FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

JOINT MEETING OF THE

ANESTHETIC & LIFE SUPPORT DRUGS ADVISORY COMMITTEE

AND THE

DRUG SAFETY & RISK MANAGEMENT ADVISORY COMMITTEE

Friday, November 14, 2008

Gaithersburg, Maryland

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P R O C E E D I N G S

(9:15 a.m.)

DR. KIRSCH: Good morning. I'm going to call to order this meeting. My name is Jeffrey Kirsch. I'm the Acting Chair of the Committee for today, and I have a little thing that I have to read.

It says for topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. 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

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Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

I'd also like to ask the members of the audience and the members of the panel to please silence pagers and cell phones so we're not interrupted.

And I would like to start the meeting with an introduction of the people who are on the Committee, and we'll start to my right, with Dr. Rosebraugh.

DR. ROSEBRAUGH: Kirk Rosebraugh, director, Office of Drug Evaluation II.

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DR. RAPPAPORT: Bob Rappaport, director, Division of Anesthesia, Analgesics & Rheumatology Products.

DR. HERTZ: Sharon Hertz, deputy director, Division of Anesthesia, Analgesics & Rheumatology Products.

DR. DeWIT: Harriett Dewit, Department of Psychiatry at the University of Chicago, and I'm a temporary voting member.

DR. KERNS: Morning, I'm Bob Kerns. I'm the National Program Director for Pain Management for VHA, and I'm a professor in the Department of Psychiatry and Neurology at Yale University School of Medicine, and I'm a temporary voting member.

DR. ROSENBERG: Jack Rosenberg. I'm an addictionist and pain management specialist at the University of Michigan, Department of Anesthesia and Rehab in Ann Arbor VA in Michigan. I'm a temporary member.

MR. YESENKO: Michael Yesenko, patient representative.

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DR. WOLFE: Syd Wolfe, Public Assistance and Health Research Group, member of the Drug Safety and Risk Management Advisory Committee.

DR. KRAMER: I'm Judith Kramer. I'm Associate Professor of Medicine at Duke University general internal medicine and clinical research, both clinical trials and observational studies of drug safety and effectiveness, and member of the Drug Safety And Risk Management Advisory Committee.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the designated federal official for the Advisory Consultant staff.

DR. KIRSCH: Again, I'm Jeffrey Kirsch. I'm the professor and chair of the Department of Division of Anesthesiology at Oregon Health Science University, and the acting chair.

DR. PAULOZZI: Leonard Paulozzi, Federal Centers for Disease Control and Prevention, and I'm a temporary voting member.

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DR. BRULL: I'm Sorin Brull. I'm a professor of anesthesiology at Mayo Clinic, and I'm a temporary voting member of the Anesthetic and Life Support Drugs.

DR. ZELTERMAN: I'm Dan Zelterman, professor of biostatistics at Yale. I'm a member of the Anesthetic Committee.

DR. KRIVACIC: I'm Susan Krivacic. I'm a patient representative on both committees.

DR. DENISCO: I'm Richard Denisco, medical officer at National Institute of Drug Abuse, National Institutes of Health, and a temporary voting member of the Drug Safety.

DR. LESAR: Timothy Lesar, director of Clinical Pharmacy Services at Albany Medical Center in Albany, New York. I'm a member of the Drug Safety and Risk Management Committee.

DR. ZUPPA: Good morning. I'm Athena Zuppa. I'm an assistant professor of Pediatric Critical Care and Clinical Pharmacologist at the Children's Hospital of Philadelphia. I'm a voting member of the Anesthesia Committee.

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DR. LORENZ: Hello. I'm Karl Lorenz. I'm a health services researcher, palliative medicine, physician and general internist with the VA Greater Los Angeles -- UCLA and Rand Health. I'm a temporary voting member.

DR. NUSSMEIER: Good morning, I'm Nancy Nussmeier. I'm chair of Anesthesiology at SUNY Upstate Medical University in Syracuse, and I'm a voting member of the Anesthetic Committee.

MS. POLLOCK: I'm Julie Pollock. I'm an anesthesiologist at Virginia Mason Medical Center in Seattle, Washington, and I'm a member of the Anesthetic Committee.

DR. TORTELLA: Bartholomew Tortella, industry representative to the Anesthetic Committee.

DR. BURLINGTON: I'm Bruce Burlington. I consult with the pharmaceutical industry. I'm a non-voting industry representative to the Drug Safety and Risk Management Committee.

DR. KIRSCH: And I would like to recognize Dr. Francis, please.

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DR. FRANCIS: Dr. Skip Francis, deputy director, Office of Surveillance in Epidemiology at FDA.

DR. KIRSCH: Next, I will ask Kalyani Bhatt to read the conflict of interest statement.

DR. BHATT: The Food and Drug Administration, FDA, is convening today's joint meeting of Anesthetic and Life Support Drugs and The Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees, SGEs, 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 Committee's compliance of federal ethics and conflict of interest laws

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covered by but not limited to those found at 18 USC Section 208 and 712 of the Federal Food and Drug Cosmetic Act is being provided to participants in today's meetings and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it's determined that the agency's need for a particular individual's service outweighs this potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the

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Committee's essential expertise.

Related to the discussion in today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses and minor children, and for purposes of 18 USC 208, their employers. Those interests may include investments, consulting, expert witness testimony, contract grants, CRADA, teaching, speaking, writing, patents, royalties and primary employment.

Today's agenda involves discussion of new drug application NDA 22-321, EMBEDA capsules, sponsored by Alpharma Pharmaceuticals, LLC, and its safety for the proposed indication of management of moderate to severe chronic pain.

The naltrexone component of this formulation is intended to mitigate abuse of

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the product when attempts are made to defeat the control or use properties of the formulation. This is a particular matter meeting during which specific matters related to EMBEDA 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.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Bartholomew Tortella and Bruce Burlington are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry.

Drs. Tortella and Burlington's role at this meeting is to represent industry in general and not any particular company. Dr. Bartholomew is employed by Novo Nordisk, and Dr. Burlington is an independent

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pharmaceutical consultant.

We would like to remind members and temporary voting members that if a discussion involves any other products 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 any firms at issue.

Thank you.

DR. KIRSCH: Thank you. I'll now recognize Dr. Rappaport for some opening remarks.

DR. RAPPAPORT: Good morning.

Dr. Kirsch, members of the Anesthesia and Life Support Drugs and Drug Safety Risk Management Advisory Committees and invited guests, thank you for returning

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to this second day of discussion of abused opioid products.

Today, we will be discussing Alpharma's application for EMBEDA, a novel formulation of morphine developed to provide abuse resistance by a completely different mechanism than the product we discussed yesterday.

EMBEDA's formulation contains an additional potentially active ingredient, the opiate antagonist naltrexone, which is intended to result in a reduction of the euphoria that abusers expect from a potent opioid if the extended release formulation is crushed or manipulated for the purpose of either oral or parenteral abuse.

As I said yesterday, we need your assistance to assess the value of these types of formulation changes intended to reduce abuse, and what metrics should be employed to measure these effects; which populations of abusers might benefit from these changes; and

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how to safely include the pertinent information and product labeling so that it will inform prescribers and patients about the value added by these changes, and not mislead them about the possible impact on actual abuse in the community, and not provide instructions for addicts and drug dealers that will allow them to more easily overcome the changes to the formulation.

As I also said yesterday, these are tough questions. I suspect that after Thursday's presentations and discussion, you likely now understand just how difficult it is for us to find answers to these questions.

And after listening to the heartbreaking stories during yesterday's open public hearing, I would guess that you now also recognize the importance of finding answers as soon as possible, no matter how difficult the questions.

Too many of our friends and loved ones are still suffering from

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inadequately-treated pain, pain that destroys any value in their lives, and not infrequently results in suicide, and too many of our friends and loved ones have suffered or died due to the abuse of prescription opioid drug products, and the addiction, overdose and death that follows from this abuse.

Both the parents were forever haunted by the memory of their child who died after an unintended and unnecessary overdose, and the patients who continue to suffer agonizing pain due to the stigma preventing their access to the drugs they need, speak passionately about their experiences.

They need to listen to each other and we need to keep their voices, both voices, present in our minds at all times as we try to find a path forward. We're asking that you as experts in pain management addiction treatment, risk management and related disciplines to think outside the box

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to help us sort through these challenges and find answers to our questions. Help us find the path, the best path, to assure the continued availability of potent opioid analgesic drug products for legitimate pain patients, and at the same time limit the impact of their availability and hopefully combat the abuse, misuse, overdose, addiction and death that continue to be associated with these products.

In this room today, we have innumerable combined years of experience; experience in research on and clinical treatment of pain, and experience and research on clinical treatment of addiction. We also have expertise on drug extractability and risk/benefit analysis.

After today's presentations by Alpharma and FDA, we will be asking you the same questions we did yesterday. As you contemplate and discuss, think outside the box, please.

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DR. KIRSCH: Thank you. Now it's time for the sponsors' presentations, and I'll recognize Dr. Joe Stauffer.

DR. STAUFFER: Good morning. My name is Joe Stauffer. I'm the Chief Medical Officer and Senior Vice President of Clinical Research in Medical Affairs at Alpharma. I would like to thank the FDA and Advisory Committees for giving us the opportunity to present our data on the ALO-01.

We are here today to present relevant information and ask for your positive recommendation for ALO-01, an extended release morphine medication for patients suffering with minor to severe chronic pain.

ALO-01 is an oral formulation in doses ranging from 20 to 100 mg. These capsules contain individual pellets of morphine with a sequestered core of naltrexone, an opiate receptor antagonist. If the pellets are crushed, as a drug abuser

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often does to get a faster high, the naltrexone is released, reducing the euphoric effects of the morphine, as we will demonstrate in our presentation.

We will also demonstrate that ALO-01 provides safe and effective pain relief over 12 to 24 hours, that when taken as directed, there is negligible exposure to naltrexone and no adverse clinical effects. And finally, the ALO-01 has demonstrated bioequivalence and similar effectiveness to Kadian, Alpharma's existing long-acting morphine.

We are also here in part today because government and law enforcement have encouraged the pharmaceutical industry to develop new formulations to address prescription opioid use. Last March, in testimony to Congress on transient unintentional drug overdose, the CDC identified opioid pain relievers as a driver for recent large increases in overdose

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deaths, and they called on drug manufacturers to modify opioid painkillers to make them more difficult to tamper with, and/or combine them with agents that block the effect of the opioid if it is dissolved and injected. These are complex problems requiring multifaceted solutions.

ALO-01 is one tool, one new resource for the medical community to consider. As Dr. Katz will discuss in a few moments, the temptation to abuse opioids affects patients with pain as well as a significant portion of the general population, resulting in numerous serious consequences.

We know that one way people abuse long-acting opioids is simply by crushing them in order to gain quick access the euphoric effects of the drug. ALO-01 was developed to minimize the high abusers are seeking when the product is misused. Alpharma also recognizes the potential risks

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inherent in a product like ALO-01. As a company, we are committed to careful, thoughtful and responsible marketing of this product. We have an ongoing risk management program that we initiated with Kadian. And are expanding this plan to include a risk evaluation and mitigation strategy, or REMS, with ALO-01. We will share the details of our program later in this presentation.

Now, here is our agenda. Dr. Nathaniel Katz will present the public health need for a prescription opioid formulation that addresses prescription opioid abuse and the potential benefit of such a formulation.

Dr. Bill Vincek will share the results of our in vitro tampering studies on ALO-01.

Dr. Donald Manning will then review the results from the clinical trial program. The in vivo abuse liability studies will be presented by Dr. Sandra Comer.

I will return to outline our

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comprehensive risk management program for ALO-01, including our REMS. I'll then wrap up our presentation and field any questions from the Committees.

Also with us today are Dr. Bill Schmidt, an expert in the field of naltrexone pharmacology, and Dr. Annette Stonehaggen, an expert in risk management.

I will now turn the lecture over to Dr. Katz.

DR. KATZ: Good morning.

For going on two decades now as a physician and clinical researcher focused on chronic pain and prescription opioid abuse, today I'm here to provide you a little bit more information on the rationale for the development of abuse-deterrent opioid formulations, to help inform your deliberations.

As a framing comment, it's important for all of us to keep in the front of our minds that prescription opioid abuse

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is more, as we know, than just data on slides. But as we heard in the open session yesterday, it affects many people's lives in a devastating way.

Since we're here in Maryland, I though I would point out that according to CDC data, there are approximately two deaths per day in this state alone related to prescription opioid overdoses, so if these rates hold true during these two days of our deliberations, an additional four more people will die related to prescription opioid overdoses, and another four more will die in my home state of Massachusetts, which happens to have about the same rate of deaths due to prescription opioid overdoses as here in Maryland.

So I therefore hope that you share my sense of urgency about making some progress, even if it's incremental, toward a solution to this problem.

During my presentation, I will make

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the following key points. The first, as you already know, prescription opioid abuse is a major problem. Tampering to alter the method of ingestion is an important part of this problem, particularly with respect to the extended release opioid formulations.

Both patients and non-patients tamper with their prescription opioids and suffer the consequences. By extension, abuse-deterrent formulations, if they are prescribed appropriately, have the potential to provide meaningful and measurable benefits to both patients and non-patients.

Since you already heard comprehensive presentations yesterday on prescription opioid abuse in general, today I'm going to get right to the point about the role of tampering in prescription opioid abuse among both patients and non-patients.

These data come from the ASINV connect database, a national database consisting primarily of individuals admitted

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for a substance abuse treatment, and are provided to me courtesy of Steve Butler from Inflection.

This database is useful for our purpose today for a couple of different reasons. First, it provides product-specific groups of abuse for each specific opioid product which are otherwise not available. And secondly, it allows respondents to indicate more than one route of abuse. This is important because most abusers take opioids orally most of the time but many also snort and inject, et cetera.

These tampering behaviors would be missed in a data set that allows respondents to indicate only one route of ingestion. These data confirm that the most common route of ingestion is indeed oral, but that tampering, including snorting and injecting, is very common, and also varies a great deal from one product to another.

For example, with Hydrocodone,

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which is, as we heard yesterday, the most commonly-prescribed medication of any kind in the United States, snorting is uncommon and injection is quite rare.

On the other hand, when one looks at the extended release opioid products, a very different picture emerges. In the case of extended-release morphine, which is shown on this slide here, the majority of patients in treatment for substance abuse -- to prescription opioid abuse -- report that they're snorting or injecting their medication. The majority.

It is also important to notice here on this slide that about 20 percent of these individuals report chewing their medication before they swallow it in the context of abuse. Most databases do not distinguish between swallowing the intact formulation and chewing it before you're swallowing it, and therefore, miss this simple but important form of tampering.

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The next question is whether altering the route of ingestion of prescription opioids has consequences, and the answer is that yes, it does have consequences. Here, for example, we see data comparing individuals in a large claims database who appear to be prescription opioid abusers versus controlled individuals who do not appear to be prescription opioid abusers. The risks of injection-related diseases, including hepatitis, HIV-AIDS and others, are much more common in the opioid abuser group.

Another critical important question is about tampering in patients, since most abusers are not patients. The only data that I'm aware of on tampering among chronic pain patients who are on opioid therapy is the data on this slide, which is again provided to me courtesy of Steve Butler from the Inflection group.

These particular patients represented on this slide are in treatment

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for prescription opioid addiction, and also, they are receiving opioids from other physicians for the management of pain. As is shown here, about half of these patients indicate that they tamper with their prescribed opioids.

Among the patients who abuse extended release products, the rate of tampering in this population is much higher, in the 70 to 80 percent range. Of course, these are patients who are in addiction treatment, and we cannot generalize these data to patients who are not in addiction treatment whose rates of tampering are undoubtedly much lower than what we see here.

However, at least in this group of pain patients, we can see that tampering is very common, and whether we like it or not, co-morbid addiction is actually very common among individuals with chronic pain, especially those on opioid therapy.

So the relevance of these data to

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pain management practice should not be too quickly dismissed.

The relationship between tampering and the progression of addiction was examined in the study of OxyContin abusers in Kentucky that many of you are probably familiar with. These investigators found that the route of ingestion changed over time, progressing from oral abuse to snorting and intravenous abuse, and illustrating that the progression of addiction to prescription opioids is associated with the progression of tampering as well. Therefore, it is possible that opioid formulations that cannot be easily defeated for the purpose of altering their route of ingestion could inhibit progression along this trajectory of addiction.

In summary, while the data in this area are far from complete, a few things are clear. The risks of tampering are relevant to both patients receiving opioids for pain and non-patients who obtain their medications

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from other sources.

Tampering is common and is associated with the progression of addiction, as well as a variety of other serious health consequences. This schema provides a framework for considering the potential benefits of formulations that resist tampering, and illustrates who might benefit, what those benefits might be and how to begin to approach the measurement of those benefits, with the ultimate goal, of course, being to optimize the balance between the access of opioids for the treatment of pain and minimizing prescription opioids abuse in its consequences.

I believe Dr. Bill Vincek is next.

Thank you.

DR. VINCEK: Thank you, Dr. Katz, and good morning.

Dr. Katz talked about the need for abuse-deterrent formulations. My presentation will focus on how we designed

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ALO-01 to block the effects of morphine.

I'll begin by explaining the objectives of our formulation development program. Our first objective is to select a fixed dose combination of morphine and its antagonist, naltrexone, to minimize systemic exposure of naltrexone when ALO-01 is taken as directed, while maximizing naltrexone's effect on morphine-induced euphoria when the product is crushed.

Second, to demonstrate the release of morphine and naltrexone from both crushed ALO-01 and intact ALO-01 pellets when subjected to a variety of extraction conditions.

Before I describe how we selected our formulation ratio, I want to highlight a couple of unique features of the product and touch on the pharmacologic mechanism of action. Each individual identical pellet is designed so that when pressure is applied to the outside membrane, the inner coat

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surrounding the naltrexone also is crushed, releasing both naltrexone and morphine.

When the drug is crushed, both are released simultaneously from each pellet. Inside the brain, the naltrexone and morphine compete for the same opioid receptors. Here, the naltrexone is represented in the pink circle, and morphine is represented by the green circle.

When the naltrexone binds with the opioid receptor, it completely competitively blocks the binding of morphine, reducing the euphoric effects that the abuser is looking to achieve. Shown in the top right panel is the PK of an extended release morphine product. In the lower right panel, you can see the time to peak blood concentrations after the ALO-01 pellets are crushed and swallowed.

Note that the morphine peak maximum shifts to about one hour, versus a peak of about eight hours for the extended release

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morphine above. Also note that naltrexone and morphine show nearly identical times to peak maximum.

Now, I'll explain our strategy or the determining the optimum formulation ratio of naltrexone to morphine in Study 201. Study 201 was designed to the guide our formulation ratio selection, which again was based on minimizing systemic exposure to naltrexone while maximizing naltrexone's effect on morphine-induced euphoria.

This double blind placebo-controlled study evaluated five naltrexone to morphine ratios versus morphine and placebo. All doses were given as oral solutions. Two critical measures were evaluated. First, naltrexone's pharmacokinetic profile. Second, drug liking, as measured by the visual analog scale of drug effects questionnaire, or revised DEQ.

Please note that the next two

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slides are not in your briefing books.

First, I show you the pharmacokinetic profile of three of the naltrexone ratios that we tested. We plotted the mean plasma naltrexone concentration in picograms per ml on the Y axis against time in hours on the X axis. The blue line represents the highest naltrexone to morphine ratio tested. The eight percent naltrexone ratio is shown in yellow, and the ratio we selected for ALO-01, four percent, is shown in green.

To put these concentrations in context, let's take a look at the plasma concentration from an oral naltrexone dose from the marketed product Revia. The normal dose of Revia is 50 mg orally, which results in a plasma concentration of about 9,000 picograms per ml, while an effective dose of naltrexone for IV heroin users has a concentration of about 2,000 picograms per ml.

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So from a safety standpoint, we want to have the lowest effective dose of naltrexone -- from an abuse-deterrent standpoint, we want to test to see if the dose will abate drug liking. The vast scale evaluating drug liking and disliking -- the four percent and eight percent ratios seen in green and yellow were the lowest naltrexone ratios that reliably attenuated morphine-induced euphoria.

As you see, the eight percent ratio, while providing double the amount of naltrexone, did not provide significantly greater reduction in drug liking. Thus, we chose four percent as the optimum ratio. Based on these data, we created the unique ALO-01 multilayer pellets. Then we conducted extractability studies on ALO-01. In this series of studies, the extraction of morphine and naltrexone from intact pellets was demonstrated in a variety of solvents.

Now, we will provide a summary of

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these data which were discussed in detail in the closed session. Here in the middle column, you see the results of our experiments to selectively extract morphine from our pellets using seven different solvents.

In the right-hand column, you see that we examined these ratios to determine ALO-01's potential to minimize oral and IV abuse under each of these extraction conditions. Our conclusions were based on the time it took to obtain an abusable concentration or amount of morphine, the extraction of naltrexone and the number of steps required.

Next, the extraction of morphine and naltrexone from crushed pellets was demonstrated in water, acid, base and alcohol after soaking or stirring at room temperature over time. Here are the results. On the Y axis, you see the percentage of the morphine and naltrexone released. On the X axis, we

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note the extraction conditions.

Morphine is shown in light blue; naltrexone in red. The data on this slide demonstrate that when ALO-01 pellets are crushed and exposed to a variety of conditions, essentially, you get proportional extraction of morphine and naltrexone.

To conclude, we have shown through in vivo studies that a four percent naltrexone to morphine ratio minimizes systemic exposure of naltrexone while maximizing naltrexone's effect on morphine-induced drug liking.

Through in vitro studies, we have demonstrated that crushing ALO-01 non-selectively releases both naltrexone and morphine, and that under certain conditions, meaningful amounts of morphine can be selectively extracted from ALO-01 intact pellets.

However, the potential for co-extracting naltrexone with morphine

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suggests that ALO-01 is a less attractive option to opioid abusers.

Dr. Manning will now present data from our clinical program.

DR. MANNING: Good morning.

Our clinical development program for ALO-01 was based on several objectives. One, to show the bioequivalence of ALO-01 to Kadian. Two, to demonstrate that pain relief with ALO-01 is equivalent to Kadian and superior to placebo. Three, to show that the addition of naltrexone does not compromise either the efficacy or safety. And four, to demonstrate that the naltrexone released when ALO-01 is crushed blunts morphine-induced euphoria.

Our clinical development program consisted of 12 studies, enrolling 262 patients in Phase I, and 1,127 patients in Phases II and III. In this presentation, I will focus on efficacy and safety studies in yellow, starting with Study 202, the first

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multiple dose ALO-01 study.

This study used a randomized crossover design which allowed us to evaluate morphine and naltrexone pharmacokinetics, as well as assess early safety and efficacy in comparison to KADIAN. Patients in pain flare from hip or knee osteoarthritis were individually optimized for analgesia over 28 days on KADIAN, up to an allowed maximum of 320 mg per day.

Subsequently, all patients received 14-day double blind treatment with both ALO-01 or KADIAN at separate crossover periods. The intermediate period crossover was on open-labeled KADIAN, to avoid opioid withdrawal syndrome. Pharmacokinetic analysis showed that ALO-01 had similar steady state morphine bioavailability to KADIAN at a medium dose of 40 mg BID. These data complement and are consistent with those of the formal bioequivalent study 101.

Study 202 also assessed clinical

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effectiveness, and showed ALO-01 relieves pain equivalent to KADIAN. During the open-label titration period, KADIAN significantly reduced pain for an average of 7.1 at flare to 2 on an 11 point scale. This release was sustained over two weeks regardless of which drug patients were randomized to, KADIAN or ALO-01.

Armed with these preliminary efficacy data, we designed our efficacy Study 301 using a randomized withdrawal design under a special protocol assessment agreement with the FDA. Patients with osteoarthritis pain of the hip or knee were optimized for analgesia on ALO-01 for up to six weeks, and an allowed maximum of 160 mg per day.

They were then randomized to placebo or continued ALO-01 and engaged in a 14-day taper to avoid un-blinding due to opioid withdrawal. They were maintained on their therapy for an additional 70 days, then

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tapered off to the original analgesic medication.

Assessments included Brief Pain Inventory pain scales, WOMAC Osteoarthritis Index, laboratory studies and recording of adverse events. The primary efficacy measure was change in average pain score from randomization baseline to 12 weeks. Missing data was handled in a very conservative manner.

The most unfavorable baseline was used to impute missing data for dropouts due to adverse events or opioid withdrawal. With this challenging study design, we achieved our primary end point, demonstrating a significant difference between placebo and ALO-01 for the difference in BPI average pain score to be baseline to week 12.

This analysis used data from week 12 only and employed an ANCOVA approach. Analgesic effectiveness was also supported by significant superiority of ALO-01 over

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placebo for several secondary measures, including the remaining BPI pain scales, BPI assessments at the clinic visit, and the WOMAC composite score. Further support for analgesic effectiveness was provided by post hoc analysis using AUC and Kaplan-Meier techniques, and analgesic durability was demonstrated over 52 weeks in our long-term safety Study 302.

The safety of ALO-01 was assessed in all three trials of our core clinical program. I will first describe our assessment of naltrexone exposure. Overall, there was negligible exposure to naltrexone or its metabolite in our core clinical program. Here, I will focus on the long-term safety Study 302.

But first, to put naltrexone concentrations into perspective, 1600 picograms per ml is the plasma naltrexone concentration required for 50 percent occupancy of CNS Opiate receptors, EC 50

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determined by PET scan studies.

2,000 picograms per ml naltrexone concentration is the lowest effective plasma concentration for the treatment of opioid abuse. Revia, a commercially available naltrexone formulation, gives a peak plasma concentration of 9,000 picograms per ml with a 50 mg dose.

In our clinical program, 21 percent of sampled patients had quantifiable naltrexone levels, and about 80 percent had 6-beta-naltrexol below a potency metabolite. Total plasma opiate antagonist activity is expressed in naltrexone equivalence, which is the sum of naltrexone and potency adjusted 6-beta-naltrexol concentrations.

These data are explained in the lower portion of this plat. 150 picograms per ml was the highest naltrexone equivalent concentration observed in these studies, approximately tenfold less than the EC 50, and an order of magnitude lower than the

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commercial naltrexone formulations. Plasma naltrexone and 6-beta-naltrexol were not correlated to dose, age, gender, and did not show accumulation.

Now let's focus on safety in light of these naltrexone levels, first looking at adverse events. During the four-week KADIAN titration period in Study 202, a typical range of opioid-related AEs were reported. Similar results were seen in data from AEs reported during the six-week open labeled titration phase of Study 301, and also in the first four weeks of titration in the open label Study 302.

It is important to understand that the incidence rate cannot be compared between trials, because they use different doses and protocols. However, it is evident from these data that KADIAN and ALO-01 had similar relative proportions of typical opioid adverse events.

Similar results are seen in data

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from the maintenance phases, where again, we see the safety of ALO-01 is uncompromised by naltrexone. These results are again displayed separately due to the different study designs.

However, in this slide within the Study 202 or 301, the AE comparisons are valid between parallel treatments. Of note, in Study 202, we do see a higher incidence of vomiting for ALO-01 over KADIAN, but the overwhelming majority of these cases were mild and did not lead to discontinuation.

The vast majority of serious adverse events, or SAEs, reported in the clinical program were not attributed to ALO-01. Out of 54 recorded events in 33 patients, four SAEs and three patients were rated as probably due to ALO-01.

This includes a report of gastroenteritis-associated abdominal pain. Of note, none were associated with known naltrexone adverse events.

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Naltrexone-precipitated withdrawal was also a focus of our safety evaluation. The Clinical Opiate Withdrawal Scale, or COWS, was employed. This is a standard validated tool where moderate withdrawal is associated with a score equal to or greater than 13 out of 48. Ten patients had COWS scores equal to or greater than 13; all were due to either assignment to placebo or non-compliance with ALO-01 dosing regimen. None were associated with per protocol dosing of ALO-01.

After seeing the efficacy and safety data for ALO-01, let's revisit the objectives of the ALO-01 clinical program. We have shown bioequivalence of ALO-01 to KADIAN, ALO-01 provides pain relief superior to placebo and equivalent to KADIAN, and the addition of naltrexone in ALO-01 does not compromise either the efficacy or safety of sustained release morphine.

The final objective, addressing the

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blunting of euphoria associated with ingestion of crushed ALO-01, will be described by Dr. Comer.

DR. COMER: Good morning.

Alpharma asked me to review their abuse liability data, as I have been doing substance abuse research with opioids for the past 15 years at Columbia University, where most of my research has been funded by NIDA.

Alpharma sponsored CU clinical abuse liability trials in prescription opioid abusers; one using oral dosing and one using intravenous dosing. I'll now describe the studies and provide you with my perspective on the results, beginning with the oral study.

The primary purpose of Study 205 was to determine the relative pharmacodynamic effects and safety of crushed and intact ALO-01 compared to immediate release morphine and placebo.

This was a placebo and

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active-controlled crossover trial in non-dependent recreational opioid abusers. The question was: how effective was the naltrexone in reducing the euphoric effects of the morphine? The primary efficacy variable was ratings of drug liking measured on a visual analogue scale.

Subjective ratings of drug value and rating on the scale were also assessed. First, I will show you the primary endpoint analysis from this study. This graph shows mean ratings of drug liking over time. These data demonstrate that immediate release oral morphine, shown at the top in blue, produced significant increases in ratings of drug liking relative to placebo.

In contrast, intact ALO-01, in green, did not increase ratings of drug liking during the same time period. Crushed ALO-01, the yellow line, produced ratings that were significantly lower than the immediate release morphine, and not different

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from intact ALO-01. Based on my experience ratings of drug liking tend to be correlated with drug taking behavior, so this would suggest a diffused liability of ALO-01 when crushed is much lower than immediate release morphine.

Looking now at secondary end point analyses, we see that the effect is consistent across a number of different measures and ways of analyzing the data. Say, for example, data for several secondary measures were analyzed as area under the curve, EMAC and drug effect at 1-1/2 hours.

When immediate release morphine and ALO-01 crushed were compared using all of these different ways of looking at the data, the same general pattern occurred as in the primary analysis. Although overall drug liking and euphoria were lower with crushed ALO-01 than with immediate released morphine, there was individual variability and response. For example, 28 of the 32

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participants, or 87-1/2 percent, had reduced drug liking within the first two hours after receiving crushed ALO-01. However, 12-1/2 percent had no drug liking reduction. Similarly, on another subscale, 22 of 32 participants, or 69 percent, showed a decrease in euphoria with crushed ALO-01 compared to immediate release morphine, and 31 percent did not.

Although there is variability in response, the main point here is that the majority of the participants did show a blunted response with crushed ALO-01 compared to immediate release morphine.

To summarize the oral study, both crushed and intact ALO-01 had lower abuse liability than immediate release morphine. Crushed ALO-01, because of the presence of naltrexone, significantly reduced the amount of euphoria or drug liking compared with immediate release morphine.

So these were the data that were

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collected to mimic recreational opioid abuse. Alpharma also wanted to understand the abuse liability profile of crushed ALO-01 in a more serious abuser, so they conducted a trial using IV morphine and IV naltrexone in the appropriate ratio.

The main objective of Study 106 was to examine the subjective effects of IV morphine alone compared to IV morphine combined with IV naltrexone and for placebo. The primary end point was the answer to the question: how high are you now? Study 106 was a double blind randomized placebo-controlled trial conducted in one center.

The three treatment arms included placebo, 30 mg of IV morphine alone, 30 mg of IV morphine in combination with 1.2 mg or 4 percent IV naltrexone from commercially available sources.

This ratio approximates what an IV drug abuser would receive if they were to

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crush ALO-01. Crushed ALO-01 was not given intravenously because of potential safety concerns with IV administration of the excipients in the products. What I'm showing you now is the time course of drug effects for IV morphine alone, morphine in combination with naltrexone and placebo.

You can see that 30 mg of morphine alone produced a significant increase in ratings of feeling high that extended for several hours after drug administration. When morphine was given in combination with naltrexone, there was a substantial reduction in ratings of feeling high.

Similarly, on the Cole Archie Euphoria Scale, the morphine alone produced significant increases in ratings of euphoria. As with ratings of feeling high when morphine was given in combination with naltrexone, ratings of euphoria significantly decreased.

To summarize the IV study, average peak ratings of feeling high were

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approximately threefold greater from morphine alone than from morphine plus naltrexone. The magnitude of the euphoric response to morphine alone was greater than for morphine plus naltrexone, in support of the primary efficacy outcome.

My overall conclusion is that if ALO-01 is crushed and used by abusers, the relative amounts of naltrexone released will decrease morphine-induced euphoria when taken orally or intravenously.

Dr. Stauffer will now present the ALO-01 risk management plan.

DR. STAUFFER: Thank you, Dr. Comer. I will now discuss the risk management plans for ALO-01.

We are in the fortunate position of having implemented a risk management program for KADIAN a year ago, and we're committed to building on its strengths with ALO-01. We have two main goals. First, to minimize the potential for misuse, abuse and diversion of

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ALO-01.

Although the product itself is a risk minimization tool, we recognize that these problems could occur. Therefore, a REMS is a prudent step. Second, although we believe that our clinical trial data suggest that opiate withdrawal reactions are unlikely to occur with ALO-01, we will implement a system to rapidly recognize and respond to any such events.

Risk management plans, or REMS, typically consist of multiphased processes, as illustrated here. We examine data from multiple sources and validate information to detect actionable signals of adverse events that can occur with our product. If our investigation determines that there is a valid signal, and the root cause can be mitigated or prevented, we implement an appropriate intervention.

For example, in addition to numerous tried and true data streams, we will

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be using NavaPro to capture data in real time from hundreds of substance abuse treatment centers during initial assessment using the standard addictions index form.

We can also gather information about geographic patterns of abuse, abuser demographics, and sources of diversion. In a recent data snapshot, we identified Tennessee as a hot spot for opiate abuse, including KADIAN abuse. In our view, gathering data is an early step in the process. It is necessary but not sufficient.

In response to the signal observed in Tennessee, we launched targeted interventions in Chattanooga and Nashville. These interventions included a number of educational programs for prescribers, teenagers of law enforcement, including an educational campaign implemented by the National Association of Drug Diversion Investigators.

This intervention is ongoing, and

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we plan to prospectively monitor the impact of this intervention. This is one illustration of our commitment at Alpharma to monitor the effectiveness of our interventions, report the results to FDA, and modify our interventions as necessary.

An additional concern of ours is that physicians or patients may develop a false sense of security about ALO-01. We have implemented a robust set of policies, procedures and training to serve as the foundation for our internal prevention detection and intervention efforts, to ensure consistent and appropriate messaging about our product.

It is based on a commitment to compliance, appropriate interactions with health care providers, and comprehensive training.

Now, turning to the physician community and further efforts to assure appropriate prescribing, Alpharma will also

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support educational efforts through a national opioid safety course, with content based on national controlled substance prescribing guidelines.

The course will be comprehensive, and will work with professional organizations to maximize its reach. This program will differ from previous programs in that we will invite other industry supporters to participate, and we'll endeavor to prospectively measure and report the outcomes of the program.

As a final example, we realize that education and training are most useful when complemented by the practical tools necessary for the day-to-day safe management of patients on opiate therapy. Our tools will include a medication guide to assist prescribers in their communication with patients on appropriate use of ALO-01; an opioid agreement between prescribers and patients to ensure safe use conditions; a

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screening tool to identify high-risk patients and consider special care when prescribing opioids; handbooks on the appropriate prescribing of opioids; and finally, instructional materials on how to perform and interpret urine drug tests for patient monitoring.

When we launch ALO-01, we will mail kits to all clinicians who were called upon by Alpharma.

With respect to the second goal of REMS, our perspective is that episodes of opioid withdrawal are unlikely to occur when the drug is used as intended. However, should any cases of withdrawal occur, the reports will be reviewed by an external adjudication committee to confirm the medical cause and evaluate the root cause. If we confirm that these patients did not take the drug as directed, our field force, including sales reps and medical science liaisons, will deploy additional educational interventions

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and other communications directed to providers and patients.

If the findings confirm that the medication was taken as directed and the patient still experienced withdrawal syndrome, we would communicate with FDA and address this from a regulatory standpoint.

In short, this is an example of how we critically evaluate information and respond swiftly with appropriate actions.

In the next slide, our timeline for REMS implementation. Significant parts of our system for clinician education and product surveillance have already begun. With the implementation of Pain Balance, our educational initiative, and NavaPro in January of last year, we will continue to educate clinicians on appropriate use of ALO-01, with the deployment of our medical risk management kit at launch at a national opioid safety course one month after launch.

We will also submit post-launch

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REMS assessment in compliance with FDA instructions. These REMS reports will recap tactics deployed, provide objective data on REMS effectiveness, and recommend areas of improvement. We will of course analyze our own data and consistently strengthen our REMS, even as our communications with FDA remain frequent.

To supplement our surveillance activities, we are also planning a series of randomized controlled trials and epidemiologic studies, the designs of which are currently underway, to assess the impact of ALO-01 in a real-world setting.

This is our commitment as a company to the FDA, to the pain community, and to the Advisory Committee, that we will take this. We look forward to working with FDA to ensure we address the appropriate issues regarding the impact of ALO-01.

To close out our presentation, I would like to summarize what we have heard

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here today. As Dr. Katz pointed out, prescription opioid use is a complex problem that will likely require a variety of strategies to reduce the many risks inherent in opioid misuse and abuse.

ALO-01 is one tool in that mitigation toolbox, which when crushed reduces euphoria, making it less attractive to opioid abusers. Clearly, the data showed ALO-01 is safe and efficacious when taken as directed.

We achieved our primary point using very conservative missing data imputation techniques, which demonstrates statistical significance between ALO-01 and placebo, and other secondary measures to support its clinical effectiveness. We demonstrated that the minimal exposure to naltrexone does not pose a safety risk to patients when taken as directed. The level of detectable naltrexone concentrations is negligible, and an order of magnitude below levels with

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clinically-accepted doses of approved products already on the market. Our data also showed that naltrexone does not accumulate over time.

From an abuse liability standpoint, Dr. Comer pointed out that across all measures in our trial for most subjects, ALO-01 reduced drug liking and euphoria, and was determined to be clinically relevant.

So our overall clinical program demonstrates that the addition of naltrexone does not compromise efficacy or safety. Also when crushed, ALO-01 significantly reduces euphoria and drug liking, and we demonstrated pain relief to periods of placebo and equivalent to KADIAN.

So Alpharma has created a medicine that is good for patients and the public health. We are committed to responsible marketing of this product. ALO-01 has demonstrated safety and efficacy, with a platform technology that is proven to reduce

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euphoria and drug liking when the medicine is crushed. It is one tool to address one aspect of the complex multifaceted problem of prescription opioid abuse. We need a multitude of such tools that are designed to address abuse.

On behalf of Alpharma, I thank you for your attention and we look forward to answering your questions.

DR. KIRSCH: Thank you. We're now going to be taking a break. The break will be for ten minutes.

Committee members, please remember that there shall be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

My watch says it's almost 15 minutes after the hour. We will come back at 25 after the hour.

(Recess)

DR. KIRSCH: In this part of the

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meeting, we will have some presentations by the FDA.

Our first presenter is Dr. Nallani.

DR. NALLANI: Good morning.

I'm Srikanth Nallani, clinical pharmacologist supporting the Division of Anesthesia, Analgesia and Rheumatology Products.

Previously, the sponsor's perspective on the abuser liability studies, particularly No. 205 and No. 106, was presented. Although we have not had a chance to formulate a final opinion on these studies, the goal of my presentation is to indicate the high availability in the data noted in these laboratory studies, and also to present underlying issues with these studies required for abuser liability claims.

As my colleague presented yesterday, the abuse of morphine extended release products occurs by different methods of physical manipulation, and also by

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different methods or routes of administration. Crushing comprises the most frequent method of manipulation, followed by chewing, boiling and dilution, and dilution being the most frequent method of administration for abuse.

Oral, snorting, also comprises significant routes. Previously, the sponsors have described Study 205, and this is a brief presentation of Slide 56 from the NDA, and this is the oral abuser liability study, where drug liking is presented on the Y axis on the scale of 0 to 100. 50 is a measure where the abuser neither likes nor dislikes the product, and 100 indicates very strong liking.

As shown here, the placebo in dotted lines, the subjects receiving placebo did not show any change in drug liking, but as they receive oral solution, they exhibit strong drug liking effect. And the peak drug effects also coincide with the peak plasma in

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the oral solution, and this is presented in table nine of the background package.

The peak drug effects with the product occur around eight hours, that's the cMAX for plasma, and although the morphine levels are comparable to oral solution when the product is crushed, the average levels, the average drug liking effect for the crushed product appear really low on an average.

But this slide shows the huge variability in the naltrexone between morphine drug liking. In fact, the sponsors do indicate on Slide 59 of their presentation of how some individuals in spite of receiving crushed product, demonstrated strong drug liking and euphoria at several points despite the release and absorption of naltrexone.

Again, I need to mention that our final analysis is pending on this. The data presented here is also sponsors analysis from the NDA. The data presented here shows the

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proportion of subjects who had any reduction in post-dose maximum drug liking effects compared to the ones who received morphine (inaudible) immediate release.

The change in maximum drug liking as it relates to a certain amount of reduction is demonstrated in the first column, and the observation for those receiving ALO-01 crushed is demonstrated in the second, and those receiving the intact product is presented in the third column.

As can be seen here, the majority of the subjects had a 20 percent decrease in maximum drug liking. None of the subjects had a 50 percent reduction. 50 percent reduction would comprise the best case scenario, and none of the subjects had best case scenario.

Now again going back to the individuals who did like the drug despite receiving naltrexone levels in the systemic circulation, and also having euphoria, the

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data indicate huge variability in the reduction of maximum drug liking response and the outliers do experience drug liking in spite of receiving the crushed product.

So the question we have is, is there adequate data to claim abuser dose by crushing and oral convention? Additionally, the Study 205 only addresses abuse of the product by swallowing after crushing. PK safety and drug liking studies were not connected to address abuse by snorting crushed product.

As we have seen before, snorting is another major group of abuse. And studies were also not done to evaluate chew and swallow, how the naltrexone, whether it released adequately to counter the effects of morphine.

The unresolved issues with the IV abuse Study 106 may be important to the premise of the study. The study assumes that both morphine and naltrexone will be

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extracted in vitro. The study, as described before, IV solutions mapped for IV administration and would be agents that are administered concomitantly. This study does not address situations where morphine alone may be extracted, and it is reasonable to say that it's not safe to administer crushed product IV, and the sponsors seem to have some evidence on the way to address this route of abuse.

With that, this -- again like I mentioned -- this presentation is supposed to give an overview of the unresolved issues we are facing during the review.

Thank you so much.

DR. KIRSCH: Thank you.

Next will be Dr. Ellen Fields whose going to talk about the history of modified opioids antagonist combinations.

DR. FIELDS: Good morning.

My name is Ellen Fields, and I'm a medical team leader in the Division of

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Anesthesia, Analgesia and Rheumatology Products.

My presentation will cover two subjects; the first being the history of the approved modified release morphine products and important labeling changes. The second part of my presentation will be the history of the approved opioid antagonist combination products.

There are currently four approved modified released morphine products; MS-Contin, Oramorph SR, KADIAN and Avinza. All are Schedule II opioid analgesics and are indicated for the management of moderate to severe pain when a continuous around-the-clock opioid is needed for an extended period of time.

The extended release products provide for improved compliance, convenience for the patient and longer duration of pain relief than the immediate release formulations. I will discuss the products in

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the order in which they were approved.

MS-Contin was approved in May of 1987. It was the first modified release morphine product and the NDA was processed as a priority review. It is available in strengths ranging from 15 to 200 mg, and is to be dosed every 12 hours.

In 2003, the box warning was added to the label. The 100 mg and 200 mg strengths were to be limited to opioid-tolerant patients. In addition, language was added regarding abuse liability, and that MS-Contin was not to be used PRN and not to be broken, chewed, crushed or dissolved.

In 2007, additional language was added throughout the label regarding abuse, misuse and diversion. This is the box warning for MS-Contin; similar box warnings are part of the labels for the other extended release morphines.

The next few slides will describe

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each section of the box. This section states that MS-Contin is a Schedule II controlled substance. It can be abused in a manner similar to other opioids, and this should be taken into consideration by prescribers.

This section of the box describes the indication, and emphasizes that the 100 mg and 200 mg tablets are for use only in opioid-tolerant patients. The final section of the box warns not to swallow broken, chewed, dissolved, or crushed tablets, which would lead to rapid release and absorption of a potentially fatal dose of morphine.

Oramorph was approved in 1991 in strengths ranging from 15-100 mg, to be dosed every 8 to 12 hours. The label is currently in the process of being updated.

KADIAN was the third modified release morphine product, approved July 1996, with initial strengths of 20, 50 and 100 mg. Since that time, additional strengths have been added, including 200 mg, which was added

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in 2005. At that time, language was added to the label stating that the 100 mg and 200 mg capsules were to be prescribed only to opioid-tolerant patients.

KADIAN is to be dosed every 12 to 24 hours, and the capsules may be swallowed whole or sprinkled on applesauce. In 2006, a box warning was added to the label similar to that shown for MS-Contin. The KADIAN box warning also has wording regarding sprinkling the contents of the capsule on applesauce.

The most recently approved modified release morphine product is Avinza, approved in March of 2002. Strengths range from 40 mg to 120 mg, to be dosed once daily. And like KADIAN, the capsules may be swallowed whole or sprinkled on applesauce. Unlike the other similar products, Avinza has a maximum daily dose of 1600 mg due to one of the inactive ingredients in the formulation.

The 60, 90 and 120 mg strengths are to be administered only to opioid-tolerant

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patients. In October 2005, language was added to the label stating that alcohol compromises the controlled release properties of Avinza and causes it to act as an immediate-release product.

This phenomenon is known as dose dumping. In 2004, the agency became aware that Palladone, modified-release hydromorphone, was associated with an accelerated release of hydromorphone in the presence of alcohol in vivo.

Palladone was removed from the market. Subsequently, all modified release opioids underwent in vitro dissolution studies in the presence of alcohol. In vivo studies followed if needed to confirm the positive in vitro studies. All four morphine products were studied in vitro with 40 percent alcohol.

Avinza and KADIAN were also studied in the presence of 20 and 4 percent alcohol. The in vitro tests with KADIAN were positive,

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and were followed by negative tests in vivo. Avinza showed positive in vitro tests. No in vivo testing was performed with Avinza, since the sponsor included specific language in the label regarding dose dumping.

Both MS-Contin and Oramorph had negative in vitro testing. These are the results of the in vitro testing with Avinza, which is illustrative of dose dumping in different concentrations of alcohol.

The graph illustrates the in vitro dissolution of Avinza in the approved dissolution medium alone, and plus four percent, 20 percent and 40 percent alcohol. The bottom-most line is the dissolution without alcohol, showing a controlled rate of release over a defined period of time; in this case, 24 hours.

The dissolution in four percent alcohol, the red line, is similar. However, dissolution in 20 percent, this green line, and 40 percent, the uppermost brown line, is

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accelerated so that over 80 percent of the drug release occurs in less than one hour when Avinza is in the presence of 40 percent alcohol.

All opioid labels contain standard language regarding their pharmacodynamic interaction with alcohol, such as that shown on this slide. Because Avinza is shown to have a positive interaction with alcohol in vitro, and no in vivo testing was done, this language was added to the label. Patients must not consume alcoholic beverages while on Avinza therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza therapy.

Consumption of alcohol while taking Avinza may result in the rapid release and absorption of a potentially fatal dose of morphine.

The next part of my presentation is the history of approved opioid antagonist

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combination products. The Code of Federal Regulations Title 21, Section 300.50, describes the combination rule.

One of the special cases of this general rule is where a component is added to minimize the potential for abuse of the principal active component. There are currently two approved products in this category: Talwin Nx and Suboxone.

Naloxone was added to both products in order to deter intravenous abuse of the drugs. Naloxone is a pure opioid antagonist used for complete or partial reversal of opioid-induced respiratory depression when administered intravenously. It also reverses the euphoric effect associated with opioid intoxication. It has very limited systemic bioavailability via non-parenteral routes.

Therefore, additional Naloxone can only impact parenteral abuse of Talwin Nx and Suboxone. Talwin, or pentazocine, was approved in 1967 for the relief of moderate

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to severe pain. At that time, it was not known to have any abuse potential and was not scheduled.

In 1968, initial reports of dependence were received. Talwin was initially thought to be abused only by a restricted patient population, but it became apparent that the abuse was more widespread. Talwin became a significant public health problem in the late 1970s, with the advent of Ts and blues abuse; that is, Talwin plus the antihistamine tripelennamine, which was a blue tablet. These were dissolved together and injected intravenously and used as an inexpensive alternative to heroin. This epidemic coincided with a decrease in the availability of heroin.

In 1979, Talwin became a Schedule IV narcotic, and labeling was changed to include post-marketing events of addiction. In 1982, pentazocine was reformulated with Naloxone, which became

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Talwin Nx, and was marketed starting in April of 1983.

Single-entity Talwin was removed from the market in January of 1983, and reports of abuse during the two years after its withdrawal declined. In 1987, a study reported the analysis of data from the Drug Abuse Warning Network, or DAWN, and IMS prescription audit that reviewed the use and abuse patterns of pentazocine before and after the Naloxone was added to the product.

This graph illustrates the number of prescriptions dispensed from retail pharmacies for pentazocine-containing products by year and quarter. The dark bars represent all pentazocine products other than Talwin Nx, and include IV pentazocine and single-entity Talwin. The white bars are Talwin Nx prescriptions.

The number of pentazocine prescriptions began to fall in the second quarter of 1982 as Talwin Nx came onto the

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market. This graph depicts emergency room mentions of pentazocine per million prescriptions by year and quarter.

The ER mentions fell sharply after distribution of single-entity Talwin ceased in January of 1983, and the introduction of Talwin Nx in April of that year. It is of note, however, that the rate of ER mentions began to fall prior to the introduction of Talwin Nx. This may have also been impacted by an increase in the supply of heroin, and consequently, a decrease in the abuse of Talwin.

Similar results are shown in this graph regarding the medical examiner mentions per million pentazocine prescriptions. The rate had already dropped prior to the removal of Talwin and the introduction of Talwin Nx.

However, it did not appear to rise again for the next two years. So the decrease in the abuse of Talwin appears to have been multifactorial. The factors

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include the scheduling of Talwin, the removal of single-entity Talwin from the market, the introduction of Talwin Nx, and the change in the availability of heroin.

Suboxone is a combination of buprenorphine and Naloxone. It was approved in October 2002 for the treatment of opioid dependence, along with Subutex, which is buprenorphine alone. The two products are interchangeable with regard to the pharmacokinetics of buprenorphine.

Suboxone was designed to be administered sublingually. In studies, absorption of the Naloxone component caused no clinically significant effect, although plasma levels were measurable.

If Suboxone was improperly administered via the intravenous route, the Naloxone component would become available and block the euphoric effects of the opioid component or precipitate opioid withdrawal.

There have been no formal studies

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to assess the impact of Suboxone in terms of abuse. There have been reports of Suboxone abuse via the usual route of administration, but also by nasal inhalation and injection. The agency has received reports from AERS, the Adverse Event Reporting System, and from the sponsor via their quarterly surveillance reports of cases of IV abuse of Suboxone.

According to the Baltimore Sun article of December 2007, "The Bupe Fix," Naloxone does not always deter abuse. Maine's health department reported in August 2007 that misuse spread rapidly as more with Suboxone was prescribed. Abusers of the drug have figured out how to separate out the Naloxone to inject the buprenorphine. And in Massachusetts, a police detective said, "a lot of people are injecting it and they're getting hooked on it."

In summary, there were four approved modified release morphine products. The highest doses are only to be prescribed

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to opioid-tolerant patients. The labels contain box warnings, and one product, Avinza, has labeling regarding dose dumping and alcohol.

In terms of opioid antagonist combinations, there are two approved products, Talwin Nx and Suboxone, and the Naloxone was added to each to mitigate intravenous abuse. There was some evidence that Talwin Nx was associated with a decrease in pentazocine abuse. However, other factors likely contributed, such as scheduling of Talwin and the availability of heroin during that time period.

There have been no formal assessments of Suboxone to impact on abuse, and there is evidence of intravenous and intranasal abuse.

This concludes any presentation.

Thank you.

DR. KIRSCH: Thank you.

Next, I will call on Dr. Governale,

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who is going to talk about outpatient drug utilization trends from morphine products.

DR. GOVERNALE: Good morning.

My name is Laura Governale, and I'm the drug utilization analyst team leader at the Division of Epidemiology in the Office of Surveillance and Epidemiology.

Today, I will be presenting the outpatient drug utilization patterns for extended release morphine products. My presentation today will follow the similar outline from yesterday's presentation, except today will be on morphine sulfate.

Again, I will be using the same methods and databases employed from yesterday's presentation, so the sales data will be obtained from the IMS Health National Sales Perspective, dispensed prescription analysis will come from the FDI or (inaudible). And the patient level analysis will also come from the SDI as well as the total patient tracker. Then I will conclude

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with a summary of my presentation.

Again, we looked at the systemic oral morphine sulfate products, and we grouped them into the following categories. The immediate release, morphine sulfate are listed below. As I said, the sales distribution data were from the IMS Health National Sales Perspective, and here we're measuring the number of bottles -- bottles, vials or packets of pills that are being sold from the manufacturer to retail on non-retail channels of distribution.

This graph shows the projected number of bottles and vials of morphine sulfate products by dosage forms sold from the manufacturer to retail and non-retail channels of distribution, and here, we see that over 73 percent of the oral solid products of the systemic long acting or extended release products, as well as the immediate release oral solids, are distributed towards the retail pharmacy

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channels; whereas for the liquid products, nearly 85 percent of the oral liquid products are distributed to non-retail channels.

Again, SDI or surveillance data is a national level projected prescription patient tracking service, and it receives dispensed prescriptions from a sample of nearly all the retail pharmacies in the country, and it accounts for nearly half of all dispensed prescriptions in the U.S.

And the retail pharmacies in the sample include national retail changes, mass merchandisers, pharmacy benefit managers and the data systems and provider groups.

This chart is similar to the graph I displayed yesterday except we're just looking at the proportion of prescriptions dispensed for selected opioids in year 2007. And here, we see that Hydrocodone and OxyCodone account for over 90 percent of the opioid market.

The morphine products each account

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for only three percent of the opioid market. In this graph here, we are looking at the bottom ten percent of the market which include morphine, fentanyl, methadone and hydromorphone products. During year 2007, all the morphine products, which include both the immediate release and the extended release account for 5.5 million prescriptions, which is represented in the yellow bars.

Fentanyl accounts for 4.5 million prescriptions, methadone 4.2 million prescriptions, and hydromorphone with 1.6 million prescriptions.

In this slide, we are breaking down just the morphine sulfate products by extended release and immediate release over the ten-year period 1998 to 2007.

The extended release formulations are shown in the red bar, and in contrast to yesterday's presentation on the extended release OxyCodone products, the majority of

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the market for the morphine products are for the extended release formulation, which is shown on the yellow bar, and immediate release formulation accounts for approximately a quarter of the market.

So again, the extended release products quadrupled in ten years from one million prescriptions in 1998 to 4.2 million in the year 2007, and it accounts for approximately 75 percent of the market; whereas immediate release formulations which include the tablet solutions and drops, account for approximately 1.3 million dispensed prescriptions in year 2007.

This slide takes a look at just the immediate release morphine sulfate products by manufacturer. The yellow bar represents the entire extended release market.

The blue line here represents the generic manufacturers, and you can see that the generic manufacturers account for approximately 70 percent of the extended

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release morphine sulfate market. KADIAN represents 15 percent, or 614,000 prescriptions; Avinza was 13 percent with 546,000 prescriptions, and MS-Contin, with one percent of the market or 55,500 prescriptions dispensed in the year 2007.

We looked at the dispensing characteristics for both the immediate release and extended release morphine sulfate products. For the immediate release or the extended release morphine sulfate, the top dispensed strength was 30 mg with 35 percent of the market, followed by 60 mg, 15 mg and 100 mg.

For the immediate release morphine sulfate market, the most dispensed strength was the 15 mg strength, and for the solution and concentration drops, 20 mg was the most dispensed strength. The most common total daily dose which was a report based on a survey of office space physicians, was 60 mg per day, followed by 120 mg per day. The

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average days of therapy per new prescription for the extended release formulation was 28 days; whereas for the immediate release, it was for 22 days.

We also looked at prescription type for the morphine products by dosage form and by prescription type, meaning whether a prescription was dispensed as a new transaction or whether it was a continuing transaction, or whether it was a switch or an add-on transaction. So looking at a three-month look-back period for the extended release formulation, we saw that the majority of transactions were going towards patients who had a prescription filled for another morphine sulfate product in the past three months, so that's 80 percent; whereas new patient prescriptions for extended release morphine sulfate was only 4.5 percent.

For the immediate release formulation, the new patient transactions and add/switch transactions were more common. In

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this chart, we are looking at the top ten prescribing specialties for extended release morphine products, and it's pretty similar to what we saw yesterday for the extended release OxyCodone products.

The leading prescribers in the year 2007 were general practice or family medicine, followed by anesthesiology and internal medicine. Here again, we're combining the number of prescriptions and the number of unique patients who are receiving these prescriptions in their outpatient retail pharmacy setting.

The blue bars represent numbers of patients, and the axis on the left corresponds to patients; whereas the line represents the number of dispensed prescriptions, and the right axis corresponds to dispensed prescriptions.

And now we were looking at patients in the ten-year age increments. And the total number of patients who received all

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morphine sulfate products, including both immediate release and extended release, was 1.2 million patients. For the extended release alone, that accounted for 867,000 patients. For the immediate release, that was 452,500 patients.

We saw that the majority of prescriptions and patients are age 40 to 59 years old. Younger patients age 0 to 19 years old were less than one percent of the market. And again on average, the five prescriptions were dispensed per patient per year for these products.

So again in summary, the morphine sulfate products account for 5.5 million prescriptions and 1.2 million patients, and represents approximately three percent of the selected opioid market. The market share for extended release morphine products, generics account for over 70 percent, KADIAN with 15 percent, Avinza 13 percent and MS-Contin with one percent.

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Leading prescribers are general practice, anesthesiologists and internal medicine. And again, the most dispensed strength for the extended release formulation was 30 mg. The most prescribed total daily dose was 60 mg. Average days of therapy approximately 28 days, and over 80 percent of new prescription transactions were for continuing patients.

Over half of all patients and prescriptions were dispensed to those age 40 to 59 years old, and less than one percent of patients were 0 to 19 years old. And again on average, five prescriptions were dispensed per patient per year for extended release morphine sulfate products.

This concludes my presentation.

DR. KIRSCH: Thank you. The next and last presentation by the FDA will be done by Dr. Cathy Dormitzer, who is going to provide a summary of drug abuse rates in the United States, particularly related to morphine.

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DR. DORMITZER: Hi, good morning.

My name is Cathy Dormitzer, and I'm an epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology. And this presentation focuses on the same topics as yesterday, but today, I will be focusing on morphine. I will provide a brief background on why we are presenting estimates on rates of drug abuse, the methods that we use to calculate these rates, the estimates themselves, and any conclusions that can be drawn from the estimates.

And yesterday you listened to a presentation by Capt. Poinette on the number of non-medical use emergency room visits that are associated with morphine.

Dr. Governale just presented drug utilization data, and that can be considered denominated data. Drug abuse ratios were calculated by dividing the number of non-medical use emergency room visits by

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10,000 retail prescriptions. And that's just to provide some context on non-medical use of opioids within drug utilization.

So do we see high numbers of non-medical use as a result of high utilization; do we see low numbers as a result of low utilization, or are some opioids more abused than others?

Please remember the following limitations. Each data set has different sampling methodologies. Confidence intervals were not used in these calculations, and these data are not linked in any way. As you can see, the number of emergency room visits that are attributed to non-medical use for morphine were considerably lower for controlled release than for immediate release morphine products. But as just presented, extended release retail prescriptions are much higher than for immediate release. And so when you take the total number of prescriptions into consideration, what you

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can see is the number of non-medical use emergency room visits per 10,000 retail prescriptions for extended released morphine is well between 8 and 17 per 10,000 retail prescriptions; whereas the number of emergency room visits for immediate release ranged between 77 and 176.

I'm going to give my epidemiological caveat right here, because I'm anticipating questions. These have very large error bars, and because we have low numbers, I would not place a lot of weight on the numbers themselves. At the same time, we can see that the number of emergency room visits for extended release is lower than for immediate release.

That concludes my presentation.

DR. KIRSCH: We're now going to have an opportunity for members of the Committees ask the presenters either from the sponsor or the FDA questions. I'd ask that you not speak until you're recognized by myself. I would also ask

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you to take into consideration there's going to be a lot of people speaking in turn. So though you may have a comment to make that you think is burning because of a previous question, I'm going to ask you to pause and go to the person in turn who is next.

So with that, I will open it up for questions by the Committee.

Dr. Wolfe.

DR. WOLFE: If you could put up the sponsor Slide C29, I just have a question on that, or two portions of that. It's the intact pellets summary of extraction test results. The first question is with respect to solvent 2 and solvent 3, you have concluded on this chart that this product, ALO-01, does not have any advantage in terms of IV abuse for solvent 2, and does not have any advantage in terms of oral use for solvent 3.

So the question is, do you conclude from that that in comparison with other extended release morphine products, that your

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product does not have an advantage in either of those two categories?

And the second question, which is similar, is for the other solvents, 1, 4, 5, 6, 7, where you state for both oral and IV use that they have a potential to minimize abuse, do you have comparisons again with the other extended release morphine products that would say that your product is distinguishable from those other ones?

DR. STAUFFER: Let me begin to answer that question by providing the criteria that we used in order to establish the potential to minimize abuse. And those criteria were for an IV abused product -- the minimized abuse, there would be extraction of naltrexone, there would be an oral abuse, there would be naltrexone present, multi-step extraction in the amount of less than 100 mg, and time to obtain an abusable amount of morphine, we set that at greater than four hours. For IV abuse, we said there would be naltrexone present, also multi-step

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extraction, but that the concentration would be less than 20 mg per ml, and time to obtain the abusable concentration would be, again, less than four hours.

So to answer your question, first, I believe I may have misunderstood your question, so let me say what I believe I heard. So the "no" in the column means that it does not have the potential to minimize abuse. So what we're saying is for solvent 2, that for an IV abuser, this has a potential to be abused, because even though extraction is low, which means that the concentration is not very high, the amount that you get out looking at a 100-mg dose could still be potentially abused by an IV abuser.

So we are actually saying that does have a potential. And for solvent 3 then, the "no" means that for oral abuse, while you get high extraction, you get very low concentrations in the studies as they were

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performed, and consequently, it does have a potential for abuse.

Did I address that directly for you?

DR. WOLFE: No, my question was -- well, you're defining in terms and that's useful, but my question was, are you concluding that in comparison with other extended dose morphine products that your product is not distinguishable in terms of how much morphine can be extracted, which is the purpose of all --

DR. STAUFFER: I'm sorry. I guess I misunderstood your question. When you look at other extended release morphine products, typically the abuser crushes those products, whether it's chewing or another form, and when they do that, the concentration is a very high, like an immediate release dosage, so the concentration is, or the amount is, very high. So we're staying compared to those -- I don't have the concentration numbers, but those would fall into the categories that I mentioned in how

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we defined the different --

DR. WOLFE: No, this is a study of intact pellets, so again, maybe I'm not being clear enough. For intact pellets of your product versus other ones, the question being there are other data that we're talking about. Other extended dose morphine products, intact pellets, are you saying here that your product does not have an advantage in either solvent 2 or solvent 3 over the other products in terms of morphine extraction from the intact pellet.

DR. STAUFFER: I'm not saying that it does -- we believe that it does have an advantage, because in order to get to these steps, it takes a step or two to get there. The other products, they would be crushed and the amount that would be present in the dosage form would be immediately available.

DR. WOLFE: That's the first part. And the other part is for the other solvents 1, 4, 5, 6, 7, are there data from the other extended release morphine products that would

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allow you to say that your product is distinguishable in terms of morphine extraction. For all of these, you are saying it has the potential to minimize abuse orally and IV for 1, 4, 5, 6, 7; how does that compare with the other extended release products for -- again, intact pellets?

DR. STAUFFER: When we talk of the intact pellets, we believe that the intact pellets often are barriers to -- making it more difficult or making it less convenient for the abuser to be able to use the pellets to take advantage -- to abuse them to their advantage. If you look at other products in the market which would have to be typically crushed or chewed or if you put them in a similar situation, they would behave in a similar fashion.

DR. WOLFE: Again, I'm talking about intact pellets. Do you have data from other intact pellets of other extended release morphine products that you can use as the basis

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for comparing the yes, yes, yes that you have on these?

DR. STAUFFER: I guess if I looked at the KADIAN as another product and compare it to KADIAN, the advantage again is that in a number of these, naltrexone is released in the process of attempting to abuse these particular products, and either the naltrexone that's released or the fear of the precipitated withdrawal from that naltrexone makes this product much less abusable, a less favorable product for the abuser.

DR. KIRSCH: I will add a question to that. I think the question is, do you have data to support that hypothesis? You're stating it as a hypothesis, and the question is, do you have data to support that hypothesis?

DR. WOLFE: On the intact pellets.

DR. STAUFFER: What I believe I was trying to get to is that the criteria used which talked about the amount of drug that's available, or the concentration of drug that's

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available from these, would be that other products would have higher -- are being abused in similar fashions, and this product offers a deterrent more difficult, it takes more steps potentially more difficult do get there.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: I guess I'm a bit puzzled because I think, basically, that I don't think there is a reason that an abuser would leave other products intact. They would crush them or do other things to them to make them immediate release because of the advantage to them.

DR. KIRSCH: So your question?

DR. LORENZ: I'm wondering if we can go to the sponsor's Slides 41 and 42. I'm wondering if you could reiterate at what point in your efficacy study these slides represent? And then two questions about the slide. First of all, I wondered if you could characterize these changes in the Brief Pain Inventory in terms of their clinical as opposed to their statistical significance, because in fact, the

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absolute differences are extremely small. And, secondly, I wondered if you measured the BPI interference scale which I think some persons might consider as an equal -- certainly an equally important indicator of pain impact.

DR. STAUFFER: To answer the first part of your question, the BPI scale was used purely for the pain scales, not for interference. It was not used.

DR. LORENZ: So intensity alone, was it immediate with the time frame of immediate pain or time frame of one week, both of which are part of the standard BPI potential?

DR. STAUFFER: It was an immediate, and also the BPI scales were measured by electronic diary basis. So let me also address the issue of the treatment effect which you see on this slide. As I pointed out in the presentation, this was performed under a special protocol assessment agreement, and we had very specific ground rules as far as conservative imputation methods used in this setting.

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I also mention -- slide up, please, that we have several secondary measures that include the BPI scale that has very significant P values, and that if we look at the clinically significant -- and again recall that this is a randomized withdrawal design study, so there was a large drop in pain from a base of approximately 6.1 to just over 2 with the adding or the addition of ALO-01 and then that randomization to either placebo or ALO-01 continued -- now look at the table on the slide is that the dropouts for placebo patients due to lack of efficacy greatly exceeded those in the ALO-01 group.

And by nature of this study, one of the ways of interpreting these results is that the subjects put on placebo as their pain rose as a perceived lack of efficacy dropped out of the study, and the imputation rules required us to use the randomization baseline for those subjects so that you would have lost all of the pain increase that the

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placebo patients would have had if they dropped out early enough -- dropped out before pain levels rose or for adverse events.

Let me show you another approach. This was a post hoc analysis of the data but in this case, not using week 12 data only but using area under the curve assessment, using ONCOVA and baseline Brief Pain Inventory scores in curve area. In this case using area under the curve analysis, there is a much greater difference in the placebo group versus the ALO-01 group.

And perhaps even more relevant in the clinical setting -- slide up, please -- we see the patients will decide whether a medication is efficacious for them partly by the staying on the medication for reasons of efficacy, and in this setting, analyzing those that dropped out due to lack of efficacy versus those in the placebo versus the ALO-01 group, that there is a

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dramatically larger group of patients dropping out for lack of efficacy in the placebo and a small number in ALO-01.

So we feel that this provides in a sense a real-world estimate of the acceptability of the analgesia for the subject in the settling.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: This is for the sponsor on Slide 73, National Opioid Safety Course. Does that not exist already? Or would that be something just for this specific?

DR. STAUFFER: That course does not exist already. As I said, it will be, I believe, one month after we launch the products, it would be available to all physicians, and we would work with other groups hopefully to help get the message out that this is something we feel is very important for physicians.

One of the things we're concerned about is we want to make sure there is not any untended consequences with our product,

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so we believe that making this available to all physicians -- we will also have one available for pharmacists as well at the time of launch -- and it would be available through the web also, and you can take this paper online, whatever.

DR. KIRSCH: Dr. Nussmeier.

DR. NUSSMEIER: This is for the sponsor. If we could go to Slide C56. This is the slide regarding drug liking. Did you do a statistical comparison between the crushed product and placebo?

DR. STAUFFER: Yes, we did.

DR. NUSSMEIER: And what was that?

DR. STAUFFER: Between the crushed and the placebo, there is a statistically significance between the two. However, in further analyses of that data, it was determined to be clinically not significant. In fact, we did a number of post hoc analyses based on ankle base methods that we can also discuss. I think Dr. Katz, who is here with us, would be able to

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provide some more clarify to the question.

DR. KIRSCH: Dr. Katz, please come to the microphone. There is one right in front of you.

DR. KATZ: Yes, one of the questions that arose when we saw results of these studies is which changes were or were not going to be important. I believe the FDA folks were trying to get at that same issue as well. So our first question was whether the reduction in euphoria that was associated with the crushed product was different compared to the immediate release product, which is the proxy for what you would get if you ingested a tampered form of an extended release morphine.

So we did a whole project to try to figure out what the actual clinically important difference is of a reduction in euphoria in such a study, which we were surprised to find that did not appear to have been explored before. So we went and figured that out. In terms of the clinically

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important difference of these measures of euphoria, it's in the nine or ten millimeter range, so if you exceed that difference, then that's the difference likely to be clinically important.

So the reduction in euphoria on average that was seen with the crushed ALO-01 was robustly and clinically significant as a reduction, and not only statistically significant -- and my recollection from when we did the comparisons to look at whether the crushed ALO-01 was clinically meaningfully more euphorogenic then the whole ALO-01, it did not rise to our threshold of clinical importance.

DR. NUSSMEIER: And I had one other question. Slide C75, slide 75, it starts out with the reporting of adverse events. How will those events be reported or collected? How will you learn of these events?

DR. STAUFFER: Adverse events come into the company through a multitude of ways.

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Sometimes they're reported by physicians themselves, patients, emergency departments, pharmacists, and so in the same way that we collect all adverse events data, we bring that in.

One of the things we want to make sure that this medication if used as directed is not posing any further risk than any other one and specifically KADIAN, because it's long-acting morphine, so we will bring those events in. Any event that would fall into the category of an opioid withdrawal as designated by the DSM-IV, we would look at those particular items, and then adjudicate those items and make sure that it is not withdrawal.

If in fact it is, then we go down the decision tree analysis here and we bring in an external group of folks to look at this. These would be specialists in the field of opioids and risk management to make sure that our medication is being used as

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directed. If it is not, then we go down the left side of the page. If it is being used as directed, then we would have to address that from a regulatory perspective.

DR. KIRSCH: Dr. Burlington.

DR. BURLINGTON: Question for the sponsor also. You showed us a development program in which you intentionally identified the minimally effective naltrexone dose to incorporate, and then you started saying it was enough to, at least for most people, reduce their likability reporting. But what if people crush a large quantity and ingest it, do you deliver enough naltrexone to block respiratory depression and potential mechanism for fatality?

DR. STAUFFER: We did not specifically study that in the trials, although the folks in these trials were opioid experienced non-dependent subjects. And both IV and in the oral studies they were the same types of patients that were studied.

We did other measures in

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pupilometry and also capinography. I believe that I can have Dr. Manning come to the podium to speak on that issue, but it was not specifically looked at as part of the intent.

Before I bring Dr. Manning to the podium, one of the things we wanted to do -- and this was in Study 201 -- we replicated that in Study 205 as well, was to simply make sure that we put enough naltrexone in the formulation such that if you took it as directed, it would not pose any ill effect if you're a legitimate chronic pain patient, and that's the most important thing for us.

However, you want to put enough in there that it actually does something to minimize the euphoric effects both orally and intravenously. I believe that we've done that, and Dr. Comer showed that data.

Maybe I don't need Dr. Manning unless there's any further questions?

DR. KIRSCH: Dr. Zuppa.

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DR. ZUPPA: The question is for the sponsor. So the product label for naltrexone states that an increase in naltrexone (inaudible) of approximately five and tenfold in patients with liver disease as compared with normal liver function has been reported. So my concern is that there would be drug accumulation of the naltrexone and in the population of patients with hepatic impairment, and I was just wondering if you guys plan on addressing that either with future studies or in the product label?

DR. STAUFFER: I'll bring Dr. Manning to the podium to discuss the issues on accumulation, and then we'll take the question further.

DR. MANNING: Within our study, we had no patient because of the inclusion and exclusion criteria, that met higher categories of liver malfunction. We plan on proposed labeling to caution against those that have severe liver disease. We are also very

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interested in working with the FDA if there are special at-risk populations to address but at this point, the proposed labeling has a warning against those with severe liver disease.

DR. KIRSCH: Dr. Rosebraugh.

MR. ROSEBRAUGH: Current methods of advanced drug users include placing the material in a spoon and heating it for injection or subcutaneous use, snorting the drug or smoking. Are any of these alternatives expected to substantially reduce the safety that you believe -- the increased safety in your product that's treated more like a regular morphine procuration?

DR. STAUFFER: The studies that we performed were oral and intravenous, and the intravenous study, what was a proxy for what would happen if someone were to crush the medication. So if you don't mind, if you could clarify the question about safety.

DR. ROSEBRAUGH: The meaning that they would defeat the ability of the added agent to

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reduce its euphoria under those circumstances of usual misuse.

DR. STAUFFER: The ways that abusers and even more hard core abusers -- let me say addicts -- may try to defeat these systems is simply by crushing. We know that that's one of the quickest and easiest ways to do it. The presence of naltrexone in that situation clearly makes these medications less attractive to those people.

Dr. Comer pointed out that if it becomes less attractive, then there are clearly other medications on the market with extended release and immediate release that they would likely go to. In this case, we believe that this is why it may deter them from attempting to tamper with this medication in that way.

Dr. Vincek pointed out that there are ways that a very determined abuser may want to try to manipulate the formulation, and there is no formulation that's perfect.

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The more important thing that we're really trying to advance here is that we know that there is a problem with prescription opioid abuse. We're trying to make these changes in a fundamental way but in a very safe way. Ultimately, the most important group is the patient with pain.

DR. KIRSCH: I don't think you answered the question. So I'm going to rephrase it. If one were to take the preparation either crushed or in its whole form and try to change it to smoke it or to put it in a spoon and melt it, what would its effect be in comparison to immediate release morphine?

DR. STAUFFER: So if you were to crush it, you would get a very similar response that you would get just as if it was a long-acting morphine. I believe the other studies that we had in Study 205 showed that you get no more or less statistically significant euphoria in that setting. If you are able to extract the morphine by itself without the naltrexone -- the

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comparison that I just made there was the comparison between a long-acting opioid if taken as directed and a crushed ALO-01.

So whether it's a long-acting MS-Contin preparation or long-acting KADIAN or any of those, if you crush ALO-01, it looks similar, from a euphoria perspective, to those medications. If you are able to extract the morphine by itself without any naltrexone after using multiple methods to tamper with it, then it will be no different than you would get if you were simply to crush a long-acting opioid formulation.

DR. ROSEBRAUGH: Can you smoke this product?

DR. STAUFFER: I've never tried to smoke the product, and I don't think it's a good idea that anyone does that. We have not done formal studies looking at smoking. It is a formulation that is beads in a capsule, so if you are able to crush those beads somehow, you will need to be able to get that into some type

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of form to smoke it. We haven't done those types of studies.

DR. KIRSCH: Dr. DeWit.

DR. DeWIT: This is sort of an issue that you've mentioned a couple of times, that the users would have to be very motivated to extract, but is it not possible within 10 or 15 minutes to get most of the morphine out without very much of the naltrexone?

DR. STAUFFER: There are methods that were described by Dr. Vincek earlier today and some here as well. You really need to know what you are doing and you need to know timing, and when you put all those steps in place, that's one choice or you could simply go and crush it, another long-acting morphine, or just take an immediate release morphine and do that.

And so those are the steps that make a product like this less attractive. In the presence of other long-acting preparations that are out there, we believe that this medication provides those

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roadblocks in the way, but nevertheless nothing is perfect. You are correct. I mean, nothing is perfect.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: I guess I'm wondering. I'd like you to just comment about the potential for adverse events in a person prescribed this medication that's dependent on the medication taking higher doses for overdose and/or withdrawal as a function of some unforetold outcome related to the release of naltrexone and/or of course in the substance abusing population, this is a deterrent, but if they do find a way to do it, are they at increased risk or death, for example?

DR. STAUFFER: We did not study those patients specifically. Everybody that was in the trials was dependent on the opioid. They were patients with chronic pain and that includes Study 301, 302 and 202. I think maybe what you're talking about are patients who are also likely to abuse because of a history of

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substance abuse, and we did not study those patients specifically in the trial. However, that is one of the patient populations that we actually want to look at in a randomized control trials, and also epidemiologic trials to sort that issue out. We believe that that's important to understand going forward. But for now, if it was taken as directed for the target population which is patients with chronic pain, we have no evidence of any type of withdrawal in that case.

DR. KERNS: So we do know, though, that you even made an attribution in one of your studies that people that had adverse events were because of non-compliance. I was curious about how you made that decision. People do make errors, particularly people with severe pain, with other medical psychiatric comorbidities who might be particularly high doses of this medicine; is there, relative to other extended release morphine products on the market, is there a potential of a greater risk related to

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adverse outcomes if they take this medication inappropriately?

DR. STAUFFER: The potential is there because maybe the presence of naltrexone. If it's used as directed, we didn't see that in any of the trials, but I certainly understand your point. I would like to bring Dr. Manning to discuss further some of the ways that we looked at those folks who went into withdrawal and those who didn't. Actually, we didn't have anyone who went into withdrawal if used as directed.

Dr. Manning.

DR. MANNING: In the core presentation, I presented the COWS score, and there were ten people with definable withdrawal syndrome. Within that, there were approximately five of those patients had withdrawal due to being assigned to placebo -- it is as if they were removed from the drug itself. The other patients within the ten, when we looked back on their histories of taking the medication and

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also looking back on the records in the sites, we find that there were days where the drug was stopped, and as typical of the withdrawal syndrome, it took about a day or so before the withdrawal syndrome started.

That would be no different than, say, if they had a standard extended release opioid preparation. So there is no increased risk in this setting, where just not taking the medication would lead to an abstinence syndrome.

We did look to the ability of the very low detectable levels of naltrexone to initiate withdrawal like signs of symptoms and -- slide up -- that we have subjects separated by those that were opioid-naïve versus those that were opioid-experienced. These actually are the general adverse events in this population. And with the exception of something such as somnolence, there really is no major difference between them.

DR. KIRSCH: Dr. Kramer.

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DR. KRAMER: Dr. Kirsch, just one question. I have two questions. Should I just ask one now and re-rotate?

DR. KIRSCH: You can ask both.

DR. KRAMER: I would like to change gears for a minute and ask a question of the FDA, maybe a question/comment. I didn't see a place in the questions that we're going to address this afternoon directly addressing the REMS strategy, and so I wanted to bring up a concern I have.

I probably should say that I'm coming from a perspective of having evaluated one of the earlier risk management programs and research studies to see the impact of the (inaudible) and also being involved with some research to evaluate the knowledge retained or information retained from patients reading med guides.

And I have some concerns about unintended consequences of risk management programs, well-intended programs, but the

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unintended impact on practitioners, and also on the use of patients who are legitimate patients.

So what I'm concerned about is not specific to this sponsor's program, but the issue that -- you may have mentioned it Dr. Rappaport -- if each company comes up with its own independent program and everyone has their packet and this hugely expanded amount of information, each practitioner, if you are taking it from the perspective from a family practitioner receiving each company's materials, educational, much of which is in similar sorts of things and the risk of how to reduce misuse of opioid, et cetera, and then the specifics of their product, it's very overwhelming for those busy practitioners dealing with patients every day.

And I just wondered if you could comment on the potential of getting some kind of integrated program. There's also

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reluctance of the individual practitioner to feel comfortable that the material may not be somewhat influenced by the marketing instincts of each individual company. I just wondered if there is a possibility that you might develop some kind of integrated education. I realize it's not just the FDA's responsibility, but could you comment on the aggregate effect of these programs.

DR. RAPPAPORT: Sure. As I said yesterday, we're still in the infancy of understanding what our authorities are under the new law in regard to REMS, but as we sort through this, the one clear voice that we have on this is that it really would be appropriate to have all the companies who have potent opioids work together to have some type of REMS program so that that would address all of the concerns that you are raising.

Now, whether we have the authority to make them do that is something we're still exploring, and the lawyers are looking into

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what the law actually says. But we certainly would be strongly encouraging that, and for other reasons you said that.

DR. KIRSCH: Your second question.

DR. KRAMER: My second question is for the sponsor. I wondered if you could describe -- I understand there may be ongoing studies to assess the effects of IV administration of extracted product, and I'm just wondering if you could comment on what those studies are?

DR. STAUFFER: You mean in vitro or in vivo studies?

DR. KRAMER: In vivo.

DR. STAUFFER: In vivo. We have no in vivo human studies ongoing and plan ongoing specifically for that issue.

DR. KRAMER: Do you have any in vivo animal studies?

DR. STAUFFER: I will let Dr. Vincek comment on those. I believe that's what you mean.

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DR. VINCEK: Yes, we have an ongoing study in rabbits to look at ear vein irritancy. Under certain conditions, it is possible for the attempt to extract it to yield some material that's in suspension which could result in vein irritancy. The type of material that's in the product is the same that's common in many products that are on the market today, both opiates -- extended release opiates and immediate release.

The most common it would cause vein irritancy is talc. That is in our product, and those solutions are undergoing the rabbit ear vein irritancy test.

DR. KRAMER: So you're not studying the effects systemically in any animal, just the vein irritancy.

DR. VINCEK: Not at this point, no.

DR. KRAMER: So you are making assumptions that would (inaudible) demonstrate it.

DR. VINCEK: That is correct. Part of

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the reason for that is also we have KADIAN on the market and in 12 years, we have not had any issues that we are aware of that would say that there is a problem with this product in that regard.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: You just stated what -- what was your last statement?

DR. VINCEK: I said KADIAN, which has been on the market for 12 years, we have not had any incidents where there has been a reaction due to IV problems that have been reported to us.

MR. YESENKO: Okay. This is for Dr. Nallani from the FDA. Slide 7, unresolved issues, studies on IV abuse of morphine, study No. 106 IV morphine and IV naltrexone solutions, it is not safe to administer crushed ALO-01 product IV, that the sponsors indicated that animal studies are underway to address safety.

Is that the rabbit deal?

DR. NALLANI: Yes, it is, sir.

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MR. YESENKO: Okay. Thank you.

DR. HERTZ: This product, we know already contains talc, so really, there are no implications from injecting that, so in terms of the safety of injecting it in contrast to perhaps some of the conversations yesterday, I think we have some very different situations here. Are there any other questions about that one element? And we wouldn't allow a human study of injection. Do we have any others or is that question sort of settled?

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: This is a question for the sponsor. If we could go back to Slide C29 on the extraction from intact pellets, on solvents 4, 5 and 6, and solvent 1, prior to six hours or four hours, would the extractability change -- in that the potential to minimize abuse would be instead a yes or no answer. That's based on some of the -- I can't make it more clear because it's the --

DR. STAUFFER: Correct. Would you

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mind just repeating it so I'm sure I've gotten exactly what you're asking.

DR. DENISCO: On that slide for solvents 4, 5 and 6 specifically, also one, prior to extraction times of six hours or four hours, would the extraction be such that the potential to minimize abuse would not be an advantage? In other words, is it only after six hours that the potential to minimize abuse exists?

DR. STAUFFER: What we are trying to depict in the table that in these particular solvents the levels of morphine would be very low, or concentrations would be very low with the morphine in it, so the abuse of those products would require many additional steps to potentially get the morphine into a concentration or an amount that would make it more abusable. That's why it has a potential to minimize abuse.

DR. DENISCO: What would happen between hours 0 to 6?

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DR. STAUFFER: The amount of morphine that you're extracting would be low, very low, and so the solution you end up with would have a small amount or a low concentration, in which case it would require either additional steps if you wanted to go through that process --

DR. DENISCO: So even if there was no crushing?

DR. STAUFFER: Yes, that's what I'm trying to say, yes.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: The question I have is for the FDA as well as for the sponsor, and it relates to two slides that are related to, actually, Study 205 -- Slide C58 for the sponsor and it's from Dr. Nallani's presentation. So on the one hand, I think it's potentially very helpful, although not necessarily so, that we have subjective data from patients instead of intermediate end point that might not be related to subjective outcomes.

But on the other hand, there is

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some significant differences in the way that the data is presented between slides four in Dr. Nallani's presentation, and Slide C58 and in fact, if I understand it correctly, it is really core data from the company's standpoint in terms of how we should understand the potential clinical impact of a change in this for its abusability.

I think from a company standpoint, you have chosen to present values without an indication of whether they represent medians, mediums or exactly what, and also, I think again, rather than understanding statistical significance, we really would like to understand the clinical significance of the absolute difference.

And from Dr. Nallani's presentation, in fact, that seems to be the very point, that perhaps this variability doesn't -- doesn't really enlighten a clinically important difference. So I would like both of you to address the extent in

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which your data shows us how this is clinically important.

DR. STAUFFER: I would like to have Dr. Comer address these issues, please.

Dr. Comer.

DR. COMER: My name is Sandy Comer from Columbia University. We have conducted several studies of an injectable form, long-lasting form, of naltrexone for treating opiate dependence. So we have lab studies where we measured subjective responses like they did in the Alpharma studies, and we have a clinical trial using the same doses of naltrexone for treating opiate dependence.

So what we did was a comparison of the amount of reduction in subjected responses, and tried to match map that onto clinical outcome. And what we found was the amount of reduction that we had in the Alpharma studies actually far exceeded the amount that was necessary to obtain clinically meaningful reductions in opiate

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use.

DR. LORENZ: That's a mean reduction. And what is the mean reduction in that case that is reflected in the statistical portrayal on Slide C58?

DR. STAUFFER: So for the mean reduction for all of these different end points when you're looking at morphine to placebo or morphine to ALO-01, which is essentially the same, those mean reductions on the scale of 0 to 100 well exceeds in the order of 15 to 20 millimeters, and Dr. Katz said that if you're about ten or beyond, you've done something meaningful. And that's true for every secondary variable as well.

DR. KIRSCH: FDA response, please.

DR. NALLANI: The point of providing that slide was to show the huge variability in the data, and in fact, we are hoping that the sponsor will explain the kind of elements of the changes, considering the huge variability.

DR. KIRSCH: Same point back on

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Slide C56. Comparing instant release morphine, which is a different kind of product, gives more favorable figures as shown in 58, but let's focus just on crushed ALO-01 versus whole ALO-01.

The peak value for the difference in terms of likability is 0.875, and I think you earlier said there is no clinical significance. One of the main reasons for including naltrexone in here is that if they crushed the pellets, then they will release naltrexone, which will presumably have a different effect on their likability than if they were just taking the whole tablet.

And what you see is for the whole tablet, the likability starts going up towards 6 or 8 hours. So have you ever done a study where you compare crushed ALO-01 with whole -- again, some other extended release morphine, to try and see whether there is some advantage there of an existing product.

If you are putting something in to

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deter likability, and in fact, the likability is no different, according to your own statistics here, then the whole product -- what is going on here. I mean, have you done that study, first of all, comparing crushed ALO-01 with another extended release product that is whole?

DR. STAUFFER: No, we have not done that study. The study that we did do was versus the product or any other, say, long-acting morphine product that you would crush. You could call it KADIAN or MS-Contin or any of the generics or Avinza. That's what the blue line essentially represents. If taken whole, all of the extended release products, at least ALO-01 and in this case KADIAN as well, would operate much like the green line that you see on the graph.

The most important comparison that we wanted to make with this study was really for assay sensitivity, the blue line versus the white line, so doing nothing versus

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crushing an immediate release morphine.

And then the second piece was comparing the crushed product, the yellow line, versus the blue line, and clearly those are statistically clinically significant relevant. More importantly, we wanted to demonstrate even a comparison even between the yellow and the green line, or the crushed, if you just took a long-acting product you can see there by the P value, it's essentially no different.

The point of the six hours is that this is a long-acting preparation, and so at about the six-hour mark, you can see the green line going up because that's the effect of the morphine coming out. This is important for long-acting pain relief for patients.

DR. KIRSCH: We're limited on time, so I'm going to go to the next person, Dr. Krivacic.

DR. KRIVACIC: Thank you. With regard

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to the clinical program, I have a question for the sponsor. I'm sorry my back is to you. My question is regarding drug accountability. I did see this in the documents, the briefing documents, that we were given. I don't remember which particular study, if that was 301 or 302, but if you can please speak to that in terms of what type of patients those were that did not return the bottles or -- you know, where they lost the bottles, were those the more experienced opioid patients; was that in uncontrolled trial or was that in the controlled trial?

Thank you.

DR. MANNING: Throughout our study, particularly in studies 301 and 302, there were several instances of drug accountability issues. There was no consistent thread that went through the accountability problems. For instance, one was a patient who was in an alcohol recovery program, and when his counselor found out about it, made him flush all the tablets or the

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capsules down the toilet and we could not account for that.

But there was another where patients just didn't return the entire bottle. There were a few capsules that were unaccounted for in that setting. We did not see a consistent pattern of whether the subject patients were opioid-experienced in the past or not. There was one occasion where the capsules were returned with a few less than what they were. Of that batch of the entire number of accountability issues, there was no consistent pattern throughout there.

DR. KIRSCH: We are going to have a total of four more questions of people who are on my list. Next is Dr. DeWit.

DR. DeWIT: I have a brief comment and then a question for the sponsor. My brief comment has to do with the distinction between clinically significant and statistically significant, and it sounds to me like you're

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using that a little bit to your advantage.

Since the abuse liability study, you had statistically submitted a difference between the crushed and the placebo, but you are saying it's clinically not significant, and yet on the efficacy study, you have a significance of .045 and you are saying that's clinically significant. Yeah, that's just -- it is clinically significant, so just a comment on the use of that distinction and it needs a little bit of follow-up.

But my question has to do with the individual liability in the abuse liability study, where it sounds as though there were a few subjects who did report the sudden euphoria that you would get without the naltrexone, and we saw a hint of that in the variance of that in what FDA showed, and I was wondering if you could comment on individual subjects.

Were there 10 or 20 percent of the subjects who did report maximal euphoria

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after the product?

DR. STAUFFER: I'm going to let Dr. Comer answer or Dr. Katz answer the second question first, and then I'll come back to your other question on clinical significance and efficacy --

DR. DeWIT: I don't really need any more expansion. I'm just noticing that.

DR. STAUFFER: There were some subjects in those trials who had no response whatsoever to the crushed ALO-01. There is high variability in some of those subjects. Some of those subjects also had baseline differences as well.

DR. DeWIT: I guess the question is, were there a few who were reporting high euphoria in the presence of naltrexone?

DR. STAUFFER: A few reporting high euphoria --

MS. POLLOCK: There were four.

DR. STAUFFER: There were four subjects who reported euphoria, but it's not

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that much different than what you would get IR morphine. I think that's where you're going. We had some of those subjects, yes, with the crushed product.

DR. KIRSCH: Dr. Katz.

DR. KATZ: I don't remember the number of subjects that had more than threshold amounts of euphoria in the naltrexone group. I think that the point to me is that there is a lot of variability in these studies as there is in all clinical trials. It is absolutely the case that not all subjects in the study who received the morphine/naltrexone combination showed reductions in euphoria, as one would expect, and I think that the FDA slide slowed that very clearly.

The question to me is whether a product like this that shows an average reduction in euphoria that is robustly clinically sufficient can still accomplish its public health goals of reducing prescription opioid abuse, despite the fact

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that there is some outliers who will not be affected by the inclusion of the naltrexone.

For example, Talwin Nx, there are reports in the literature of people very happily injecting themselves with Talwin Nx and getting high, despite the fact that on a societal level, the abuse of that product went down dramatically after the introduction of that medication, and adds to the shift of distribution of the euphoria that it produced.

Similarly, Suboxone and Naloxone continue preparation and there are case series in the literature of people very happily injecting themselves with Suboxone and getting high, but yet when you look at the countries in which Subutex was first introduced and then switched to Suboxone, we see significant reductions in the abuse of buprenorphine as a result of the introduction of the Naloxone-containing preparation. So I think the answer to the big question is if

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you can produce a shift in the distribution of euphoria that on average is clinically meaningful, despite the fact that there is some outliers that will not be individually affected by the inclusion of the antagonist, you still can accomplish your public health goals.

DR. KIRSCH: Thank you. Dr. Paulozzi.

DR. PAULOZZI: Question for the sponsor and it has to do with the map on slide 70, which is the surveillance of (inaudible) capsule abuse. I was puzzling over this. I assume that these measures of the percent or number of 100 clients in the substance abuse treatment programs represented by the dots who reported misusing KADIAN in a particular calendar quarter. Is that correct?

DR. STAUFFER: That's correct, it's in that specific area.

DR. PAULOZZI: So that one dot on the border of Alabama and Tennessee is representing Alabama, for example. But my question is how do

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you use this to interpret geographic variations, or whatever you want to do with it without the denominator of the number of prescriptions that could be in either of those communities that are represented by the individual effects?

DR. STAUFFER: If I could have this slide up, please. This data is only one data stream, and to your point, it only represents one. There are multiple sources that we use for surveillance. This one is only looking at those folks in the inpatient treatment center in that locale. They may be getting the drug from other places, maybe even from other geographic distributions as well. This only represents where we can pick it up. So I think you are fair in your assessment when you say there is going to be some variability there.

DR. PAULOZZI: I'm saying that it's very hard to use the data without the sense of the volume in the community as a true measure of risk.

DR. STAUFFER: The volume does not

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necessarily come from the prescribers in that community. It could come from other prescribers in other areas. It does simply represent the place at least input where we can start gathering the information -- understanding the good thing that we liked about it is that it can give us that real time data and we can at least react to it on a monthly basis because all that data is uploaded into the database.

DR. KIRSCH: Dr. Brull.

DR. BRULL: Thank you. This is a disadvantage here to going last. I wanted to go back to one of the questions, and perhaps this is going to be revisited, but I still don't have a clear picture of what the answer was. In the FDA data, they showed clearly that the variability of response was very large, and we all know that all patients have a very wide variability in responses to drugs, all drugs, but particularly narcotics.

So my question is, is the variability in the data that you showed any

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different than the variability of the data that's in this ALO-01 compound? So is the standard deviation or the variability greater with ALO-01 than it is with extended release morphine?

DR. KIRSCH: If I could just get clarification. Are you speaking specifically to the sponsor or --

DR. BRULL: I'm sorry, this is to the FDA. Thank you.

DR. NALLANI: That's a good question. I do not have the final deviation numbers for each treatment. Sorry, but that is something we will definitely look at.

DR. KIRSCH: The last question of the session is from Dr. Rosenberg.

DR. ROSENBERG: This is Dr. Rosenberg.

I was wondering about the confidence that you have in the DAWN data given that DAWN comes from retrospective chart review of emergency room visits, and heroin would show up on those drug screens as

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morphine unless they actually injected the heroin right outside the door of the ER. Whether or not the people reviewing the charts use drug screens of either blood or urine that show positive for morphine, would they be recorded as morphine when in fact it was actually heroin use? Or that the doctor would quiz the patient saying your drug screen shows heroin so it's morphine --

DR. COMER: So your question is regarding the DAWN data?

DR. ROSENBERG: Whether or not you believe that the numerator is an accurate figure, unless you have some other way of getting to that numerator -- and if that numerator is inaccurate, does that suggest to you that perhaps the amount of morphine used or at use leading to significant morbidity in our emergency rooms is actually overstated?

DR. COMER: The reports themselves are actually coming from the emergency room visits from the medical records and a lot of them are

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not tox-screened confirmed.

At the same time, what Dr. Poiliame presented was what reported -- and what was reported for the extended release products was that a large percentage of them were MS-Contin. I'm trying to recall what she said was for immediate release.

First of all, they will have more than one drug on board in all likelihood. I think she said 80 percent had four or five drugs onboard. So the people who wind up in the emergency room have more than one drug onboard. At the same time, they are reporting whether it was OxyCodone, if it was morphine, if it was Hydrocodone.

So the error bars are large, but I have confidence that when a reporting is morphine, yes, it's morphine. But the error bars are large. So I don't have confidence in the numbers -- the ratio I provided is not a precise estimate. It was simply examining in the context of drug utilization -- are the

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numbers we're seeing the result of, you know, low use, low numbers, or is it high use, high numbers, or what we are seeing is that some drugs are more likely to be abused than others? And so we are seeing differences in extended release and immediate release.

Does that answer it?

DR. KIRSCH: Thank you. I apologize to the Committee and to the audience that we have run a couple of minutes over time, but I think the discussions have been well worth it.

I have two announcements. First, FDA and this Committee favor public input, and therefore, it's important that we hear from you. If anyone who has registered for the open public hearing but has not signed in please see the desk immediately. You won't be allowed to speak unless you signed in.

Second, we are now going to break for lunch. We will reconvene in this room in one hour from now, which will be ten minutes after one. Please take any personal

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belongings you may want with you at this time.

Committee members, please remember that there should be no discussions of the meeting during lunch amongst yourselves or any member of the audience.

Thank you.

(Whereupon, at approximately 12:10 p.m., a luncheon recess was taken.)

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