZ: These are just pain.

DR. FLICK: These are single-point pain
scores and the question would be, do they differ
statistically.

MS. MEAKER: My name is Kate Meaker. I'm the statistical reviewer for this application. And these are pain intensity scores at each of these times. This is descriptive information. To test at each of those time points, they were listed as secondary endpoints, but there was no intent. It was specifically stated in the protocol that the intent was not to make statistical inference on those secondary endpoints.

So we're not presenting the statistical analyses at each of these time points.

DR. WINTERSTEIN: I actually have a follow-up question if you want to keep standing. So there is the statistical significance, obviously, but we're also, I think, very interested in the clinical meaningful difference and there's different ways of looking at individual pain scores.

One would be, these are not pain scores, these are average pain scores. And of course, averages tend to navigate into the middle, which
means we don't really see the extremes here. And what I would be interested in is, if you have that data, what is the proportion of patients with uncontrolled pain, which is typically defined as more than 7 for each of those time points?

I think all of us are probably interested in just the high dose and the placebo group, just in case you have that. And then likewise what is the proportion of patients and at what point do they actually fall below 4 or lower, which is clinically one of these other time points that we usually are interested in?

MS. MEAKER: I don't have those data or graphs with me. I can tell you that, in the analysis, if a subject requested rescue medication for pain, the pain observed prior to rescue medication was imputed for these pain averages.

DR. WINTERSTEIN: So it was carried forward basically, then.

MS. MEAKER: Yes. It was carried forward for 4 hours and then, if they asked for more pain medication, it would be carried forward, so that 4-
hour window would reset every time. So the pain before rescue is what would have been carried forward.

So anybody who was not getting adequate pain relief, that information is reflected in these means through that method of carrying forward with the pain. Is that helpful?

DR. WINTERSTEIN: It doesn't answer my question. It's another part to think about, how will people deal with missing values, and essentially that is something like a missing value if you will. Right? And so I mean, that certainly makes sense. I was more interested in the issue of that averages may not really reflect the percent of patients who really cannot get controlled with this product, which I think is a very important piece here, because that seems to be a substantial proportion.

So why would I try to treat somebody with a product that doesn't really seem to work with a majority of patients? And so that's kind of where I was trying to get at here. I mean, we know that
there is a good proportion of patients who need rescue medications, obviously, and so that's kind of where I was trying to get at.

MS. MEAKER: Unfortunately, I don't have the data with me to provide that kind of distribution among the groups at each of the times.

DR. WINTERSTEIN: Great. Thanks. Any other questions for the FDA?

(No response.)

DR. WINTERSTEIN: There was way more interest in the sponsor, so we'll move back there. So next on the list was Ms. Joniak-Grant.

DR. JONIAK-GRA NT: Hi. So my first question, I guess, would be best targeted to, excuse me, Dr. Mariano. What was the length of time of meaningful relief. We talk about time to meaningful relief, but how long was meaningful relief lasting?

DR. MARIANO: The length of time for meaningful relief wasn't a time point that we studied, but looking at some of the secondary endpoints for clinically meaningful utility, can
you pull up the SPID 0 to 20 and then please bring up the 0 to 4 or 0 to 12? Slide 1, please.

We saw, initially from the SPID 0 to 2, they started to separate at approximately 1 hour and continued to grow, and slide 2, please. Again, can you go back to SPID 0 to 2? And pull that back up, slide 1.

Again, when we were looking at this, everything continued to grow and especially increase from 0 to 4, it also increased in slide 2 up to the 4-hour time mark. At 0 to 12, when we actually gave the second dose, the separation went more granular at slide 3, please.

Also, at the 8-hour time point, which was just mentioned about the possibilities of having some ineffective pain control, we see at the 8-hour time point from placebos, the 125 to 25 and the 0.5 milligrams all separated from placebo at the 8-hour time point using the SPID 0 to 12 hour as a secondary endpoint instead of using the SPID, which was kind of comparing a secondary endpoint to a secondary endpoint for that analysis.
If we continue looking at all the way up to SPID 48, slide 1, they all had statistical meaningful separation from placebo at the primary endpoint of 48 hours. I have data on the TOTPARS as well that showed that they were continuing to grow over time, so really, where it was, they had time to meaningful pain relief and it continued to grow.

Also, their global satisfaction scores at 48 hours show that a majority of the patients -- slide 2, please -- reported at least a 30 percent clinically meaningful pain difference -- slide 2, please -- of 82 percent in the lowest dose up to 97 percent in the highest dose and a global evaluation score at 48 hours -- slide 3 -- please - showed very good, good, and excellent rating all the way through the 48-hour time frame.

DR. JONIAK-GRANT: I'm glad you bring that up because I have a question about that as well, but going back to the meaningful relief, it's one thing to look at it at certain time points that kind of align with when you're getting the best
pain relief, but there are times where people are sitting there going how much longer to their next dose, how much longer to the next dose.

So if it's giving you great relief at 2 hours every time after you take it, then of course you're going to have that, but it doesn't mean that you're not having 4 hours of where you're just waiting and feeling like crap essentially until your next dose.

I think that information would be useful. You guys did cite many times this global evaluation. How exactly was the question worded? How did you ask it?

DR. MARIANO: At the 48. Could we please pull up the global evaluation chart? Slide 2, please. This is how it was defined, as either poor rated as 0, fair of 1, 2 is a point score of good, very good was 3, and excellent was 4.

The patients on the 5-point categorical scale were instructed to score his or her global evaluation of the study treatment using those descriptors. And this also occurred --
DR. JONIAK-GRANT: I'm sorry. Can I interrupt? You went to the patient and said what is your global evaluation of this medication and here are your options?

DR. MARIANO: That is correct.

DR. JONIAK-GRANT: That seems rather vague. Was there any controls put in place to help balance out an effect -- you had a lot of females -- any effects that you would get from social desirability responses?

DR. MARIANO: No. We did not.

DR. JONIAK-GRANT: Then just my final question; I wanted to clarify. I feel like we've been switching back and forth a little bit. Is the indication for this to be in a hospital setting or is it to be in an outpatient setting for outpatient surgeries and things?

MR. SHERMAN: We're recommending initiating treatment in a medically supervised setting. That's a broader definition than just a hospital setting, but we want to initiate treatment in a medically supervised setting and then for those
patients who the healthcare professional deemed suitable, they can then be used in an outpatient setting.

DR. JONIAK-GRANT: Why I asked is, as a person who's had many -- I've had 4 outpatient surgeries on my spine and I know a lot of other people that have. You're going to be there for 12 hours after you get the medication. With a recommendation, a lot of times you're there maybe 3 or 4 hours before you even get the procedure.

You're there another couple of hours for the procedure and then you were talking about administering this medication from 0 to 4 hours after, so you could have another, say, 2, 3, 4 hours and then another 12 hours after that. So essentially, you could easily be looking at being there for 24 hours.

How would that really play out in the real world with bad -- I mean, do you go sit in the waiting room. There's not beds available. And also along those lines with giving patient education, when would this patient education
happen? Because a lot of times, you get information and you don't remember it because you don't even know if a doctor came to talk to you.

So would there be controls put in place to help balance that? So the question is how do you see this 12-hour thing happening in the real world and at what point and how would this patient education take place?

MR. SHERMAN: The patient education will takes place when the physician or healthcare provider provides the medication. And to help them recall, we will be providing education materials. One of them was the patient instruction form that I had in my presentation, slide 3, please, to help them mitigate the risk of respiratory depression, hypoxia in the outpatient setting.

As to how that actually plays out in the medically supervised setting, I'm going to let Dr. Pergolizzi, who can give you the clinical insights to that --

DR. PERGOLIZZI: That's a very good question. I think, as I mentioned earlier on,
there are about 40 million surgical procedures that are done in the United States that are in institutional settings and not the outpatient discharge ambulatory setting.

So in my own clinical experience, that'd probably be a place where I would be looking to initiate this type of therapy.

DR. WINTERSTEIN: Dr. McCann?

DR. MCCANN: I have a couple of questions for Dr. Mariano. The first is, what was the rationale for designing studies that were mainly for females under the age of 50 who have the highest nausea and vomiting rates after surgery to begin with, so I can't get a clear idea from the data what the real risk of post-operative nausea and vomiting is from this drug because of this population you chose.

MR. SHERMAN: The bunionectomy study is actually a model that's widely used with the agency. They know it and accept the results. And unfortunately, a bunionectomy study, although
in an acute pain setting, the preponderance of recipients of that surgery are female.

That's been a consistent bias through most bunionectomy studies.

DR. MCCANN: I have another question. On study 62, I think you said, Dr. Mariano, that there was 8 percent rate of non-completion. Was the non-completion because the patients didn't have pain that lasted 7 days or the non-completion because they said this drug's just not working, I need some other therapy, I'm out of the study.

MR. SHERMAN: I just wanted to correct one thing and then I'll let Dr. Mariano speak. Study 062 was a 48-hour study, not a 7-day study.

DR. WINTERSTEIN: Dr. Mariano?

DR. MARIANO: In the patients that did discontinue, it was either due to an adverse event or such a request in the 062 subject. Can I see the slide of the study design, please? Slide 3, please.

As you can see in the breakdown at the subject's withdrawal, there was adverse events in
1, subject requests in 2 in the 0.5, and actually
this is 062 I need, please, slide 3. I'll
rephrase. May I see slide 2, please? Sorry about
that.

The discontinuation rates in 062 were broken
down into either adverse events of nausea,
vomiting, dizziness, lack of effect, loss to
follow-up, and withdrawal of subject.

DR. MCCANN: My last question is on Study
111. I think the study design allowed the
anesthesiologist to give as much rescue narcotics
as they felt was needed before the patient was
randomized to the drug? Correct?

DR. MARIANO: They were allowed to give
doses, rescue narcotics, yes, but as much as they
needed, but at least in fentanyl, it was either a
100-mic or 200-mic dose.

DR. MCCANN: Single dose or could they give
multiple doses?

DR. MARIANO: Yes.

DR. MCCANN: So in my experience, a lot of
the anesthesiologists will try to get ahead of the
pain and pre-dose before the patients is really in significant pain at all. So is there any correlation or did you look to find any correlation between the total dose of rescue narcotics they got before they were randomized in these episodes of hypoxia that they had after they were randomized?

DR. LEVIN: We have not looked at that yet.

DR. MCCANN: Thank you.

DR. WINTERSTEIN: Dr. Zeltzer?

DR. ZELTZER: Really, to either of you, in terms of AEs, were any of these women given any age of the subjects and the fact that most were women, were any of them breast feeding during this time? Were they worried about breast feeding? Does the drug go through the breast milk, in other words, inadvertent AEs?

DR. LEVIN: I have to confirm, but I believe that would be an exclusion criteria for this trial.

DR. ZELTZER: For the trial, women were warned about that, even after they went home, because you're talking about 7 days?

DR. LEVIN: Let me confirm it, but if they
were breast feeding, they would have been excluded from the trial completely, so there would be no risk at home after surgery when we sent them.

DR. ZELTZER: Did you look at women, given the age group, who were pre- versus post-menopausal in terms of side effect profile?

DR. LEVIN: No. We have not conducted that analysis.

DR. ZELTZER: Thank you.

DR. WINTERSTEIN: Ms. Robotti?

MS. ROBOTTI: Hi, Suzanne Robotti. Dr. Mariano, I just lost my questions. There, there. Dr. Mariano, if the patient takes Buvaya for 7 days, would he or she have withdrawal symptoms?

MR. SHERMAN: Dr. Mariano?

DR. MARIANO: In the patients in our Study 111 who did go home with study medication for the 7 days, there is no signs of withdrawal from study medication at discontinuation.

MS. ROBOTTI: No signs being no complaints or you followed up and asked that question?
DR. MARIANO: They had an evaluation post-7 days at day 8 and day 10 after completion.

MS. ROBOTTI: How many doses does a patient get at one time to take home? Is it 7 times 2 or 1?

DR. MARIANO: It would be 7. Well, we have a 12-hour medically supervised, I think, which would be 2 doses and then an additional 19 doses would be issued if they wanted to use it up to 7 days, but that would be different and based on state legislations as well because certain acute pain medications are limited to 3 days, 5 days, and the other ones are 7 currently.

MS. ROBOTTI: Sure. And what's the cumulative effect on the opioid naïve if they misuse it mistakenly, they partially spray it in their mouth they think they missed it, so they use a second one or they use it too quickly? Is there a cumulative effect?

DR. MARIANO: We have no data that show any signs of misuse. We did not study that in our clinical program.
MS. ROBOTTI: The only study that we know of showed higher misuse.

MR. SHERMAN: Well, in the PK, we looked at day 1, 8 hours, and then we looked at day 6, 8 hours, and there was a less than twofold increase, so according to the pharmacokineticist -- and I'm not one -- less than a twofold increase is not concerning.

MS. ROBOTTI: I think I have one more question for Dr. Pergolizzi. In Study 111, how long were the prophylactic antiemetics given? Was it for just the first four doses or was it throughout the entire run?

MR. SHERMAN: Actually, that's more of a Dr. Mariano question.

MS. ROBOTTI: Sorry. Dr. Mariano?

DR. MARIANO: Would you repeat it, please, again for me? I just want to make sure I heard the whole thing.

MS. ROBOTTI: Sure. How long were the prophylactic antiemetics given?

DR. MARIANO: In Study 111?
MS. ROBOTTI: I think that was the only study in which prophylactic antiemetics were --

DR. MARIANO: They were given antiemetics preoperatively. They were also given antiemetics if needed in the postoperative inpatient up to 48 hours using IV ondansetron, 4 milligrams. They were also given orally disintegrating tablets of 4 milligrams to be used at home if they needed rescue.

MS. ROBOTTI: So prophylactically, it was only given before surgery. Afterwards, it was on me.

DR. MARIANO: As needed.

MS. ROBOTTI: That's it. Thanks.

DR. WINTERSTEIN: Just real quick, too, to Ms. Robotti's question about a cumulative dose, I think you can make some inferences on the higher doses that were not followed later. Right? So if you take 2.5-milligram doses at once, you basically have a 1-milligram dose because everything is sublingual.

MS. ROBOTTI: Or 2 .5s within an hour of
each other.

DR. WINTERSTEIN: Right. Yes.

MS. ROBOTTI: So that's a significant problem.

DR. WINTERSTEIN: It's this initial study that was discontinued where you have a 1-milligram dose that would be the effect of taking 2 at once, 2.5 at once, because sometimes with tablet, that might be a different pharmacokinetic profile, but here we have immediate absorption sublingually, so I would imagine that's the same.

MR. SHERMAN: When you initiate in a medically supervised setting, if there is a missed dose or something like that, you're reducing the risk of re-dosing for either that reason or if their onset of analgesia isn't as quickly as they were expecting.

DR. WINTERSTEIN: Sure. I think it was just Ms. Robotti's question was, is there a cumulative effect if you took more for whatever reason. And so there's some data that we would have based on these higher doses than there is. Right?
Dr. Dasgupta?

DR. DASGUPTA: Hi, this is Dr. Dasgupta. I'm trying to understand, we've heard this insinuation that the study is 111 and the pivotal trial were in female patients that have a higher risk of vomiting and nausea. And I'm not seeing that in the data. Slide 88 from the sponsor deck, please.

So one way to look at that is that left column, right, placebo, where we're seeing fairly low percentages of vomiting. So on slide 84, I would say that, given the study design, the Apfel scale is totally irrelevant because 50 percent of the patients were supposed to be getting opioid therapy for the first 4 points and 96 percent of patients were female, which is the third point.

So I think this particular metric is not really useful. The reason why I bring that up, is on slides 81, I am curious what does the stratification by baseline PONV risk factors mean? And given that we're not seeing a lot of placebo, nausea, in this population, I'm just a little
confused that this insinuation keeps coming up, that this is a population that is prone to nausea and vomiting. I have one more quick question after that.

MR. SHERMAN: Why did we stratify by their Apfel score? And I'll let Dr. Mariano address this further if necessary, but really, we were looking to see in the higher-risk patients really did it result in higher nausea and vomiting rates.

DR. DASGUPTA: So then presenting those stratified analyses would be useful.

DR. MARIANO: Can you repeat your question one more time?

DR. DASGUPTA: Sure. Was the baseline nausea risk factors stratification done before randomization or was this like an analytical stratification after the fact?

DR. MARIANO: In Study 111, this was looked at prior to randomization. It wasn't a post hoc. Slide 1, please.

DR. DASGUPTA: We'll have to interpret this on the fly. That might take a second. So while we
look at that, the second question I had is the patient experience for most spray delivery of medication is nasal, over-the-counter sprays, things like that. Were there any studies looking at what would happen if this was inadvertently sprayed into the nose?

MR. SHERMAN: If you look at the particle size, the guidance for nasal administration, the sublingual form has less than 10 percent of the particles that would allow for administration nasally. So the risk of that happening is fairly finite.

DR. WINTERSTEIN: Dr. Flick?

DR. FLICK: Dr. Mariano, excuse me. Slide 65, I'm curious just as I look at this slide, why you've displayed the data in this way, the rescue medication and specifically focused on ketorolac. Was there a particular point you wanted to make by displaying only ketorolac in a cumulative way rather than by dose?

If you look at the study design in your slide 49, the breakthrough pain was treated with
ibuprofen first and then, if insufficient pain relief or subject was unable to tolerate ibuprofen, they were given ketorolac.

I'm curious why you displayed the ketorolac dose and didn't break it down by dose, the dose of the study drug. Was there a point that I missed? Could we go back to that slide?

DR. MARIANO: The dose that they were given was a 30-milligram IM or IV per utilization of ketorolac, so the dose was a standardization of 30 milligrams, up to 90 milligrams in a 24-hour period for rescue.

DR. FLICK: So are you understanding the question?

DR. MARIANO: I was trying to figure out, do you want to just stratify based on --

DR. FLICK: No. I'm asking why you displayed the data in this way. This doesn't tell me anything about breakthrough pain because it's not the drug that was primarily used for breakthrough pain.

DR. MARIANO: Slide 2, please. Here's the
rescue medication at least for the first 8 hours looking at comparisons of ibuprofen and ketorolac and from placebo in 125. And I'll also display the one for the time points in one second, but we did look at it in both ways, showing decreasing doses of rescue medication as increasing in a dose-dependent manner up to the .5.

In slide 1, we have the rescue medication at time points, which I think is more particularly what you're asking about and about the amount of rescue medication that was used at specific times from 0 to 8 hours, 8 to 16, 16 to 24. And there was higher uses of ketorolac and ibuprofen in the first 8 hours with all doses, including placebo, with placebo being the highest in a dose-dependent manner, decreasing down to the .5 dose, through pretty much all time periods.

DR. FLICK: I guess I hadn't seen these slides before. Were they presented?

DR. MARIANO: This was not presented in the core deck.

DR. FLICK: I'm just curious to know why.
DR. MARIANO: Time.

DR. FLICK: I mean, the obvious conclusion here is that you didn't want to display those data.

DR. MARIANO: It's not that I didn't want to display, but ketorolac itself, when you look at a rescue medication compared to ibuprofen, could be representative of actually treating more of a moderate to severe type of pain symptomatology versus an ibuprofen, which is more mild to moderate, because there are some information out that ketorolac could have the same efficacy as morphine when given IM or IV.

So that's why I presented the data using the more potent of the two rescue medications besides just the ibuprofen.

DR. PERGOLIZZI: The information is represented in the briefing document and, for reasons of time, we couldn't have an exhaustive amount, but the information is in the briefing document.

DR. WINTERSTEIN: Dr. Goudra?

DR. GOUĐRA: Yes, thank you. A couple of
questions; I think a couple of speakers mentioned that one of the advantages of sublingual administration is first class effect. Can anybody tell me in terms of comparison of sublingual tablet, was it a spray, sorry, sublingual tablet was this older tablet was this spray in terms of bioavailability? Is there any big difference?

MR. SHERMAN: Study 104, 105, one of them where we compared the sublingual spray and the tablet. Let's go through the IV, Subutex. I don't know if we have those data in a slide, but if we do, we'll try and find it.

DR. GOUDRA: The second question I have is to Dr. Pergolizzi that, as a clinician who practices anesthesia every day, I want to where exactly is the role of this spray, considering a majority of the patients nowadays with this surgery. And this drug is basically off the shelf for us. That's a concern unless you're hoping that, once it comes into the hospital, people will start using it in an off-label indication.

The second is, say, once we start using it,
can we still use other opioids if they're still in
the hospital? If it is because the kind of
conclusion I'm making with this is, they say it's
got less addiction liability. That's the biggest
advantage. The advantage has gotten incidence of
nausea, vomiting, dizziness, and less effective
pain control.

MR. SHERMAN: Just in part, we have never
studied the use of buprenorphine in conjunction
with other opioids, so we have no data on that ad
we would not be recommending that. I'll let
Dr. Pergolizzi answer the rest of your questions.

DR. PERGOLIZZI: The only insight I can give
to this and based on the clinical study is, during
the perioperative anesthetic regimen, they did have
fentanyl, so that's as far as I can extrapolate on
that part of it again. I think these things have
been discussed in the labels of other buprenorphine
products and the same type of warnings and
precautions should be adhered to. Second, I would
also like to explain. I think the question was,
what is the absolute bioavailability. Right now,
the parenteral Buprenex is .3 milligrams.

This absolute oral bioavailability would be approximately 2.4 milligrams in that single dose.

DR. GOUDRA: Thank you.

DR. PERGOLIZZI: Again, just to reiterate, the analgesic dose ranges for buprenorphine where it acts as an analgesic in the United States have been approved at 75 micrograms up to 1.8 milligrams, which would include the spectrum of both the acute and chronic indications as I know of them.

DR. WINTERSTEIN: Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. I have a couple of questions, three questions exactly. The first one I think could go to the sponsor, which is more of a design question than a clarification. And this is mainly about study 062, for the primary endpoint, SPID 48, how was it powered, and how was the effect that was actually observed compared to the delta that were used to power the study?

MR. SHERMAN: I'll let Dr. Bittman explain
that. Dr. Bittman?

DR. BITTMAN: Good morning. My name is Dick Bittman. I'm a statistician consulting with Insys. I'm being compensated for my time and expenses. And other than that, I have no financial interest in the company. So the pivotal study 062 was powered on the basis of an assumed effect size of 0.45. I think that's probably the most direct answer to your question.

DR. TCHETGEN TCHETGEN: How does that compare to the observed effect?

DR. BITTMAN: The observed effect, slide 3, please, ranged from .71 to 85 depending on the statistical assumptions that we used in the modeling. That's for the highest dose. The effect sizes of the lower doses were accordingly lower, .3 to .37 range.

DR. TCHETGEN TCHETGEN: Thank you. My second question had to do with how was -- this is again still with study 062, how salvage therapy and other sources of missing data were handled for the primary endpoint. There was an allusion of last
observation carried forward. I just wanted to get a better understanding of how SPID 48 was computed, accounting for possible missing data.

MR. SHERMAN: When you say salvage therapy, I just wanted to clarify you're referring to rescue medications.

DR. TCHETGEN TCHETGEN: Rescue medications, yes, thank you.

MR. SHERMAN: Thank you. Dr. Bittman?

DR. BITTMAN: If a patient took rescue medication for the purposes of the SPID calculation, their pain intensity just before taking the rescue was carried forward for 4 hours and, if necessary, carried forward again. So that's how the pain intensity wasn't actually imputed. It was replaced by one that was not confounded with the use of rescue medication.

DR. TCHETGEN TCHETGEN: So my concern -- and you can tell me if I'm wrong -- I'm looking at the plot that was put up by FDA with the time-specific scores, pain scores. There was a general trend, downward trend. However, there was a lot more risk
mitigation being used in the placebo world, in any of the other arms.

Therefore, carried forward would flatten the slope of decrease whereas the general trend in any of the active arms will continue to decrease, therefore favoring rejecting the null hypothesis with any alternative ways of trying to account. I mean, last observation carried forward is no longer considered a standard for missing data for some of these reasons, but others as well.

Were there any other kinds of statistical techniques that were used to account for missing data?

DR. BITTMAN: Yes. There were. We used a couple of different multiple imputation methods. We used one approach with linear modeling that did not use imputation at all. So why don't we put up slide 2, please?

So I'll point out I'm going to show the panel of a bunch of analyses, but I'd like to point out at the beginning that all of them will show more or less the same trend in terms of the dose
response and also the same degree of statistical
significance that we saw with the presented
analysis.

But for example, there was a completers
analysis which excluded the 23 patients who didn't
complete 48 hours of pain observation. That's
about 7 percent of the study population. The ITT
analysis with all patients was based on modeling of
the pain intensity difference with whatever data
was available and then using the model to construct
the SPID endpoint.

We also did multiple imputation with the
missing at-random assumption and we did one with
using the so-called jump-to-reference approach
where patients' missing data were assumed to follow
a placebo response regardless of what the patient
actually had been randomized to.

We also did for completeness last SPID
carried forward, but as you pointed out, the single
imputation methods are not considered the
appropriate method anymore. So in all of these, we
got somewhat similar results. Certainly, the
separation between the various doses is what we've seen previously.

Then if we pull up slide 3, please, these are the p values for the comparisons of each dose versus placebo and they're all quite statistically significant.

DR. TCHETGEN TCHETGEN: Thank you. That's very helpful. My last question has to do with, again, still, study 062 and the extent to which the study, the endpoint was meant to be observed during hospital stay versus going back home.

This is also related to reporting of adverse events and there was an allusion earlier of possible either overreporting or under reporting, homesteading or not recalling homesteading as opposed to in a hospital setting.

I just want to understand the impact of possible confounding by setting in the reporting of adverse events.

DR. BITTMAN: In 062, they were all inpatient the whole time, so there shouldn't be any underreporting, or overreporting, or confounding
variables.

DR. TCHETGEN TCHETGEN: For the last study that was mainly --

DR. BITTMAN: In Study 111, the first 48 hours were inpatient. The subsequent 4 days were outpatient. And on the exit interview so to speak, I forget exactly what they call it, but patients were prepped on if they experienced any AEs, they were supposed to contact the investigator.

DR. TCHETGEN TCHETGEN: Was there any attempt to try to account for possible confounding by setting, which is, I mean, arguably going to be present, just because it's not directly observed?

DR. BITTMAN: We did no statistical analysis on the safety data, so we can't answer your question.

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

DR. WINTERSTEIN: Dr. Boudreau?

DR. BOUDREAU: Hi, Denise Boudreau, two questions. One, on the rescue medications for Study 111, for the outpatient period, do I
understand it correctly they were not recommended
to use any NSAIDs? Is that correct? So the only
rescue machine recommended there was Tylenol.

MR. SHERMAN: Was acetaminophen, yes.
That's correct.

DR. BOUDREAU: So I ask, and I'm sorry if I
missed this, what was the reasoning for that study
to not allow NSAIDs versus any others?

MR. SHERMAN: The two rescue medications
that were allowed in the inpatient setting were
acetaminophen or ketorolac. Ketorolac isn't really
appropriate in the outpatient setting, would be the
rationale.

DR. BOUDREAU: So they were specifically
instructed to not use NSAIDs then in the outpatient
setting, in the outpatient period?

MR. SHERMAN: Right. That would be
confounding to the study.

DR. BOUDREAU: I ask partly just because of
the results reporting with regards to the GI
effects and combining products that have, potential
of combining those products with NSAIDs that would
further increase, potential TI adverse events.

Second question is just refreshing me on my pharmacokinetic, pharmacodynamics. So you mentioned that buprenorphine is metabolized to the norbuprenorphine and the potentially CYP3A4 agents should be used with caution.

So am I remembering right that norbuprenorphine is also an active opioid? So the interaction there would be potential increase in both pain efficacy, I guess, but also potential increase in side effects.

MR. SHERMAN: That is accurate because norbuprenorphine is a mu opioid agonist. And so you do get efficacy, but you also get AEs due to the norbuprenorphine.

DR. WINTERSTEIN: The last person on the list is Dr. Zacharoff, short question or long question?

DR. ZACHAROFF: Short.

DR. WINTERSTEIN: You're on.

DR. ZACHAROFF: Kevin Zacharoff, Mr. Sherman. This is with respect to your slide
CC-102 in your mitigation of hypoxia or risk of respiratory depression. In the label section, it says instruct patients on proper administration of the Buvaya to reduce risk.

Am I correct in assuming that proper administration means self-administration?

MR. SHERMAN: Self-administration every 8 hours, yes.

DR. ZACHAROFF: So it's not intended to be administered by anyone else for the patient.

MR. SHERMAN: In the inpatient setting --

DR. ZACHAROFF: I'm talking about when they're discharged.

MR. SHERMAN: When they're discharged, if they're not able to, it could be administered by a caregiver because the instructions, at least in the risk mitigation program are really to either the patient which is going to be the case in the preponderance of examples, but sometimes it is administered by a caregiver.

DR. ZACHAROFF: So it would instruct patients or caregivers on proper administration.
MR. SHERMAN: Right. That is correct.

DR. ZACHAROFF: The second bullet there says, "Get help right away if you take too much Buvaya." That's in bold. And I guess the way that someone would take too much is if they dose themselves or if somebody dosed them more frequently than the instructed time period. Is that correct?

MR. SHERMAN: Yes.

DR. ZACHAROFF: Then the next sentence says, when you first start taking it or if you take too much, the breathing problems could occur, but actually breathing problems could occur potentially along the continuum of taking this medication. Correct?

MR. SHERMAN: Yes.

DR. ZACHAROFF: Thank you.

MR. SHERMAN: But the preponderance generally occurs at the beginning.

DR. ZACHAROFF: The first dose is going to be institutional, though, so it implies that you only need to worry about it if you take too much in
this wording. Thank you.

DR. WINTERSTEIN: We will now break for lunch. We will reconvene again in this room in one hour from now, at 1:00 p.m., 57 minutes from now. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting, during lunch, amongst yourselves, with the press, or with any members of the audience. Thank you.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)
AFTERNOON SESSION

(1:06 p.m.)

Open Public Hearing

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial 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. And for the speakers, the FDA and this committee place great emphasis in the open public hearing process. The insights and comments provided by you 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 chair.

Thank you for your cooperation.

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

DR. WOLFE: I'm Sidney Wolfe with the Public
Citizen Health Research Group. I do not have any financial conflict of interest. I've tried to organize my comments around the questions for discussion and ultimately for vote. And the first is whether the efficacy findings support the indication "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate".

I think that that's an important phrase because the adequacy of alternative treatments has, I think, been focused on more by the FDA than by the company. Also, it says include any concerns regarding the time to onset of analgesics for Buvaya in the context of an acute pain indication.

Now, these next three comments are taken verbatim from various parts of the FDA briefing document. I think they cover the points having to do with at least the effectiveness. Even for the high-dose group, it is important to note that more than one-third of patients did not experience onset of analgesia.

The applicant's time to meaningful pain
relief analysis also indicates a long latency to clinically meaningful benefit. Median time -- and you've seen these data before -- to pain relief was 92, 122, and 166 minutes for the three decreasing doses, which means that half of the patients in the .5 dose had to wait at least an hour and a half.

If you look at the 95 percent confidence intervals, a number of them had to wait more than that before they got meaningful relief. The second thing from the FDA briefing documents. For analgesics intended to treat acute pain, there is an expectation that meaningful pain relief will be experienced soon after taking the first dose of drug, generally with 1 hour.

More than half of the patients treated with .125, .25, buprenorphine sublingual spray never experienced meaningful analgesia, never, never. In the final one on this question number 1, although assessments of pain intensity, pain relief, and the patient global assessment show a benefit from treatment with BSS.

The analysis of the use of rescue medication
and the time to onset of action casts doubt on the appropriateness of BSS for the treatment of pain. This is said to be question 1. It's actually question 2 on the safety. The benefits and harms, as I call them, as opposed to risk, because they're actual harms that have occurred to people or relayed it anyway.

The second question was, based on available safety data, discuss whether the safety profile of Buvaya is acceptable for the proposed indication. And you've seen this all. These are the data at the placebo and three doses. And you can see that, at the highest dose, the only one that's even clearly by statistical means effective, the vomiting is 73 percent to 41, 29.

On a page after this chart, the FDA says 37 percent of patients receiving .5 experience moderate to severe vomiting, not mild to moderate, moderate to severe vomiting, a total of 5 percent of patients to placebo compared with 21 percent of patients with .125, 40 percent of patients with .25, and 55 percent of patients treated with .0.
So we have the vomiting as a serious problem here and as has been mentioned before the nausea and dizziness as well. And this is again the Study 111, which again was done for safety reasons.

Total, again, you see the sharp contrasts that have been pointed out, particularly by the FDA between the standard opioid therapy, an alternative which does exist, particularly if you're in an inpatient-like setting and the BSS, the nausea was twice higher with the BSS as you mentioned before, 4 times for the vomiting, twice for the dizziness, and 4 times or so for the hypoxia.

So here, what do you do about these adverse effects, you have another kind of rescue, not for pain its, but for the nausea. A total of 78 percent of patients required at least 1 dose of antiemetic drugs some point after the first dose of .5 compared to 12 or 24 percent of patients treated with the standard opioid regimen, so this is the remedy for the complaints that have arisen because of the use of this drug.

The maximum number of doses of antiemetic
drug in any single patient was 16 in the BSS group and 9 in the standard opioid group.

So now the voting questions; do the benefits of Buvaya outweigh the risks or harms as I prefer to call them for the indication? The management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. So does this support the approval?

FDA, I think, has accurately described the 062 as the one adequate and well-controlled study. And in this study to assess efficacy and provide safety data, it seems evident that, to me, the risks of Buvaya actually outweigh the benefits instead of the required opposite.

The FDA stated that the acute pain relief was so deficient that the use of rescue medication and the time to onset of action casts doubt on the appropriateness of BSS for the treatment of acute pain.

Just as the inadequate pain relief required rescue with pain meds for a large proportion of trial participants, the extremely high rate of
nausea and vomiting required an analogous rescue with antiemetic medications.

A total of 5 percent of patients with placebo required at least 1 dose of antiemetic drug compared with 21 percent at the .125, 40 percent at the .25, and 68 percent, two-thirds, treated with .5 milligrams of BSS.

So in terms of what the answer at least that I would have to this question, the voting question, the quite unfavorable ratio of harms to benefits of Buvaya argue strongly for rejecting Insys's application for approval.

FDA's summary of this on page 25 of the briefing document sums this up quite well and I think it's very clear and I certainly could not offer anything that was better than this in terms of encompassing all the issues that should be considered when you're wondering whether the benefits outweigh the risks or, in this case, the risks outweigh the benefit.

In conclusion, this is a quote from the FDA, "The applicant's efficacy data demonstrates
superiority of BSS over placebo for all doses tested. However, time to onset of analgesia is later than is optimal for a drug intended to treat acute pain and the need for rescue analgesia was high.

From a safety perspective, there is an unexpectedly high rate of nausea, vomiting, and dizziness from BSS. Again, the Study 111 where you're comparing it to what are frequently used alternatives for acute pain, unexpectedly high rate of nausea, vomiting, and dizziness, and the applicant showed in the comparator safety Study again, 111, that the rates for BSS are markedly higher than rates for other opioids, morphine, IV, and oxycodone, used in similar acute pain settings.

The totality of data submitted by the applicant does not support the use of this product in an acute pain setting based on both efficacy and safety findings. Thank you.

DR. WINTERSTEIN: Thank you, Dr. Wolfe.

Will speaker number 2 step up to the podium, introduce yourself? Please state your name and any
DR. POLANIN: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am director Megan Polanin, a research center analyst of scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from industry, so I have no conflicts of interest.

As with any other drug the FDA evaluates, opioids should be held to a high standard for approval. Given the well-known risks and high rates of misuse and abuse, I think we can all agree that we should practice extra caution with opioids.

Please consider these question as you evaluate Buvaya's benefit-risk ratio. One, so the FDA approved new opioid products with unknown risks of abuse. Commissioner Gottlieb has stated that it is critical that the FDA promotes the development and encourages use of opioids that are harder to manipulate and abuse over opioids that do not offer any forms of abuse deterrence.
Buvaya was not intended to be an abuse-deterrent formulation, and does not have any abuse-deterrent properties, and thus does not align with this goal. The sponsor has stated that this drug has a lower potential for abuse compared with other opioids. However, they have not provided evidence to support this claim. By now, we should know not to assume a product is less likely to be abused unless there is evidence involving patients to support that assumption.

Two, do the benefits of Buvaya outweigh its risks? This drug is intended to help patients with acute pain. Results of study 62 demonstrated that Buvaya can reduce patients' pain intensity and benefit pain relief. However, it did not contribute to meaningful pain relief.

Most of the patients administered either of the two lower doses of this drug never experienced meaningful pain relief. In order to experience meaningful pain relief more than one-third of those patients took an additional dose of Buvaya or a rescue drug. The higher dose also had problems.
As the FDA pointed out, patients reasonably expect pain relief within an hour of taking the first dose. However, the median time to meaningful pain relief for patients on the higher dose was an hour and a half. We agree with the FDA that this makes it more likely that patients would take an extra dose or use another opioid before the recommended time for the next Buvaya dose.

This could increase the risk of adverse opioid-related events or even overdose. Regarding adverse events, the rate of nausea, vomiting, and dizziness were higher for Buvaya compared to opioids use in similar acute pain settings.

In addition, if opioid-naïve patients experience clinically significant respiratory depression, this drug could make symptoms worse. If this occurs, the FDA noted that standard doses of naloxone are not sufficient to reverse buprenorphine-induced respiratory depression.

Three, what are the potential unintended harms of Buvaya in the real world? We are concerned that several factors could potentially
lead to inadvertent misuse or abuse of Buvaya. First, the spray medication might be misinterpreted as less dangerous than an opioid pill. Patients may be less apt to consider the serious risks of administering an opioid spray and less concerned about using a higher-than-recommended dose.

Second, taking this drug is very easy. Patients may not perceive this spray as drug-taking behavior as compared with taking a pill or placing a patch. As a result, patients may be less likely to remember when they last took the drug and are less worried about taking the next dose too soon.

Third, this drug does not work quickly to meaningfully relieve pain, even at the highest dose. This may influence patients to take more of the drug or another rescue medication sooner or more often than they shoulder to adequately relieve their pain.

Fourth, as patients who would take this drug are likely to be opioid naïve, they will seemingly have less knowledge and experience with opioids and thus be more susceptible to these real-world risks.

A Matter of Record
(301) 890-4188
The FDA reported that available data provide very limited insight regarding the risks of misuse, abuse, or overdose associated with Buvaya compared with other buprenorphine products or opioid analgesics.

In addition to the poor efficacy and unknown yet potentially high risk of overuse, it is not clear that the novel delivery mechanism will greatly help patients. Only about 5 percent of dispensed prescriptions for buprenorphine and buprenorphine-naloxone products were for drugs indicated for pain management.

Most were for products indicated for treating opioid dependence. Of those for pain management, the vast majority of prescriptions were dispensed for the buprenorphine transdermal patch and only 13 percent for the buprenorphine buccal film.

Thus, it is questionable how many patients will benefit from a sublingual spray form of buprenorphine. In conclusion, opioids can be greatly beneficial and, as we all know too well,
can also produce tremendous harms for patients suffering from pain. Buvaya presents concerning safety issues. Its benefits seem minimal and the delayed benefit for patients may result in overuse or misuse in the real world.

Please carefully consider the risks of putting another non-abuse-deterrent opioid on the market and whether the sponsor's attempts to reduce misuse and abuse are sufficient. We do not think so and, more important, there's no evidence demonstrating that this product will misused less often than other opioids.

We therefore urge you to vote that the benefits of Buvaya do not outweigh its risks. Thank you for the opportunity to share our perspective.

Clarifying Questions (continued)

DR. WINTERSTEIN: Thank you. The open public hearing portion of this meeting has now been concluded and we will no longer take comments from the audience. Before we move on to our tsk and deliberation of the questions, the sponsor has one
slide for us that shows pharmacokinetic data that came up, I think Dr. Boudreau maybe. Some people had asked about that. Do you want to share that with us real quick?

MR. SHERMAN: The gentleman next to Dr. Choi had asked about the pharmacokinetics for the sublingual spray versus Subutex, the tablet, if you'll pull up slide 3, please, you'll see that, for all 3 doses, you see the Cmax and the AUC are below the Cmax and AUC for Subutex, either 8 milligrams or 16 milligrams.

DR. WINTERSTEIN: Anyone, any follow-up to this?

MR. SHERMAN: I have a comment to make.

DR. WINTERSTEIN: Yes. Thank you. Dr. Meisel? If there are any other questions to the FDA or the sponsor since we have some time, please let us know. Dr. Meisel?

DR. MEISEL: This is Steve Meisel and you may not have the answer to this, to the agency. I know that the DEA classifies this drug as a Schedule III, but some states have the ability to
change the classification of any drug to a higher level if they so choose. Are you aware of any states that have kept buprenorphine in a Schedule II?

DR. HERTZ: This is Sharon Hertz. No, I am not aware of any that have done that.

DR. MEISEL: You're not aware or, no, they haven't?

DR. HERTZ: I don't know the data on whether or not they have.

DR. MEISEL: Thank you.

DR. WINTERSTEIN: I have one question for probably the FDA and the sponsor. And that is in anticipation of our discussion. I was looking at the voting question and the verbiage is the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

My question is about for which alternative treatments are inadequate. The intents; what does that mean? Is that alternative opioids are inadequate? And if alternative opioids are
adequate, what would be a situation that is envisioned where alternative opioids would be inadequate but this product would be adequate?

DR. HERTZ: This is Sharon Hertz. We have taken several actions over the past few years to try and provide for prescribers with more of a balance of risk and benefit associated with opioid analgesics. Part of that effort has looked at the indication and tried to add more to it.

There's also typically a limitations of use statement as part of the indications section for most opioids now and that provides a little bit more information on what the alternatives might be for any given opioid because, clearly, the alternatives for oxycodone are not the same as the alternatives for codeine-acetaminophen combination.

So the idea is to say, if you're going to start with a codeine-acetaminophen or maybe something that's got a higher schedule only go to an opioid if non-opioids cannot provide adequate analgesia or cannot be tolerated.

Then if you're going to go beyond
combination products to a single-entity product, it should be a setting where the combination opioid/non-opioid, you can't dose sufficiently to provide analgesia in this situation and the non-opioids are not adequate.

So we try to step it up piece by piece and lay this out to say there's inherent risk in any analgesic. We all know very well now the risks that are associated with opioids. So where perhaps in some prescribing instances it's become very routine to simply turn to an opioid, perhaps a Schedule II single-entity opioid.

What we've tried to do with the language in the indication is have a little bit more sense of, don't forget there's risks right up in that indication section of the labeling. For this particular product, Schedule III opioid analgesic, I don't know how we would necessarily rank all of the alternatives, but certainly it should be in settings where non-opioids are either not sufficient to provide analgesia or not adequately tolerated.
Not everybody can take an NSAID. Not everybody can tolerate even a few doses of ketorolac in the hospital. So it's a stepped-up process that we try to convey in the labeling.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: This question is for Dr. Pergolizzi and just so we can maybe clarify this point for me and other members of the committee just a little bit. It's not crystal clear for me in terms of who the prescriber of this medication is. I'm assuming it's a surgeon if there's a surgical procedure and we're dealing with a post-operative case, so I'm also not clear on what we've heard with respect to the timing, the need to monitor the patient for 12 hours once the medication is given.

So could you give me a very succinct example of a patient, a surgical procedure, and a type of institution where this medication would be utilized?

MR. SHERMAN: Dr. Pergolizzi?

DR. PERGOLIZZI: Thank you, Dr. Zacharoff.
Just as a quick and prompt one, let's say we have a 67-year-old woman, status post-hip surgery with renal impairment. And this patient is now an inpatient, going to be moved up to the floor. She's not going to be able to tolerate IV NSAIDs. She's NPO or she has intravenous access, but again, we have to worry about IV fluids with these people.

So this is a perfect example where this may be helpful. Other patients that I probably would see a possible opportunity for would be maybe not even post-op day one, but maybe post-op day two with my head and neck cancer patients, right, where we're starting to advance them?

Things to that effect potentially could be an opportunity there as we get by further down in the rehabilitation process. But I think the first patient is a good example of someone who has NSAID tolerability issues, renal failure. I don't like to call them old because I'm from Naples, but slightly older adult, and that may be appropriate patients for that.

DR. ZACHAROFF: In that first patient you
referred to, the hip replacement patient, you would see that patient at some point in time during the course of her hospitalization, be trained on how to administer the medication to herself, and then be discharged with the plan that she would self-administer the medication to herself every 8 hours?

DR. PERGOLIZZI: I think that may be the optimal situation, that they would have medical monitoring for the first 12 hours. That could take place in the PACU. It could be part of standing orders for certain surgeons. It could be something that the acute pain team, if there is one, at the hospital would then follow through, but yes. That would be the type of situation. Thank you.

DR. WINTERSTEIN: 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. Dr. Sharon Hertz will now provide us with our charge.

Charge to the Committee – Sharon Hertz

DR. HERTZ: Good afternoon. So I think it's
an understatement to say that we as an agency are aware of the devastating problems of opioid abuse, overdose, addiction, death in the U.S. and we're attempting to facilitate the development of non-addictive analgesics to its fullest extent permitted by our regulatory authority.

Also, we're also attempting to support development of products that may have a lower abuse potential, even if they are opioids.

So it seems like there would be a good case to look at potential benefits for a buprenorphine process for acute pain. It is Schedule III. It is different than our Schedule II opioids. And today, you've heard about the safety and efficacy from studies actually of Buvaya, which is of course buprenorphine.

So while we recognize the need for pain treatments with lower abuse potential than the Schedule II immediate-release opioids that are currently available, we want to hear from you about whether Buvaya meets this need.

There are several changes in the applicant's
plans that were not part of the actual application that we either became aware of today or recently.

So we haven't necessarily included all the things in our questions that we might have in other circumstances. So as you respond to the questions about the efficacy and safety of this product for the proposed indication, please consider the proposal to dose Buvaya on an around-the-clock basis, which is unusual for acute pain.

Xartemis XR is not intended for around-the-clock use. We looked at the language. It is a little bit different than usual, but it's for every 12 hours, but not necessarily around the clock. Also, the original application didn't include a proposal for routine antiemetic prophylaxis and I'd like you to comment on whether we'll need data for how long that would be used and any potential combined risk for buprenorphine and ondansetron, the most commonly used antiemetic, given possible potential for QT prolongation.

You've already given us a lot of information about the medically supervised period or a loud
discussion, so that's good. And we're not quite
sure yet what the additional elements for the REMS
would look like either, but if you have thoughts
for what could be useful as you go through the
questions, please provide some suggestions. Thank
you and I really look forward to hearing your
deliberations.

Questions to the Committee and Discussion

DR. WINTERSTEIN: We will now proceed with
the questions to the committee and panel
discussion. I would like to remind public
observers that, while this meeting is open for
public observation, public attendees may not
participate except at the specific request of the
panel. So did I miss something?

So we have three questions and one vote.
Starting with question number one, which is
displayed now, discussion number one, discuss
whether based on the available data the efficacy
findings support the indication management of pain
severe enough to require an opioid analgesic and
for which alternative treatments are inadequate.
In your discussion, include any concerns regarding the time to onset of analgesia for Buvaya in the context of acute pain indication. Consider each dose of Buvaya in your discussion. And just to remind you about the content of the next questions, the second question talks specifically about the safety profile and the third question talks about abuse and misuse issues.

So let's try to focus our discussion on the question at hand. So question number one would look specifically at the indication that is proposed and whether we agree with that indication. Dr. Meisel, I just looked at you.

DR. MEISEL: Steve Meisel. So if this were a standard Schedule II opioid with the efficacy profile of this drug, we probably wouldn't be here today because the efficacy profile is so weak compared to other opioids.

If this were a non-steroidal with the efficacy profile that we've heard about today, we wouldn't be here if this was ketorolac or some other drug like that. We wouldn't be here today
because the efficacy would be so weak compared to what's out there already. We probably wouldn't be meeting like this today.

It seems like the only reason we're here is that this is a Schedule III opioid. And the applicant has made the case in their slides that there is a public health need for a Schedule III opioid for acute pain.

I guess I disagree with that premise. We don't need a Schedule III opioid. We need a drug that is safe and effective. And forget the scheduling of this. If you take that part aside, if you look at the efficacy data, the .125 and the .25 are almost not effective at all. And the .5 is effective maybe in half the patients after you wait an hour or two. In even that, there's a fair amount of breakthrough.

I mean, this is an ineffective agent. It just doesn't work for acute post-op pain in any way that any patient or provider would expect it to work.

DR. WINTERSTEIN: Dr. Flick?
DR. FLICK: With regard to the efficacy, I think the sponsor has shown that it's efficacious, though weakly efficacious. It's not a particularly good drug if one looks at the armamentarium available to us. I think the chair pointed out one of the operative statements is that, when alternative treatments are inadequate, I think many of us who are anesthesiologists here could imagine that these patients would do just as well with no opioids if there was another arm to the study in which the patients were treated with non-steroidals up front and many of these patients would benefit from regional anesthesia or wound infusions.

So I'm not sure that the alternative treatments were really explored in any of these studies in any adequate way. So although the drug is efficacious, it is really quite weakly efficacious and one could easily design something that would probably benefit patients more with less risk.

DR. WINTERSTEIN: Dr. Runa?

DR. RUHA: Just addressing the specific
discussion one items, I do think that the .5-milligram dose seemed to be efficacious, although I wasn't convinced at all that the lower two doses are. And I'm not especially concerned about the time to onset of analgesia because alternatively somebody has an oral medication which is still going to take some time to get absorbed and have onset to analgesia. So yes, those are my thoughts on that first item.

DR. WINTERSTEIN: Dr. Warholak?

DR. WARHOLAK: So I think, in theory, it would have been a really interesting innovative novel use for this particular medication. But I think that the data that I've seen because of the ask for it to have an indication for acute pain and then the very, very slow time of onset of the 92 to 166 minutes' median time to pain relief is really concerning.

Also, with the need for people to be re-dosed and a third of the patients in some circumstances not getting onset of analgesia, I do not think that this would be effective for acute
pain.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you, Ron Litman. So just keeping my comments just to efficacy, I do believe that the .5 dose was efficacious and I'm also not concerned with the timing. When we send patients home with oxycodone or hydrocodone, it can be quicker than that, but often it's not and patients with very, very painful conditions often have such nausea baseline that it's difficult for them to take their medicine.

So I think the sublingual approach is a great breakthrough if it could replace some of those pills. So those are my feelings from this and I'll have other comments about the risks with the next questions. Thank you.

DR. WINTERSTEIN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I too, especially from the patient perspective, like the idea of being sublingual. I know a lot of us that have had to try to get stomachs settled enough to even be able to take a pill, and then you
get sick, and you don't know what's been left in your system and what's out of your system.

    So the form of it could be really useful.
There is, I think, some sign of efficacy at that .5 dose, but you still come in with a third not having meaningful relief and, as a patient, those aren't odds I'd really want to go for of, like, hey, try this. You have a 33, 35 percent chance that it's not going to work for you, so you just got to hang in there and we'll find out if it does, and then we'll try something else.

    I think this is especially important as more and more research comes out, showing that women and minorities -- their pain is not often taken as seriously. They're not usually treated as well and so for individuals, what would happen in those individuals where they're saying, "This isn't really working for me," and you're on the ground. Would they be believed? Would they not be believed? That's something else to consider with that.

    We really need data on how long it's
meaningful for. If it's meaningful for an hour and you're taking it every 8 hours and it's taking up to 3 hours to work, is that efficacious? Maybe. In my view as a patient, no, not really. Ice could work just as well.

The other thing I wanted to raise a point about in terms of -- this could be efficacy and, I'm sorry, might go into safety a little bit, but I was concerned that looking at the data, that there were hardly any Asians in the study. It was mostly white females. I think there wasn't as much consideration for different races, different ages, and males as well.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: With respect to question 1 and Sharon's clarification about what we've heard already, I guess, if it said alternative non-opioid treatments are inadequate, maybe I would consider that to be a part of the way I would think of this. Otherwise, I would have to consider the fact that other opioids failed. With respect to concerns about time to onset and doses, I would
just reiterate what we've already heard. The only one that really showed any evidence to me was the 0.5-milligram dose.

I am concerned about onset of analgesia in a controlled setting of 90 minutes plus. It doesn't seem to me to be responsive or what I think patients would expect in a controlled situation.

Thank you.

DR. WINTERSTEIN: Dr. Beyrer?

DR. BEYRER: I just want to agree with what others have said in the consensus about the two lower doses. I think it's clear that the efficacy there is negligible. At the .5-milligram dose, I think the third of patients having no measurable benefit to me is a real counterindication in terms of efficacy.

I don't see that as reaching the standard you'd want to see if there are alternatives that achieved much better levels of efficacy and there certainly are. I think the time of onset is actually in some ways related to that just because of the likelihood of if you expect that it may or
may not work for you and you have a long way to
begin to have measurable benefit.

Those two things may not be experientially
so easily unpacked as we have been talking about
them, so just to say.

DR. WINTERSTEIN: Dr. Ruha maybe? Ms.
Robotti?

MS. ROBOTTI: Thanks. Most of the points I
wanted to make were made well and I won't repeat
them. I am not happy about the fact that it seems
to have been tested in a group that probably
wouldn't end up being prescribed it if you're
sending home, for example, people who just had
abdominal surgery or bunion surgery and the they're
going to have to get up to puke every time they
take this drug and rush to the bathroom.

It just doesn't seem like an effective drug
to give them. Also, it was being compared to
placebo in many of the trials and placebo is not
treating the pain after surgery like that. It's
just not a realistic comparison. It really should
have been compared to something that is a
clinically used method.

DR. WINTERSTEIN: Dr. Goudra?

DR. GOUĐRA: Thank you. I think two things I want to point out. One, obviously, the best part of the medication seems to be the way it's delivered. That might have a role in a certain category of patients who cannot swallow, for example, and are extremely nauseous.

So it probably has a role. And the second thing is, I know it isn't efficacious in one-third of the patients, but then it's efficacious in two-thirds of the patients. So maybe that's something, a problem we should look into as well. So there could be some patients who just cannot take anything orally, that with this route of administration could be a very good idea. And it still works in two-thirds of the patients.

DR. WINTERSTEIN: Any more comments?

(No response.)

DR. WINTERSTEIN: So my summary from what I heard, four major points; one, I think there was agreement among the committee that the two lower
doses seemed to be so marginally efficacious that they probably don't need consideration. Second, there is a mixed assessment within the committee about the relevance to a delay in time to onset. Third, I think the committee sees this drug in efficacy more similar to NSAIDs than to higher potent opioids.

I think that raises the discussion whether the benefit of having a Schedule III outweighs the fact that there is not that much efficacy that can be accomplished beyond what is already done with ketorolac or higher-dose NSAIDs in the outpatient environment.

Four, there is enthusiasm about a sublingual route for those patients who cannot take all drugs or are nauseated, but it's not clear whether this is really the right sublingual opioid or whether there should be another one.

Are these the major points? Did I get this right?

(Affirmative nods.)

DR. WINTERSTEIN: Great. Moving on to two,
safety, I anticipate there is more commentary here, so based on the available safety data, discuss whether the safety profile of Buvaya is acceptable for the proposed indication. Consider each dose of Buvaya in your discussion. Dr. Flick?

Dr. Flick: During the discussion of efficacy, there were several comments about the time to onset and I think the time to onset is probably more of a safety concern than it is an efficacy concern. So the time to onset will inevitably prompt the user to switch to some other opioid or non-opioid or dose earlier with the sponsor's drug. So I am concerned that this long time to onset is really a safety problem rather than an efficacy problem.

Dr. Winterstein: Dr. Zeltzer?

Dr. Zeltzer: Thank you. I guess, even if people would know that it could take a while before they get significant effect or for a certain population and their recommendations for other meds to tide them over for that, my main concern with this drug is the risk profile in terms of nausea.
and vomiting.

Given the kinds of situations, I could see oral surgeons who typically give an opioid for acute post-oral surgery pain, maybe have them sit and be available if the requirements were 12 hours, but this is a population for whom nausea and vomiting would really be a major problem following oral surgery with potential for bleeding.

Again, this is a population you may not want to give NSAIDs because of bleeding risk, but the high prevalence of nausea and vomiting with this medication, even more than the post-op morphine in the, was it, third final review, comparison, just seems to far outweigh any potential benefit and makes it kind of not doable.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you. I have a few points to make about the safety. First is the nausea and vomiting. Nausea and vomiting is also possible not only from post-surgical conditions, but also from the other opioids that people typically get afterwards like hydrocodone and oxycodone.
I think that we do not know what the rate of vomiting will be with this particular drug, when a patient is also taking the fast absorbable ondansetron that absorbs under the tongue. And in my own practice, we used to have incident rates of up to 80 percent of children that got opioids intraoperatively. And with the administration of ondansetron routinely, it's got to be below 5 percent.

So I think it's extremely effective and the answer is, we just don't know. So one of my recommendations to the FDA would be possibly to ask for a study where patients routinely get ondansetron. Or it doesn't have to be ondansetron, another type of effective antiemetic and see if that changes this kind of data.

Second thing is this. We've tossed around a lot at this meeting about the schedule. And so I really would just want to continue with the point that Steve was trying to make before. The schedule is completely arbitrary. I mean, just because it's Schedule III does not mean anything compared to
Schedule II.

For example, ketamine is a Schedule III drug. It's a great analgesic. It causes nausea and vomiting. I can't imagine any of us would allow patients to go home with a spray of ketamine. So I don't want people to think that, just because this is a Schedule III and not a Schedule II that there's something magical about it, that it's just so much better or less abusive or any of those.

I want to make a comment about the REMS programs. Even though it's a very popular way for the FDA and society now to try to improve opioid safety, there's really no good proof that that's going to happen. And there is no really good way to monitor whether or not REMS program is helping, it's beneficial. It's just really difficult.

Finally, my last comment about the risk is I'm really concerned about the hypoxia that was seen in Study 111 and I know that it wasn't seen in the other studies. It's really hard to tease out from the methodology and the results of 111 what
caused that hypoxia and whether or not that will be
continued if this drug is, you know, released into
the marketplace.

So I would ask that the FDA really look into
whether or not that is going to be seen in future
patients with this medication. It's a big concern.

DR. WINTERSTEIN: Dr. Litman, one quick
follow-up -- Zofran was used in 111 as far as I
understand. There was pre-dosing with
dexamethasone and Zofran before then.

DR. LITMAN: Right. But I don't think the
patients went home. And maybe they can clarify
this, but they went home with the Zofran under
their tongues?

MR. SHERMAN: They experienced nausea and
vomiting. They went home with the oral dissolving
tablet. That is correct. Yes

DR. LITMAN: If they did and they were told
to take it, if they were experiencing nausea and
vomiting at home.

MR. SHERMAN: Yes.

DR. LITMAN: Thank you. And that actually
clarifies a little bit more that maybe the Zofran wasn't as effective as we would like. Thank you.

   DR. WINTERSTEIN: As 10-milligram oxycodone and q6.

   DR. LITMAN: As an antiemetic. Say that again. I'm sorry.

   DR. WINTERSTEIN: Relative to 10-milligram oxycodone, q426, I think. Yes, 26, I think.

   DR. LITMAN: I'm not sure we saw any data here that compares the difference between oxy or hydrocodone.

   DR. WINTERSTEIN: Plus the randomization.

   DR. LITMAN: I see what you mean. Yes. That's right.

   MR. SHERMAN: They both went home with it, whether it was standard narcotic therapy or Buvaya.

   DR. LITMAN: Thank you for the clarification.

   MR. SHERMAN: Also, can I clarify one thing on the previous discussion?

   DR. WINTERSTEIN: Please.

   MR. SHERMAN: When you were talking about
the efficacy of the product, there was something
that I wanted Dr. Mariano to share with you. And
it's really when you're talking about meaningful
pain relief. The conclusion was that it wasn't
occurring. If you look at the 30 percent and 50
percent reduction in pain that Dr. Mariano's going
to share with you, I think that will help on your
discussion.

DR. HERTZ: This is Sharon Hertz. If that's
data that's already been seen -- we did see your 30
and 50 percent rates -- then we're not going to go
back over it again. They already have the
information.

MR. SHERMAN: It was 8 hours, but it wasn't
in the core.

DR. HERTZ: Still, we saw the 30 and 50
percent data.

MR. SHERMAN: Thanks.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: Yes. With respect to the
available safety data, just two main points; one is
that post-operative nausea and vomiting is not the
same thing as opioid-induced nausea and vomiting.
And one of the questions I asked earlier in the day
was the concern about anesthetic administered to
patients and my understanding is all general
anesthetics.

So I'm not 100 percent clear about what the
incidence is of administration of this medication
with resulting nausea and vomiting in the absence
of a general anesthetic, which would have given me
a lot more confidence. I can't separate the two
out.

That's one. And the other thing now, just
elaborating on what Dr. Flick said, in a real-world
situation, if you wait 90 plus minutes for a
patient in an institutional setting, whatever it
is, and there's no pain relief, the likelihood of
me reaching for ketorolac at that point in time or
IV acetaminophen is pretty low.

I had no clue as to what would happen to a
patient who is given these medication, who then got
some other type of opioid co-administered with it.
Unless I missed something, I just don't know, but I
know that that's what would happen in the real world. Somebody's going to reach for another opioid.

I doubt that they're going to spray a second spray sublingually. Somebody's going to reach for another opioid and we're going to be in water that I have no clue as to where we might end up. So co-administration with other opioids after a dose is important missing safety information for me.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: Michelle Ruha. My biggest concern is definitely the hypoxia. In the Study 111, that went as low as 86 percent, but then there was a healthcare provider to intervene and move the patient, stimulate them, and put them on oxygen. And these episodes of hypoxia did not all occur early.

It is hard to figure out why they happened. I know they happened mostly in the people with abdominal or breast augmentation surgery, but there's so many factors that we can't predict like body habits, undiagnosed sleep apnea, things that
patients might have where you could conceive they
would be sleeping at night, have these drops in
stats, no one is there to intervene, they may be
aspirating, we just don't know. Would the
respiratory depression worsen?

So I'm really uncomfortable with the high
rate of hypoxia.

the stats

DR. WINTERSTEIN: Dr. Meisel?

DR. MEISEL: Steve Meisel. First, I want to
echo what Dr. Flick and Dr. Zacharoff have both
side about the timing and delay causing an
increased risk and then to your point as well,
Dr. Zacharoff, about the potential that that gets
treated with another opioid. Then what?

I think that that's key and that's absent
information. But a couple of other points here;
one is, you know, we talked about this being used
because it's sublingual for people who are nauseous
and can't take pills.

If we're going to give them something
sublingual, that 80 percent of the time they're
going to get nauseous, and we're giving to them because they're very nauseous, I'm not sure that's, say, prescription for successful outcome. I think that's problematic. That's a population you'd want to avoid this sort of product in, not that you target this sort of product in because of its high rate of nausea.

As somebody said earlier and I think it's quite true in the world, the notion of being observed for 12 hours after your first and then your second dose -- and you come in for surgery and that takes up 2 or 3 hours. And you have your procedure done and then you have pre-procedure work.

You're getting into 16, 18 hours at best before they go home. In the real world, that's not going to happen. With finances and healthcare the way they are, people aren't going to stay in the same-day surgery are for that kind of time. Same-day surgery is often closed after a period of time.

So with the delayed hypoxia that we've seen, these people going home before that 12-hour period
and who knows what's going to end up happening when they get home and the risk of respiratory depression in the home environment, which is an uncontrolled environment where nobody is waking them up and monitoring, attending to them like they would in an institutional setting to me is very high risk and very frightening.

DR. WINTERSTEIN: Dr. Coffin?

DR. COFFIN: My comments echo a lot of Dr. Meisel's comments and the comments of others, the adverse event profile to nausea, vomiting, and hypoxia seem out of range of the other opioids. In the trial 111 and the proposed remediation of that, keeping somebody in house for 12 hours just doesn't seem workable.

I'm also still a little bit concerned about the proposal for it to be around the clock for up to 7 days. I don't feel like that's been sufficiently explored. It's not used in other management of acute pain and I think it carries some risks that are not really well explored or well defined.
DR. WINTERSTEIN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: One of the big things I kept thinking about is obviously, at the lower doses, given the nominal efficacy and the increased rates of nausea and vomiting, it doesn't really seem worth it. But I just kept thinking about, with nausea and vomiting, that the vomiting especially could cause the patient to have more pain.

There's all kinds of body parts that get involved when you're vomiting. And so whether you've had stuff done on your head, your neck, your shoulders, your back, or your stomach, that could certainly lead to the individual having more pain that has to be dealt with and could lead to a slow recovery.

Also, it could lead to damaging yourself, depending on what type of work you've had done. There was the example of the possible hematoma because of the strain on the body. It's also more likely that you could be getting infection at times if you're throwing up on yourself, which I have
unfortunately done because of certain meds or
you're in the bathroom, in and out all the time,
and you're not totally with it. And you're not
making sure you always wash your hands really well
and do this really well.

So there's other risks for vomiting than
just the vomiting itself. It could also lead to
people not taking the medicine as they're supposed
to, especially if it's supposed to be this around-
the-clock thing because I'm finally feeling better.
I don't want to get sick again. I'm just going to
avoid it.

Then with this requiring the antiemetics, I
think one thing we have to be mindful of is more
meds mean more money for people. And that's
another thing that sort of piles on a lot of times
when people have different types of bills and
things coming in. It also means more risks.

One thing I was thinking of is, we have to
imagine that some of these people might also be on
muscle relaxers. They might have reactions to the
Zofran, as a lot of people I know do, where it
makes them more drowsy.

So if we have this issue of hypoxia, right, and they're already going to be somewhat drowsy from the opiate, and then they're also getting the Zofran, which might make them a little drowsy and they might be on some other medication that makes them a little drowsy, not to mention you're drowsy from having gone through a procedure or being in pain, the issue of the hypoxia; I think there could be a really strong cumulative effect going on when you put all these pieces together.

DR. WINTERSTEIN: Dr. Flick?

DR. FLICK: This question is for Sharon. Sharon, if this were to be approved, I presume it would be labeled that therapy has to be initiated in an inpatient setting or monitored setting and the patient has to be observed for 12 hours. Is there an example of another medication that is labeled like that?

The reason I'm asking is, it's been alluded to by others here. The likelihood that that's actually going to occur would seem to be low.
DR. HERTZ: I remember, when we first started using sumatriptan, we were advised to do that first dose under observation and with an ECG. I think quite a few people did that, but that was in the office and it wasn't for a prolonged period of time.

DR. FLICK: Not for 12 hours.

DR. HERTZ: We do have products that are labeled just for inpatient use. ketorolac is the IM and all and it's also labeled for very limited duration of use because of risk. And from what we can tell, for the most part, people adhere to that.

There might be examples of other situations with observation, but I don't know of any in the analgesic arena. If they exist, they're in other therapeutic areas.

DR. FLICK: Thank you.

DR. WINTERSTEIN: Dr. Goudra?

DR. GOUADRA: Thank you. I am sorry. I might end up repeating some of the things which Drs. Litman and Zacharoff said. Yes. I mean, trying to fight this post-op nausea and vomiting...
for decades now and it looks like we got somewhere, I don't know how much extra this new drug is going to contribute to the PRN in the elderly. I know there are new drugs which are coming.

So that's one major problem, we don't want to adapt. And many patients often tell me that their worst experience of the whole hospitalization was post-op nausea and vomiting.

The second thing is, as it has been pointed out because of 60 to 90 minutes' window before the clinical efficacy starts, not many patients will be as tolerant and, worse, they might end up using the same spray twice or three times and that somebody who sees hypoxia on a daily basis in endoscopy area, once it goes below 90, it can hit bottom very, very quickly and that could be a point noted.

So I think these are probably important things to bear in mind.

DR. WINTERSTEIN: Dr. Rich?

DR. RICH: Jody Rich again. So thinking about the safety, I was really kind of excited about this because I see so much damage to people
on the pure opiate agonists and I thought this
would be great. This is probably the safest opioid
we could use for pain.

So I was very concerned about the hypoxia
mostly. I mean, I've played with those little
pulse oximeters, and tried to hold my breath, and
see how low I can get it, and see how low I can get
it, and I can't anywhere near 90, let alone 92 or
95.

So I think that's surprising. I've also had
occasion to look at a lot of overdose death
records. And I'm also struck by the rarity of an
overdose death with buprenorphine. We almost never
see it and, if we see it, there's always other
substances in the midst of this opioid epidemic.

So this is kind of confusing to me. Why
would there be such toxicity and yet we haven't
seen that. And then I'm thinking now that there's
probably something that has to do with the timing,
that you're giving general anesthesia and then
you're giving this buprenorphine.

So I'm wondering if maybe there's an
interaction and I don't know what anesthesiologists
do, but I have a feeling they do a little bit of
this and a little bit of that. But if there's any
correlation between what certain of these patients
got, particularly with the hypoxia and maybe even
the vomiting, that that might be a clue as to
what's going on here. Thanks.

DR. WINTERSTEIN: Dr. Zeltzer?

DR. ZELTZER: I was just thinking that one
way to differentiate how much of the nausea and
vomiting is left over from common side effects of
general anesthesia, especially in this population
that's been tested, may go back to the oral surgeon
tooth extraction where, typically, that's done
under regional anesthetic, not a general
anesthetic.

Doing a study, I think Vicodin is used most
often for short-time post-op, but to have some
comparative study in a situation where the
individual needs post-op acute pain management for
what could be a moderate pain for a short period of
time, but not have a general anesthetic, that might
be a model to really tease out how much of this side effect of nausea and vomiting that we're seeing, which is pretty high, relates to the condition in which the drug was studied or compared.

DR. RICH: Could I just respond to that?

DR. WINTERSTEIN: Sure. Go ahead.

DR. RICH: I think that's true, but it's really striking also when you look at the O26 and the O62 studies, that there's just such a clear dose relationship with the buprenorphine. As you go up in dose, you go up in both nausea and vomiting, both in the same linear fashion, and presumably, those patients all have the same, the bunionectomy patients anyway, general anesthetic exposure.

So the dose-response relationship with nausea and vomiting in the buprenorphine is pretty clear and rather striking. And compared to the historical controls, it's also off the charts in the 111.

DR. WINTERSTEIN: Dr. Warholak?

DR. WARHOLAK: So as we're talking, I agree
that the nausea and vomiting is an issue, but the
hypoxia even more so, so I would worry about that,
especially when the patient is at home and not
being monitored. But for the nausea and vomiting,
if we're going to give, like, let's say ondansetron
on a regular basis with this medication,
ondansetron has been known to cause Torsades and
buprenorphine is also associated with the possible
risk of Torsades.

So we don't have any data on that right now,
but what does that lead to?

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thanks. I just wanted to
respond to a couple things. So a lot of the
studies that were done on buprenorphine were done
by Dr. Dahan, who has been referenced here. And he
came and studied these in our lab in the 1990s.

So I've spoken to him about it. He was
always so impressed by the amount of nausea and
dysphoria that this drug causes, out of proportion
to the other opioids because he's an
anesthesiologist, so that's one thing.
The second thing is, Dr. Rich, I would imagine that mostly overdose data that you're looking at is probably due to the oxycodone, or hydro, or maybe fentanyl-laced things, but as anesthesiologists, we just don't use buprenorphine. And so I just don't think it's out there in the marketplace. That's my sense. I don't know anybody that uses it. I think that the vast majority of it is used as suboxone or one of its derivatives.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: Just in response to the point about the dose relationship and the nausea and vomiting, it's not clear to me as to whether that had anything to do with other medications that the patient might have been administered to as part of the general anesthetic.

The only way to factor that out is to look at it in people who didn't have a general anesthetic. To this point, if there's any surgical model that I have seen in my 30-year career, where the surgeon looked at me square in the eyes and
said "Do not let this patient have nausea and vomiting," it's an abdominoplasty because the act of retching could cause tearing of the sutures and wound dehiscence.

So while I think it's a really good idea that that was considered to be one of the models, I cannot in any way -- and again, I'm still not clear as to who the prescriber of this medication would be because I think, if a surgeon saw the rates of nausea and vomiting with the .5 dose, they would stay away from it.

I think patients do say, "No matter what happens to me, don't let me be nauseous after the surgery. I can deal with pain, but I don't want to deal with nausea and vomiting." So when a surgeon looks at me and says, "Don't use nitrous oxide, don't use fentanyl, don't use this, don't use that," because they relate that to nausea and vomiting, I can't separate out whether the buprenorphine interacts with other medications that are part of that general anesthetic regimen, but I could if it was a regional or local anesthetic.
regimen.

DR. WINTERSTEIN: Anyone else?

(No response.)

DR. WINTERSTEIN: So to summarize this, I'm a little unorganized here because there was so much. So there is one major theme that has to do with the time to onset, the potential for redosing, and the cumulative effect that might happen related to this as well as the lack of efficacy and the need that someone might want to use another opioid alternatively and what would happen then.

So essentially, the safety data related to that as well as the efficacy data related to that are missing. And the safety of course isn't particularly concerning in the outpatient environment. And that relates to the other big theme of hypoxia. I think that everybody on the committee is very concerned about the high rate of hypoxia that were observed.

I think the committee also sees this as a major threat to the potentially assumed safer profile of this drug as Schedule III. My personal
concern would be that practitioners consider it safer because it is a Schedule III drug, yet looking at the hypoxia rates at the dose that appears to be efficacious, we may actually have an un-safer product in front of us, which is counterintuitive and might be difficult to communicate to providers.

In that context, there was also a lot of discussion where that product would be used. And while most of us would probably agree that, in the inpatient environment, it might be safe, there's also concern that very few people in the inpatient environment might use it because of the increased risk for nausea and vomiting. I cannot imagine that, when I have the opportunity to use more potent opioids with less nausea and vomiting, that I wouldn't make use of that.

That then relates to the question and the concern about the outpatient use and the issue with the proposed REMS and necessity to monitor a patient's responses. With respect to respiratory depression, I think most on the committee feel

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that, in the outpatient environment, it will be
difficult to monitor that and that 12-hour
monitoring requirement or suggestion that's put
forward by the sponsor would really not be feasible
in outpatient surgery.

As discussed in inpatient surgery, there may
be a preference for other products, so the 12-hour
monitoring there may not happen either.

There were some mentioned about the around-
the-clock dosing and what really the advantage of
this is over PRN schedule and whether that is the
safe alternative. There was also some puzzling
about the lower overdose rates related to exposure
to buprenorphine, which I agree with some previous
comments. It's most likely related to just smaller
prevalence of use and not necessarily a safer
safety profile.

Then the final comment related to QT
prolongation and the concern for Torsades, in
particular if the product is used consistently with
Zofran. Did I capture everything?

(No response.)
DR. WINTERSTEIN: No comments. Moving on to 3, discuss any concerns you may have regarding the abuse or misuse of Buvaya and whether, based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse and misuse. Dr. Zacharoff?

DR. ZACHAROFF: I don't know that I heard any data presented about what would happen if somebody sprayed this into a diluent and tried to inject it, spray it intranasally, what might happen. So I'm very concerned about abuse and misuse of this particular delivery system.

I do get the idea that having to have a pair of scissors available to open the packages is some baseline form of deterrence, but I don't really consider that to be much of a problem except if somebody gets home and they have a bunch of these medications and they can't find the scissors, which would probably happen to me.

I also am not sure of what the concern is if people use this medication in ways other than the way it's directed. As we've heard, people may want...
to double up on doses and things like that. I'm not sure that somebody's going to do a spray count and require the patient to bring in at post-op day 3 the number of sprayers.

Then just lastly, I did hear mention of the fact that you would need tools to disassemble the spray mechanism and reference to the website Bluelight. If it's not up there already, I'm sure there will be directions on how to disassemble the sprayer on Bluelight shortly.

I'm concerned about that because people who abuse and misuse drugs do have tools. And they do have ways of getting into things. And if they could pool all of the medication out of all the sprays that they're given and do something with it, it would concern me from an abuse-misuse perspective. Thank you.

DR. WINTERSTEIN: Dr. Meisel?

DR. MEISEL: There are two elements here. There's a misuse and an abuse perspective. The misuse I think potential is very high, as we talked about with the previous question. The long onset
of action, and combined with the fact that it may not even work all that well, will lead people to be spraying more often than they should with all the adverse effects that they go along with. That's a misuse element of it.

From the abuse, I think the sponsor is relying on the fact that this is a Schedule III agent and therefore the risks are lower and we don't have to worry about it. They're relying on the fact that they've got a similar delivery system with fentanyl.

So they've heard of problems, but are not aware of any problems. They haven't really looked for the problems, it seems to me. The fact that this drug has not been high on the list of abuse until now can be because of the properties of the drug, but it could also be because of why and how the drug was used.

As Dr. Litman pointed out, nobody uses this really for pain anymore on an inpatient setting. All of its use is for people with narcotic addictions. That's a different population than
we're talking about here. Will people try to get
into this and use it in ways that they shouldn't
get high and that sort of stuff? That hasn't been
explored. We just don't know.

That research hasn't been done. I think
there was a lot of assumptions being made on the
part of the sponsor on this basis, that I for one
am uncomfortable with. And as Dr. Zacharoff
pointed out, we asked the question before and the
answer was they haven't looked.

There is a possibility that people will
spray this thing into cups or whatever and do God
knows what with it, inject it, inhale it, do
whatever. Yes, they can break it up. And then
from a diversion point of view, these little
packets that you put it in and seal it up and do
whatever, put it under the Christmas tree with, I'm
not convinced that that is effective because I'm
not sure people will actually go and do it.

Maybe you can explain to them really well
and they'll understand it. Will people really go
through the motions of doing all that stuff? I
don't think so. And then you see the 13-year-old come home from junior high school and he's looking to abuse and he sees this.

I think the risks are just unknown, unexplored, and we shouldn't be making assumptions.

DR. WINTERSTEIN: Dr. Dasgupta?

DR. DASGUPTA: Having conducted post-marketing surveillance on buprenorphine products in the United States, I for one actually am not particularly concerned about the abuse and misuse of this particular one, partially because we don't know. We don't know what the form factor does to the desirability of this product and we see people putting heroin into nasal sprays and selling that online. Right?

So there's all sorts of form factor experimentation that's happening in the background. But given that this is going to be a new branded opioid, it's going to be expensive and there are a lot cheaper ways to get high.

I think at this point, given people we would expect to be a very limited distribution of this
product, very expensive, tightly controlled, I'm not particularly concerned.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thanks. I was actually going to just say almost the same thing as Dr. Dasgupta. I think that the side effects are going to drive away potential abusers. And the way it's packaged, I mean, listen, there's always a way to abuse things in the community. There will always be a way. But when you compare it against the pills, I agree. I'm not concerned.

DR. WINTERSTEIN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: One concern I have for a possibility of misuse is in regards to the method of delivery. Does the person feel like they took it? When you take a dissolving tablet, you have the tablet. You put it in your mouth and then it's gone or with certain injections. You take them. You feel the needle, but they even will have indicators on them to be like, did the medicine actually go in, did I do this right.

So this might be different if they're in an
inpatient setting, but I could see, depending on how much liquid there is, how much spray there is. Doing it and going, well, is that it? Did I do it right or did I not? And then if you're not getting much relief later, thinking I must not have done that right.

So I could see where the potential would happen. I mean, if you go online, you could see people being like, did I do this right, did I take this right, I'm not sure. So if there were some way to indicate that, yes, the medicine is out of it, yes, this has worked.

I think the other thing is that it was mentioned that people might take it sooner if they're not getting good relief, but they also might take it with other stuff. They might go, you know what? This has barely made a dent. Clearly, this is like -- might as well be aspirin. I'm just going to go take the stuff I usually take or my friend has stuff I can take or whatever.

I think, by taking a long time for it to work and by it not making a big dent, people might
think it just sort of doesn't really do anything, I can go take what I want or even a lot of times people will go have a glass of wine or have alcohol with the medications as well.

So that's something to be mindful of, but they think, I'll just take the edge off.

DR. WINTERSTEIN: Dr. Flick?

DR. FLICK: I would just like to take one moment to congratulate the sponsor on making, it, a serious attempt to address a public health concern by bringing something to market that would appear to have a lower abuse potential than what exists currently. We have to keep in mind that the alternative to this are drugs like oxycodone, hydrocodone, that we know are the cause of death of many people every day.

So although this doesn't seem to be as efficacious or safe as we would hope, I think nonetheless this was a laudable attempt to address a real concern.

DR. WINTERSTEIN: Dr. Kaye?

DR. KAYE: I was just going to add that
there's been a big push for enhanced recovery after surgery protocols which basically the theme is that the patient leaves the hospital quickly. And so under this thought of misuse, I'm including not only the patient, but as well as providers who may add another medication and have a drug-drug interaction that can potentially cause an adverse effect.

You say we're all smart and we're going to do the right thing, but if you look at, say, PCA, which has a much different onset in duration than say an oral or injectable medication, we have almost regularly physicians blowing it and basically causing severe catastrophic respiratory depression just because of a fundamental lack of understanding of PCA, which started in the early 1970s.

So this would require a lot of education of all stakeholders to get it right so that it's okay to keep them longer and basically do a lot of the things that we've been teaching ourselves to do currently.
DR. WINTERSTEIN: Ms. Robotti?

MS. ROBOTTI: Dr. Joniak-Grant made a very good point that I wanted to make, but you made it so well I'll go fast. That's good. And the other point I wanted to make was that the only real benefit offered by this drug that I see is the assumption that it would lower the number of people who become addicted to opioids post-operatively. This is an assumption that's neither tested nor proven.

Buvaya will be given to opioid-naïve patients. It has euphoric effects and it could lead to just as many addictions as higher-impact opioids among that particular population. We just don't know.

DR. WINTERSTEIN: Dr. Coffin?

DR. COFFIN: So I want to actually go back a little bit to Dr. Rich's comment about buprenorphine overdose fatalities and I, too, have followed overdose epidemiology for over the last 20 years. And Dr. Rich is including the millions of people who are using buprenorphine for opioid use
disorder in those data.

It is quite rare. Even in that population, it's quite rare that we see a buprenorphine mono death. It's usually with other drugs and it's still fairly uncommon. So I, to, give the sponsor some credit for trying to bring a product that is safer. Buprenorphine is a safer opioid than other opioids.

I devoted much of my career and continue to addressing substance using, addressing the opioid crisis, and I don't have concerns about this product in terms of intentional misuse, diversion issues. I think it's a very small dose and there's plenty of other products that are a much higher dose. If you wanted to get a buprenorphine product through diversion, I think you would go for the sublingual tablets long before you would try to access a product like this. It's just too little of an amount of a drug.

Then in terms of accidental exposures, I think the sponsor has done a good job trying to prevent accidental exposures with their approaches.
I would agree and it comes back to my comments about the around-the-clock approach. That's what I don't like because I think that the longer exposure post-op to opioids is what potentially leads to issues with use disorders.

DR. WINTERSTEIN: Dr. Goudra?

DR. GOUDRA: Thank you. Just one point to make, rather extension of one point -- we all know buprenorphine has got a ceiling on respiratory depression, which is a great thing. Keeping that in mind, I'm a bit surprised that, even in therapeutic doses, it caused hypoxia.

So whether it has got anything to do with the route of administration, if that's the case with multiple doses, I don't know whatever the degree of respiratory depression and, as a result, walking into the same problems with opioids.

But I guess, on the upside, one, it's not very effective and, second, it causes lots of nausea and vomiting, which is probably another thing somebody was trying to use for recreational purposes looking for it.
DR. COFFIN: Thank you.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: This is a question for Sharon. I'm just wondering, if somebody is prescribed just a 7-day supply of this medication, they no longer need it after day 3. Can we assume that there's something specifically in the label about disposing of unused spray devices?

DR. HERTZ: Yes. There would be. It would probably mimic what's in the label for the fentanyl product.

MR. SHERMAN: Can I address that question, too?

DR. WINTERSTEIN: Was there a question?

MR. SHERMAN: For the use package, in the packaging there would be an individual bag that you use for disposing the used products. Any unused products, there's a bigger bag that is lined with an absorbent. You spray the unused devices into that bag, seal it, and then it's just like the disposables.

DR. WINTERSTEIN: So to summarize, I think
there is consensus among the committee that the potential for misuse is there and it might be high because of the potential need for or perceived need to have to re-dose because of a delayed effect and relatively low efficacy.

There was also a concern that patients might feel that the dose was even not administered and any kind of indication that would ensure them that the product was actually released might help, but I think overall, just the perceived effect might be delayed or might not be as effective as desired, might result in a redosing.

We have seen that this results in higher risk for hypoxia under respiratory depression. I think the committee also agrees that the potential for abuse is low just because there's not that much in there just because it has a good amount of side effects that are clearly not desirable.

So it would probably not be the target for a large population of abusers, but along that note, I have thought a little bit about how practice might start using this product. And given that it is a
Schedule III product and given that it is perceived to be safer from an addiction perspective, I'm actually specifically worried that this could be used in a population with a history of substance use disorder.

Then we basically have an exposure to somebody who might have already other opioids on board or benzodiazepines. We have exposure of a product that actually has a higher risk for hypoxia than alternative products that could be abused.

That seems like a set-up for a big safety issue and potential increase in opioid overdoses.

Anything that I forgot?

DR. FLICK: Do you mind if I comment?

DR. WINTERSTEIN: Dr. Flick?

DR. FLICK: I just think that this drug probably has a higher safety profile than the alternative drug, so these patients are going to get something else if they don't get this, and I think that buprenorphine has a better safety profile than oxycodone does. So I think that probably should be reflected, that the public
health risk related to abuse and misuse is lower for this drug than would be for alternative drugs.

At least that's my sense. I don't know if others share that sense.

DR. WINTERSTEIN: From an abuse potential, not from use of regular dose potential, because if we look at Study 111, that doesn't really say --

DR. FLICK: Right. So that's a misuse.

DR. WINTERSTEIN: Yes.

DR. FLICK: But the potential for abuse and as a public health concern or question; I think this drug has a favorable profile relative to the alternative.

DR. COFFIN: This is Phillip Coffin. I would agree

DR. BEYRER: Yes, I think that's right, too.

DR. WINTERSTEIN: Then I think we are ready to move on to a vote. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and they 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. If there are no questions or comments concerning the wording of the question, we will now --

DR. MEISEL: Just for clarity, if we vote yes, we're voting to recommend approval and, if we vote no, we're voting to not recommend approval? It's worded a little funny here. I just want to make sure that we don't misinterpret the question.
DR. WINTERSTEIN: Yes. So let's read it.

So overall, the benefits of Buvaya outweigh the risks for the indication of the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, supporting approval of Buvaya.

So I think we do vote in favor or against approval. Does everybody agree on that?

DR. FLICK: So yes means what and no means what?

DR. WINTERSTEIN: Do the benefits outweigh the risks? So do the benefits support approval? So yes means approve, no means don't approve.

DR. HERTZ: This is Sharon Hertz. Yes.

DR. WINTERSTEIN: Yes.

DR. GOUDRA: Just one more question; can we say yes in very limited circumstances? Say inpatient under the supervision or prescription [indiscernible] analysis [indiscernible] in patients who cannot take orally, or say waiting for surgery, they have a lot of pain, and as a result, they're [indiscernible].
So can you qualify the yes vote?

DR. HERTZ: This is Sharon Hertz. The way to qualify a yes vote is, after the vote, we'll go around and ask everyone why they voted the way they chose. And you can provide that input there for any type of yes or no decision.

DR. WINTERSTEIN: Any discussion?

(No response.)

DR. WINTERSTEIN: Looks like we're ready. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or if you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. WINTERSTEIN: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 1 yes, 18 no, 0 abstentions.
DR. WINTERSTEIN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to you can state the reason why you voted as you did into the record. Let's start with Dr. Joniak-Grant. You're already prepared.

DR. JONIAK-GRANT: Dr. Elizabeth Joniak-Grant. I voted no for the reasons I've already state, not efficacious enough, too many people didn't have meaningful relief, and the much higher rates of adverse events and side effects.

MS. ROBOTTI: Hi, Suzanne Robotti. I think I've expressed most of my concerns about this drug already. Thank you.

DR. DASGUPTA: Dr. Nabarun Dasgupta. I voted no. I think it was a commendable effort and a good public health mission, but the product isn't perfect at this time.

DR. COFFIN: Dr. Coffin, I voted no. I also feel that it was a commendable effort. However, marginal efficacy and high AE rates made it non-viable.
DR. BEYRER: So I'm the outlier vote here. And for me, the only really compelling thing that shifted my vote is the alternatives and the relatively lower risk of abuse with this drug, not misuse.

DR. RICH: Jody Rich. I concur with the previous people.

DR. BOUDREAU: Denise Boudreau, and I voted no. While there was some indication of efficacy, it wasn't very strong and was especially concerned about some of the adverse events and especially the hypoxia.

DR. MEISEL: Steve Meisel, I voted no. As just to summarize, the rationale for this drug, that it's Schedule III, as the public health imperative here I think is misguided. Maybe efficacy problems, particularly at lower doses, but even at the higher doses, the onset of action is placebo-controlled and will lead to secondary problems such as misuse or rescue opioids or whatever have you.

I'm not convinced that the abuse potential
has been well assessed, the disposal tactic has been tested. I think the idea of a 12-hour watch in a controlled environment is not practical and will lead to other kinds of problems.

Then just as a side note that we haven't talked about before, the delivery system and delivery form with all of that packaging, the amount of plastic in the waste stream that would result from this would be tremendous and I think that can't be discounted.

DR. WARHOLAK: This is Terri Warholak, and I voted no. And I do really think this is a laudable attempt. It's an innovative interesting dose form and I commend the sponsor for trying to find a safer alternative than full opioid agonist. But I am really concerned about the limited efficacy and the higher rate of adverse events.

DR. RUHA: Michelle Ruha. I would like to see a sublingual buprenorphine spray. I think that was a great idea, but the adverse, especially the hypoxia, is just too high rate of hypoxia. It's not worth the risks.
DR. WINTERSTEIN: Almut Winterstein. I voted no. There was three safety issues, side effects, misuse, and abuse, and it really depends on which is rated higher. For me, the nausea, the respiratory depression, and the misuse, the chance for misuse in overdoses seemed more relevant than the lower abuse potential.

I'm still intrigued by the extremely high hypoxia, nausea, and vomiting rates relative to other buprenorphine products, and I mean, I would love the sponsor to look into what that is, whether this is the kinetics or what is it with that delivery method that seems to create clearly a safety profile that I'm sure the sponsor didn't expect, either.

Is there anything that can be done to attenuate that? I think, if that were possible, everybody here would love to see you again.

DR. GOUDRA: I'm Dr. Goudra. I did vote no for the reasons which have been elaborated. However, I do see a role in very limited circumstances which I kind of mentioned. Thank
DR. ZACHAROFF: Hi, Dr. Kevin Zacharoff. I also would like to commend the sponsor on looking for something that mitigates the societal risk of use of opioid medications for the use of acute pain management. I voted no. And probably the single biggest reason is because of the lack of data of exposure to this medication and other substances that could potentially depress the central nervous system.

I don't expect that this drug would be abused by itself. I expect that it would be abused if it were going to be abused along with other substances. But my greater concern is what would happen when somebody would go to treat breakthrough pain with another opioid and total absence of any evidence of what that could lead to. Thank you.

DR. LITMAN: This is Ron Litman and I voted no because of the hypoxia. That was my main concern. I would like nothing better than to envision this drug that we would send our surgical patients home on a little sublingual spray instead
of the oxy or hydrocodone. And there is even a libertarian molecule in me that says, the nausea and vomiting, let the market sort that out. Surgeons are going to have one bad experience and never prescribe it again.

But I can't walk away from this meeting with that hypoxia data and vote yes. So if there was a way that that could be teased out better or more patients, a different kind of trial, or even possibly, as Dr. Goudra said, a very limited use in the hospital with a monitored bed and certainly then the other side effects would sort themselves out really fast as to whether or not physicians would prescribe it.

DR. MCCANN: Hi, my name is Mary Ellen McCann and I voted no also. I think the delivery system would be great innovation and I do believe this drug would be less abused than other narcotics. I was stuck with how limited the indications for this drug could possibly be and, in the real world, just absolutely not possible to keep patients after bunionectomies for 12 hours.
So that bothered me. It appears to have limited efficacy and I think the safety profile, especially with the hypoxia, is a real problem.

DR. ZELTZER: Hi, I'm Lonnie Zeltzer, and I voted no. Again, I commend the company for creating a sublingual form that could be easier to use post-op in acute pain situations. I was concerned about the delay in time of onset and lower than optimal likelihood of efficacy compared to other opioids that are out there, which might then increase risk because people might then end up using other analgesics.

You get combined risk and I was concerned about the nausea, vomiting, and hypoxia profile. I would love to see testing in another acute pain situation in which there isn't a combination of general anesthesia and a compounding, at least trying to sort out some of the confounders in this case.

DR. FLICK: Randall Flick, I voted no just simply because the risk-benefit ratio is unfavorable. I would echo previous comments that
the market for this drug given the restrictions around its use would seem to be very small.

DR. KAYE: My name is Alan Kaye. I voted no for similar reasons, weekly efficacious, slow onset, rescue very high, and we have lot of non-opiates that have shown efficacy in this realm. We mentioned NSAIDs, but there's acetaminophen, gabapentin, ketamine, alpha 2 agonist, other agents that are out there that work in real time and don't have this 12-hour window.

We talked about side effects, nausea, vomiting, and hypoxia being very high, and abuse and misuse. Thank you.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen, I voted no for reasons that have already been mentioned. I think the risk-benefit ratio for me, the safety issue really outweighed everything else.

I also thought, while the sponsor made a great effort in developing a new form of delivery that has some appealing aspects or features, particularly with respect to abuse, I wasn't
particularly compelled with the data that were
presented regarding use outside of a controlled
environment and understanding particularly with the
hypoxia side effect and trying to address that in
the data that they presented.

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

DR. HERTZ: I just want to, once again,
thank you all for coming, providing your comments
and your thoughts. It's always very helpful and
much appreciated.

Adjournment

DR. WINTERSTEIN: Thank you, everyone.
Panel members, please take all your personal
belongings with you, as the room is cleaned at the
end of the meeting today. All materials left on
the table will be disposed of. Please also
remember to drop off your name badge at the
registration table on your way out so that they may
be recycled.

We will now adjourn the meeting. Thank you.
You were a great committee, very focused, very
targeted. We are even early here.

   This was actually my last meeting as chair
   of DSaRM, but I'm sure I'll see many of you in one
   way or the other again.

   (Whereupon, at 2:57 p.m., the meeting was
   adjourned.)