FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Psychopharmacologic Drugs Advisory Committee

Thursday,
September 16, 2010

8:31 a.m. to 4:45 p.m.

The Great Room,
White Oak Conference Center,
Food and Drug Administration Campus
10903 New Hampshire Avenue, Building 31
Silver Spring, MD

PRECISE REPORTING, LLC

PRESENT:

Susan Schultz, M.D., Acting Chair

Yvette W. Waples, Pharm.D., Designated Federal Official, PDAC

**PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)**

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Robert Wood Johnson Medical School,
University of Medicine and Dentistry
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Serious Mental Illness Program Manager,
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Charleston, South Carolina,
and University of Iowa,
Iowa City, Iowa,
Adjunct Professor,
Department of Biostatistics & Bioinformatics,
Duke University,
Durham, North Carolina

**PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)**

William Z. Potter, M.D., Ph.D.
Industry Representative,
Philadelphia, Pennsylvania

PRESENT: (Continued)

**TEMPORARY MEMBERS (Voting)**

Louis E. Baxter, Sr., M.D., FASAM
Executive Medical Director,
Professional Assistance Program of New Jersey, Inc.,
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Institute, Cleveland Clinic Foundation,
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Acting Deputy Director,
Division of Pharmacotherapies and Medical,
Consequences (DPMC) of Drug Abuse,
National Institute on Drug Abuse (NIDA),
National Institutes of Health,
Bethesda, Maryland

PRESENT: (Continued)

**TEMPORARY MEMBERS (Voting) (CONTINUED)**

Rodney Mullins, Consumer Representative
National Director, Public Health Consultants
and Advocates,
Duluth, Georgia

Susan K. Schultz, M.D., Acting Chair
Professor of Psychiatry,
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Iowa City, Iowa

Sharon L. Walsh, Ph.D.
Professor, Department of Behavioral Science,
Professor, Department of Psychiatry,
Director, Center on Drug and Alcohol Research,
University of Kentucky,
Lexington, Kentucky

Chung-yui Betty Tai, Ph.D.
Director, Center for the Clinical Trials Network,
National Institute on Drug Abuse,
National Institutes of Health,
Bethesda, Maryland

PRESENT: (Continued)

**FDA PARTICIPANTS (Non-Voting)**

Celia Winchell, M.D.
Clinical Team Leader, DAAP, ODE II, OND,
CDER, FDA

Bob Rappaport, M.D.
Director, Division of Anesthesia and
Analgesia Products (DAAP), ODE II, OND,
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Robert O'Neill, M.D.
Director, Office of Biostatistics,
Office of Translational Sciences,
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Rigoberto Roca, M.D.
Medical Officer, DAAP, ODE II, OND,
CDER, FDA

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1 P R O C E E D I N G S

2 (8:31 AM)

3 **Call to Order**

4 DR. WAPLES: Good morning. If everyone

5 would take their seats, we're about to begin.

6 I would first like to remind everyone to

7 please silence your cell phones, BlackBerry or other

8 devices if you have not already done so.

9 I would like to also identify the press --

10 FDA press contact, Sandy Walsh. If you are present,

11 please stand. Thank you.

12 **Introduction of Committee**

13 DR. SCHULTZ: Good morning. My name is

14 Susan Schultz from the University of Iowa. I'm

15 delighted to chair this morning. I'd like to begin

16 with introduction of the members and consultants

17 around the table. So if we could begin with Dr.

18 Potter, we'll proceed with introductions.

19 MR. POTTER: Yes. My name is Bill Potter

20 and I'm the industry representative. Non-voting

21 industry representative.

22 DR. MAXWELL: I'm Jane Maxwell with the

1 Addiction Research Institute at the University of
2 Texas at Austin.
3 DR. MONTOYA: I'm Ivan Montoya, the Division
4 of Pharmacotherapies of NIDA.
5 DR. TAI: I'm Betty Tai. I'm the director
6 for Center for Clinical Trials Network at NIDA.
7 DR. BAXTER: I'm Lou Baxter. I'm executive
8 medical director for the Professional Assistance
9 Program of New Jersey and I'm the current president of
10 the American Society of Addiction Medicine.
11 DR. WALSH: I'm Sharon Walsh, and I'm a
12 professor of behavioral science and psychiatry and the
13 director of the Center on Drug and Alcohol Research at
14 the University of Kentucky in Lexington.
15 DR. HWANG: I'm Michael Hwang, associate
16 professor of psychiatry at the Robert Johnson Medical
17 School, New Jersey and also at the FDR VA in
18 Westchester, New York.
19 DR. WHITE: I'm Tonya White. I'm a U.S.
20 citizen but working at Erasmus University Medical
21 Center in Rotterdam in the Netherlands.
22 DR. WAPLES: Yvette Waples. I'm the

1 designated federal official for this meeting today.
2 MR. WILSON: I'm Skip Wilson. I'm a
3 biostatistician. I'm emeritus at Iowa and MUSC and
4 I'm presently adjunction professor at Duke University.
5 DR. MICHNA: Ed Michna, anesthesiologist,
6 pain management, at Brigham-Owens Hospital in Boston.
7 DR. COVINGTON: Ed Covington. I'm the
8 director of the Neurological Center for Pain at
9 Cleveland Clinic.
10 DR. ROCA: I am Rigoberto Roca. I am deputy
11 division director of the Division of Anesthesia,
12 Analgesia, and Rheumatology Products.
13 DR. WINCHELL: I'm Celia Winchell. I'm the
14 medical team leader for Addiction Drug Products.
15 DR. RAPPAPORT: Bob Rappaport. I'm the
16 director of the Division of Anesthesia and Analgesia.
17 DR. SCHULTZ: All right. We'll begin with
18 the introductory statement.
19 For topics such as those discussed at
20 today's meeting, there are often a variety of
21 opinions, some of which are quite strongly held. Our
22 goal is that today's meeting will be a fair and open

1 forum for discussion of these issues and that
2 individuals can express their views without
3 interruption. Thus, as a gentle reminder, individuals
4 will be allowed to speak into the record only if
5 recognized by the chair. We look forward to a
6 productive meeting.
7 In the spirit of the Federal Advisory
8 Committee Act and the government in the Sunshine Act,
9 we ask that the Advisory Committee members take care
10 that their conversations about the topic at hand take
11 place in the open forum of the meeting. We are aware
12 that members of the media are anxious to speak with
13 the FDA about these proceedings; however, FDA will
14 refrain from discussing the details of this meeting
15 with media until its conclusion. Also, the Committee
16 is reminded to please refrain from discussing the
17 meeting topic during breaks or lunch.
18 Thank you.
19 **Conflict of Interest Statement**
20 DR. WAPLES: Good morning again. The Food
21 and Drug Administration (FDA) is convening today's
22 meeting of the Psychopharmacologic Drugs Advisory

1 Committee under the authority of the Federal Advisory
2 Committee Act (FACA) of 1972. With the exception of
3 the industry representative, all members and temporary
4 voting members of the Committee are special government
5 employees (SGEs) or regular federal employees from
6 other agencies and are subject to federal conflict of
7 interest of laws and regulations.
8 The following information on the status of
9 the Committee's compliance with federal ethics and
10 conflict of interest laws covered by but not limited
11 to those found at 18 U.S.C. Section 208 and Section
12 712 of the Federal Food Drug and Cosmetic Act is being
13 provided to participants in today's meeting and to the
14 public. FDA has determined that the Committee members
15 and temporary voting members are in compliance with
16 federal ethics and conflict of interest laws. Under
17 18 U.S.C. Section 208, Congress has authorized FDA to
18 grant waivers to special government employees and
19 regular federal employees who have potential financial
20 conflicts when it is determined that the agency's need
21 for a particular individual's services outweighs his
22 or her potential financial conflict of interest.

1 Under Section 712 of the FD&C Act, Congress has
2 authorized FDA to grant waivers to special government
3 employees and regular federal employees with potential
4 financial conflicts when necessary to afford the
5 Committee essential expertise.
6 Related to the discussion at today's
7 meeting, Committee members and temporary voting
8 members have been screened for potential financial
9 conflict of interest of their own, as well as those
10 imputed to them, including those of their spouses,
11 minor children, and for purposes of 18 U.S.C. Section
12 208, their employers. These interests may include
13 investments, consulting, expert witness testimony,
14 contract grants, CRADAs, teaching, speaking, writing,
15 patents, and royalties, and primary employment.
16 Today's agenda involves discussion of the
17 available safety and efficacy data for a supplemental
18 new drug application sNDA 21-897/015 Vivitrol, generic
19 naltrexone for extended-release injectable suspension
20 sponsored by Alkermes, Inc. for the treatment of
21 opiate dependence.
22 This is a particular matters meeting during

1 which specific matters related to Alkermes' Vivitrol
2 will be discussed. To ensure transparency, we
3 encourage all standing Committee members and temporary
4 members to disclose any public statements that they
5 may have made concerning the products at issue.
6 With respect to FDA's invited industry
7 representative, we would like to disclose that Dr.
8 William Potter is participating in this meeting as a
9 non-voting industry representative, acting on behalf
10 of regulated industry. Dr. Potter's role at this
11 meeting is to represent industry in general and not
12 any particular company. Dr. Potter is an independent
13 consultant to the pharmaceutical industry.
14 We would like to remind members and
15 temporary voting members that if discussions involve
16 any other products or firms not already on the agenda
17 who as an FDA participant has a personal or imputed
18 financial interest, the participant needs to exclude
19 themselves from such involvement and their exclusion
20 will be noted for the record. FDA encourages all
21 other participants to advise the Committee of any
22 financial relationships that they may have with the

1 firm at issue.

2 Thank you.

3 DR. SCHULTZ: We'll now proceed with the

4 Division's introductory remarks. So we'll welcome Dr.

5 Sylvia Winchell's introductory comments.

6 Yes. We'd like to recognize Dr. Rodney

7 Mullins has arrived. Would you like to introduce

8 yourself?

9 MR. MULLINS: Good morning. I'm from the

10 National Council on the Advocacy and Consultancy on

11 Public Health and my name is Rodney Mullins. Thank

12 you.

13 **Opening Remarks**

14 (Sound system failure.)

15 DR. WINCHELL: (Off microphone) clinical

16 trials (inaudible) treatment for (inaudible) creating

17 the most commonly used medications to treat opioid

18 dependence or (inaudible) treatments. They are

19 controlled substances. Treatment of addiction with

20 Methodone is limited to (inaudible) treatment programs

21 which have (inaudible) treatment schedules for some

22 patients and this (inaudible) to treatment (inaudible)

1 treatment is available in (inaudible) prescribed only
2 on specially qualified physicians.
3 In addition, these medications are also
4 subject to abuse (inaudible) Vivitrol is not a
5 controlled substance. It does not carry risks
6 (inaudible) of respiratory or CNS depression as
7 (inaudible) used to. It does not require the patient
8 to obtain treatment at a specialized program and is
9 not subject to abuse (inaudible) so the (inaudible)
10 briefing documents that Vivitrol has the potential to
11 meet an important public health need.
12 The original application for Vivitrol for
13 (inaudible) did contain in addition to the efficacy
14 (inaudible) some safety data (inaudible) opioid
15 dependent (inaudible) dependent population as well as
16 pharmacodynamics study demonstrated (inaudible)
17 opioids for 28 days.
18 (Technical difficulty resolved.)
19 And shortly after the approval of the
20 initial application, Alkermes embarked on a program to
21 support an efficacy supplement for the use of Vivitrol
22 in treatment of opiate dependents by showing that the

1 pharmacologic effect translated to a clinical effect,
2 mainly prevention of relapse.
3 So this development program was taken with
4 advice from the Agency. The current paradigm for
5 clinical trials in addiction treatment is evolving.
6 We have greater focus on individual treatment response
7 rather than group meetings, and we at FDA have been
8 requiring that the trials be of sufficient duration
9 that patients who make substantial improvements in
10 their drug use behavior would be likely to accrue some
11 degree of physical or psychosocial benefit. And we
12 didn't have any evidence to support the idea that a
13 very brief period of abstinence could translate into
14 clinical benefits, so six months was chosen as a
15 reasonable observation period.
16 However, during our discussions, Alkermes
17 expressed a concern that complete abstinence could be
18 impossible to document in a clinical trial of this
19 length, but rather than agreeing a priori that
20 complete abstinence was an unreasonable expectation or
21 arbitrarily selecting some other drug use pattern
22 short of abstinence that could be considered

1 successful, we encouraged Alkermes to look at the full
2 range of responder definitions from complete
3 abstinence to no abstinence, but of course,
4 emphasizing the effect of the drug on promoting
5 abstinence or near abstinence. And this is the
6 analysis that Alkermes is calling their response
7 profile.
8 Now, other approved products for treatment
9 of opioid dependence -- methadone, levomethadyl
10 acetate, which is called Orlaam or LAAM not currently
11 marketed, and buprenorphine, had their approval
12 supported by a variety of placebo-controlled studies
13 with treatment as long as 40 weeks. Various analytic
14 approaches were applied to these -- to evaluating
15 these results. So the Vivitrol study design itself, a
16 randomized placebo-controlled parallel group study of
17 six months duration, is not actually novel but the
18 analytic approaches and concepts sum may be.
19 We agree with Alkermes that the efficacy
20 study provides evidence that Vivitrol prevents relapse
21 to opioid use in recently detoxified opioid-dependent
22 patients. And in fact, even comparing just the

1 proportion of patients who were completely abstinent
2 provides that evidence without reference to the
3 response profile. So our sources of efficacy data for
4 this application include a study showing that Vivitrol
5 blocks exogenous opioids for the four-week intradose
6 interval and an efficacy study demonstrating that this
7 pharmacologic effect translates into clinical effects.
8 The efficacy study was conducted in Russia.
9 And while you will hear from Dr. Purohit-Sheth of our
10 Division of Scientific Investigation that we do have
11 confidence in the quality of the data, there are some
12 demographic and cultural differences between the
13 studied population and the population of opioid-
14 dependent patients in the United States. We'll ask
15 the Committee to address whether the available
16 efficacy data from these sources are sufficient to
17 conclude that the drug is effective for the intended
18 use in the U.S. population.
19 Turning to safety, our review of the
20 expanded safety database did not identify major new
21 safety issues compared to the established safety
22 profile in the alcohol-dependent population, but we

1 noted that the rate of adverse event reporting was
2 distinctly lower in the Russian study compared to the
3 completed studies in the United States that we
4 considered under the original NDA review. And we were
5 advised that cultural norms in Russia might influence
6 the propensity to report adverse events -- for the
7 subjects to report them, not for the investigators to
8 report them to the sponsor.
9 While the safety profile in the United
10 States alcohol-dependent population has been
11 established through the studies that we reviewed for
12 the original approval, we think there are some
13 indication-specific issues -- safety concerns specific
14 to the new population.
15 For example, the risk of opioid overdose in
16 opioid-dependent subjects who either attempt to
17 overcome blockade while under blockade with Vivitrol
18 or who use opioids after missing a dose or after
19 dropping out of treatment and misjudge their
20 tolerance. This is a risk that’s really not seen in
21 the alcohol-dependent population.
22 Additionally, viral hepatitis and HIV

1 infection are much more prevalent in the opioid-
2 dependent than in the alcohol-dependent population,
3 and if either of these conditions were to predispose
4 patients to adverse events related to Vivitrol --
5 potentially hepatic effects or some type of immune
6 response -- it would be important that these risks be
7 adequately characterized in opioid-dependent patients.
8 And we'll ask the Committee to address
9 whether these or any other indication-specific
10 concerns that you might identify have been adequately
11 addressed and adequately characterized by the existing
12 safety data or whether additional safety data might be
13 needed in the American population.
14 Your deliberations and recommendations will
15 play an important role in our decision-making. And
16 I'd like to thank you for taking time from your other
17 extensive responsibilities to participate in this
18 process.
19 DR. SCHULTZ: Thank you. At this time we'll
20 proceed with the industry presentation. So we'd like
21 to proceed with sponsor presentations. And I believe
22 that would be Dr. Elliott Ehrich.

1 **Sponsor Presentation:**

2 **Introduction**

3 DR. EHRICH: Good morning. I'm Elliott
4 Ehrich, chief medical officer and senior vice
5 president of Research and Development at Alkermes.
6 I've been working on Vivitrol for over 10 years. In
7 reality, however, Vivitrol is the culmination of over
8 40 years of effort. So it's very exciting to be here
9 today and to reach this milestone.
10 In addition to our efforts at Alkermes,
11 Vivitrol is the result of work at numerous academic
12 institutions, the NIH, including NIDA and NIAAA, as
13 well as the FDA and other organizations that
14 contributed to prototype formulations -- formulations
15 that laid the groundwork for Vivitrol.
16 Our presentation today will proceed as
17 follows: First, Dr. Charles O'Brien will discuss the
18 growing rate of opioid-dependence in the U.S., a major
19 health issue that is growing despite existing
20 therapies. He will also discuss the pharmacology of
21 new opioid blockade and naltrexone.
22 After Dr. O'Brien's presentation, I'll

1 introduce the Vivitrol clinical program and efficacy
2 results for the pivotal study. The results were
3 statistically significant and clinically important.
4 There are two key reasons why we believe the pivotal
5 results are applicable to the U.S. patient population.
6 First, the study was conducted by a clinical trial
7 network that emulates the treatment context of
8 Vivitrol in the United States.
9 And secondly, the patients enrolled in the
10 study have similarities that are relevant to the
11 American target population. We will also review
12 results from U.S. studies which show correspondence to
13 the pivotal study and function as bridging studies.
14 They provide data and experience with Vivitrol
15 directly in American patients and demonstrate the
16 applicability of Vivitrol to the treatment of opioid
17 dependence in the United States.
18 Next, my colleague, Dr. Bernard Silverman,
19 will review the Vivitrol safety data from the clinical
20 studies on opioid dependence. The safety profile of
21 Vivitrol is well characterized and no new safety
22 findings were observed in the opioid program. Dr.

1 Paul Earley, an addiction specialist from the Talbott
2 Recovery Campus will characterize his experience in
3 treating opioid-dependent patients with Vivitrol. And
4 I'll end with some closing remarks regarding the FDA
5 questions.
6 A number of experts are here with us today
7 to address questions. Dr. Evgeny Krupitsky is the
8 principal investigator of the 13 study, the pivotal
9 study, and chief of addiction psychiatry at St.
10 Petersburg Medical University. Dr. Elena Blokhina,
11 also from St. Petersburg, is an investigator with the
12 pivotal study. Dr. Walter Ling, from UCLA, is an
13 expert in addiction psychiatry. Dr. Mack Mitchell is
14 a gastroenterologist from Johns Hopkins. Dr. Lee-Jen
15 Wei from Harvard is a noted biostatistician.
16 We are also fortunate to have with us Dr.
17 Charles O'Brien, who has worked with naltrexone for
18 more than 40 years. Dr. O'Brien is the Kenneth Appel
19 professor and director for the Center of Studies of
20 Addiction, Department of Psychiatry at the University
21 of Pennsylvania School of Medicine. He has won
22 numerous awards and accolades in his career, and just

1 this year he was honored with a mentorship award from
2 the College on Problems of Drug Dependence. Dr.
3 O'Brien.

4 **Opioid Dependence and Naltrexone Overview**

5 DR. O'BRIEN: Thank you, Dr. Ehrich. I'm
6 here as a consultant to Alkermes and I've actually
7 been in this field for a long time. I became
8 interested in problems of substance abuse when I was a
9 medical officer in the U.S. Navy during the Vietnam
10 War. I discovered at that time that a major reason
11 for my patients being unfit for duty and incapacitated
12 was drug abuse. And the most important drug in that
13 category was heroin. So I learned what we knew about
14 heroin and how to treat it at that time. And when I
15 was discharged from the Navy in 1971, I founded the
16 treatment program at the Philadelphia Naval Hospital -
17 - excuse me, the Philadelphia VA Hospital -- and began
18 trying to set up programs for dealing with not just
19 opiate addiction but all kinds of addiction.
20 Heroin at that time was a major public
21 health problem, as it is today, but the history is
22 interesting because it goes back to the 1800s after

1 the Civil War. And over the 20th Century, opiate
2 addiction remained a problem but it began hitting more
3 in the middle class in the 1960s and '70s. And with
4 the return of the veterans from Vietnam, we had a
5 major epidemicrophone. And then just in the past 10
6 years it's gotten even larger. And you see beginning
7 in 2003 it's really shot up, but not as much with
8 heroin, even though heroin is on the street, and very
9 potent heroin, but it's because of prescription
10 opioids. So we have a major problem with both kinds
11 of opioids.
12 Now, the treatment of opiate addiction is
13 very difficult, and we've tried all kinds of talk
14 therapy without success. People relapse more than 90
15 percent in just a short time after they're discharged
16 drug-free. A major advance was the discovery of
17 methadone treatment in the 1960s, and in the early
18 1970s it became widespread. Methadone is a wonderful
19 drug. It's great for the majority of patients, and
20 now we have, as Dr. Winchell mentioned, since around
21 2000 we have buprenorphine. So we have agonist
22 therapy. And agonist therapy works by acting at the

1 opiate receptor and activating it in a similar way to
2 the way heroin and oxycodone and the other opiates and
3 opioids that people are abusing so that people can get
4 high from these drugs but if they're maintained at a
5 level of tolerance, they can function very well in
6 community and it's a good treatment. But not all
7 patients really want or even are appropriate for that
8 kind of treatment.
9 So in the early 1970s, naltrexone was
10 discovered. Naltrexone is pretty much a pure
11 antagonist. It has very high affinity for the same
12 receptor but it doesn't produce any agonist effects.
13 And it blocks the receptor for other drugs, like the
14 morphine equivalent from heroin or from methadone or
15 oxycodone or any of the other opioids. So while it
16 doesn't have subjective effects on its own, and if a
17 person isn't already on opiates they will get little
18 or no effect from an antagonist such as naltrexone,
19 but they'll be blocked.
20 Now, it's important to realize when
21 evaluating treatment results that naltrexone only
22 blocks the receptor; it doesn't keep people from doing

1 what they've always done, which is taking drugs. So
2 that a person on naltrexone may take heroin, they tend
3 to have less craving for heroin or other opiates, but
4 they won't get high from it. And so that's why it's
5 more than just looking at urines but it's also relapse
6 to opiate addiction.
7 Now, clinical trials were conducted that
8 were placebo-controlled in the 1970s and they were
9 pretty much a failure because of high dropout rate.
10 So finally in 1984, the FDA approved naltrexone for
11 its pharmacologic blockade. Now, those of us in the
12 field have been using it to treat opiate addiction
13 since the 1970s and we continue to use it in the oral
14 form. But it's difficult to use because patients, for
15 various reasons, stop taking it, mostly because the
16 drug is too good, too effective. Patients really
17 don't like the fact that if they inject heroin they
18 don't feel it.
19 In the 1980s, my group at the University of
20 Pennsylvania discovered that naltrexone also works for
21 a subcategory of alcoholics. And this was replicated
22 by other groups. And in 1994, alcoholism was added to

1 the indications for oral naltrexone. Now, in the
2 1970s, we all realized and NIDA formally called for a
3 depo preparation of naltrexone. And we actually had a
4 few kinds in clinical trials but they were very
5 unsatisfactory. They didn't work. However, during
6 the 1990s, Alkermes got a grant from NIDA and
7 developed the Medisorb with microsphere, combined with
8 naltrexone, developed this technique that gave a slow
9 release of naltrexone over 30 to 40 days. This
10 technique was first approved, as Dr. Winchell said,
11 for alcoholism in 2006.
12 So now we are in 2010. We have a medication
13 that was approved by the FDA in the context of opiate
14 addiction in 1984. It was a delivery system approved
15 in 2006 for alcoholism. And the issue now is whether
16 or not opiate addiction should be added to the
17 indications for the new delivery system of the same
18 medication that was already approved.
19 Now, you're about to hear the details of the
20 study that was done in Russia. And as someone who as
21 not connected with the study I would like to tell you
22 that I think it's a study that is highly relevant to

1 my practice in the United States. We have confidence
2 in this Russian group because we've been collaborating
3 with them for about 10 years. They actually have had
4 a supplement to our NIDA-sponsored center and we were
5 working with them on oral naltrexone and anti-
6 depressants. And we were very impressed with their
7 skill and reliability, so much so that last year Dr.
8 Krupitsky was given an adjunct professorship at the
9 University of Pennsylvania.
10 A question that is reasonable to ask is
11 whether or not the data obtained in Russia are
12 relevant to the United States. Everything that we
13 know about opiate receptors is that an agonist is an
14 agonist all over the world; an antagonist is an
15 antagonist. Now, there are genetic variations in the
16 receptors, especially the μ-receptor that we know
17 about, but these genetic variations do not change the
18 fundamental characteristics that I described earlier.
19 Also, the patients that were in that study
20 were very similar to the patients that we see. Of
21 course, few of them were taking oral opiates, but the
22 receptor and the antagonist doesn't care how the drug

1 got to the receptor. By mouth or by injection, it's
2 the same thing.
3 So, I believe that this work that you're
4 about to hear is highly relevant. I believe that this
5 is a question that has great public health importance
6 because we need all the options that we can get for
7 the treatment of opioid addiction. And there is a
8 subcategory of patients who will respond, who will
9 prefer this treatment, who will do better on this
10 treatment than other kinds of treatment that we have
11 available. So I think that this is an important
12 option and I'm now going to turn it over to Dr.
13 Ehrich, who is going to give you the details of the
14 Russian study. Thank you.
15 **Review of Efficacy**
16 DR. EHRICH: Thank you, Dr. O'Brien.
17 I'll now discuss the Vivitrol program and
18 efficacy results.
19 As you heard from Dr. O'Brien and Dr.
20 Winchell, the FDA approved oral naltrexone for the
21 blockade of exogenous opioids on the basis of its
22 pharmacologic activity. However, the clinical utility

1 of oral naltrexone in treating opioid-dependent
2 patients is limited by poor adherence. Naltrexone is
3 an antagonist, is non-reinforcing, it does not produce
4 drug reward. This is precisely why a long-acting,
5 injectable preparation has been sought for decades by
6 NIDA and the treatment community to reduce the
7 frequency of dosing, increase adherence, and enhance
8 clinical outcomes.
9 Delivering on the promise of long-acting
10 naltrexone was enabled by the development of Medisorb
11 microsphere technology. Medisorb is comprised of
12 polylactide-co-glycolide polymer. It is the same
13 polymer found in dissolvable sutures and the
14 technology is well known as it is the basis for the
15 antipsychotic Risperdal Consta. In the case of
16 Vivitrol, the microspheres are embedded with
17 naltrexone.
18 The photographs on this slide are electron
19 micrographs of the microspheres incubated ex-vivo.
20 They provide representation of what occurs following
21 an intramuscular injection of the microsphere
22 suspension. Following injection, the microspheres

1 absorb water and increase in size. They gradually
2 erode through spontaneous hydrolysis and the polymer
3 is ultimately metabolized to carbon dioxide and water.
4 During this process, which lasts several weeks,
5 naltrexone is released from the microspheres and into
6 the circulation. The resulting PK profile of Vivitrol
7 shows prompt release of naltrexone with extended
8 levels beyond 30 days post injection.
9 A pharmacodynamic study, the 004 study, was
10 performed to assess opiate blockade with a Vivitrol
11 formulation. The study was a collaboration between
12 Alkermes, George Bigelow at Johns Hopkins, and Dr.
13 Kenzie Preston from the intramural group at NIDA. In
14 this study, single doses of 75, 150, and 300
15 milligrams Of Vivitrol were evaluated in 27 opioid
16 experienced patients. During a two month, post dose
17 observation period, patients were challenged with
18 escalating doses of hydromorphone. The cumulative
19 hydromorphone challenge dose of 13.5 milligrams is
20 substantial, the equivalent to about 50 milligrams of
21 heroin or 100 milligrams of morphine.
22 Blockade was assessed by subjective and

1 physiologic measures. On day 28 we saw evidence of a
2 dose response. The greatest degree of blockade
3 occurred following 300 milligrams of Vivitrol. Dose
4 response would be expected given the underlying
5 mechanism, competitive antagonism.
6 Once monthly administration of Vivitrol was
7 first studied in the treatment of alcohol dependence.
8 Vivitrol demonstrated efficacy and safety, which
9 resulted in FDA approval for alcohol dependence in
10 2006. And over the past four years, approximately
11 45,000 patients have been treated with Vivitrol.
12 That's about 10,000 patients per year.
13 Following approval in alcohol dependence, we
14 turned our attention to opioid dependence. Our
15 efforts in opioid dependence gained a sense of urgency
16 as we became aware of the growing epidemicrophone. In
17 addition, it became clear that Vivitrol was being
18 prescribed for patients with opioid dependence and
19 prescribing was taking place without labeling to guide
20 its use.
21 An end of phase II meeting was held in 2007.
22 The Agency indicated that a single convincing study,

1 if sufficiently compelling, together with
2 pharmacodynamic data, could potentially suffice. One
3 pivotal study makes sense given the existing body of
4 evidence, particularly the pharmacologic evidence that
5 exists with oral naltrexone. The other 13 pivotal
6 efficacy study design was finalized following an end
7 of phase II meeting in 2007, and the statistical
8 analysis plan was agreed to and finalized in 2009
9 prior to unblinding.
10 In April of this year, we submitted a
11 supplemental new drug application, a sNDA for opioid
12 independence, and the submission was granted a
13 priority review by the FDA. Priority review was
14 granted on the basis that Vivitrol provides a
15 potential significant improvement over existing
16 therapy. There is a public health need for a product
17 which is not a controlled substance street opioid
18 dependence, a product that does not carry the risk of
19 respiratory or CNS depression, and a product that is
20 not subject to abuse or diversion.
21 The Vivitrol application was submitted under
22 the 505(b)2 statute. And 505(b)2 means that the

1 application references the existing FDA approval of
2 oral naltrexone. Also referenced is the published
3 literature, previously conducted Vivitrol clinical
4 pharmacology studies, as well as Vivitrol safety and
5 efficacy data in patients with alcohol dependence.
6 For the sNDA, we conducted four studies
7 specifically in patients with opioid dependence.
8 There is the 13 study, the pivotal efficacy study
9 conducted in Russia, which provides demonstration of
10 efficacy, as well as long-term safety experience. The
11 other three studies were all performed in the United
12 States. They include the 004 study, the opioid
13 challenge study, which we briefly reviewed a few
14 moments ago. The 006 extension, done as part of the
15 original alcohol submission, provided long-term, open
16 label exposure up to three years in opioid-dependent
17 patients. In the 021 Study, which is ongoing, which
18 is a long-term, open label study in health care
19 professionals with opioid dependence. The 004, 006,
20 and 021 studies provide bridging experience to the
21 U.S. opiate-dependent population as discussed in the
22 ICH guidance document.

1 From the perspective of efficacy, I'll focus
2 first on the 13 study and then discuss its
3 relationship to the 006 and 021 studies. 013 was a
4 multi-center, double-blind placebo-controlled study.
5 The study enrolled 250 adults with a current diagnosis
6 of opioid dependence based on DSM-IV criteria. All
7 patients had recently completed opioid detoxification.
8 The study was conducted at 13 sites in Russia.
9 Why did we conduct the study in Russia? We
10 considered conducting the study in the United States.
11 A defining feature of the American target population
12 is high motivation. As such, our target patients are
13 less motivated to participate in a placebo-controlled
14 clinical trial. We conducted the study in Russia for
15 two principal reasons -- treatment context and patient
16 population.
17 First, treatment context. We identified a
18 network of expert clinical investigators led by Dr.
19 Krupitsky. We were first introduced to Dr. Krupitsky
20 through his publications in the peer review clinical
21 literature, through his colleagues at Yale University
22 where he completed an addiction psychiatry fellowship,

1 and through his collaborators at University of
2 Pennsylvania, in particular Dr. George Woody.
3 Dr. Krupitsky and his colleagues comprise a
4 group of treatment centers that resemble Vivitrol
5 treatment settings in the U.S. These are centers with
6 expertise and experience in research and medically-
7 oriented treatment of addiction. Dr. Krupitsky
8 adapted individualized drug counseling, IDC, for use
9 in their clinical trials of opioid dependence. IDC is
10 a standardized psychosocial therapy that was developed
11 in the United States by George Woody and Delinda
12 Mercer under the egis of the NIDA Clinical Trials
13 Group. IDC, specified psychosocial counseling themes
14 commonly invoked in U.S. clinical practice.
15 These treatment centers had the personnel
16 and logistics to store, reconstitute, and properly
17 administer IM Vivitrol on a longitudinal basis. Taken
18 together these features of the study centers --
19 medical orientation, personnel, and logistics for IM
20 injection -- emulate the 400 or so treatment centers
21 that administer Vivitrol in the United States.
22 And second, the patient population. Now, it

1 wouldn't be credible for anyone to get up here and say
2 Russia is the same as the United States, and within
3 the opioid-dependent population at large there are
4 differences in racial makeup. There are differences
5 in the specific types of opioid used. But if you look
6 at the study patients, they have important
7 similarities with the American Vivitrol target
8 population. Similarities that make the study results
9 applicable to the use of Vivitrol here.
10 There is the motivation factor. The
11 motivation to undergo antagonist treatment, which is
12 non-reinforcing. There's also the motivation required
13 to undergo monthly IM gluteal injection. Both the
14 study patients and the Vivitrol target population in
15 the U.S. share this feature.
16 The study patients typically have strong
17 extrinsic support, such as an involved parent or
18 family member. And Dr. Krupitsky highlights this
19 characteristic in his recent article reviewing his
20 clinical trial experience. Extrinsic support is also
21 a theme in the American target population. Young
22 adults with an involved parent is a common scenario.

1 And finally, and perhaps most importantly,
2 antagonist therapy is not an option for the study
3 patients. Buprenorphine and methadone are not legally
4 available as substitution therapy in Russia. In
5 contrast, buprenorphine and methadone are available in
6 the U.S. However, for the American target Vivitrol
7 population, agonist therapy is often not a desired
8 option or not an option at all. Some patients are
9 philosophically opposed to substituting their
10 addiction with another addictive drug. For others,
11 agonist therapy is not an option due to professional
12 constraints, such as physicians, pilots, interstate
13 truck drivers, public safety officials, and military
14 personnel. In that regard, the study patients in the
15 American Vivitrol target population have important
16 similarity.
17 The study was designed in collaboration with
18 Dr. Krupitsky, as well as leading researchers in the
19 United States, including Dr. Ling, who is here with us
20 today. The protocol specify a two-part treatment
21 period -- Part A and Part B. During the first six
22 months, referred to as Part A, patients receive six

1 doses of either Vivitrol 380 milligrams or placebo in
2 a 1:1 ratio. And study medication was administered
3 every four weeks. Patients were seen once a week for
4 assessments and evaluations.
5 It is important to note that the efficacy of
6 Vivitrol was evaluated in the context of psychosocial
7 therapy. All patients, both Vivitrol and placebo-
8 treated patients received psychosocial therapy, IDC,
9 throughout the study. During Part B, which followed,
10 patients returned to the clinic once a month, received
11 counseling for 13 additional doses of open label
12 Vivitrol 380 milligrams.
13 Efficacy was evaluated using several outcome
14 measures. These include visit attendance, urine
15 opiate screen, and in the case where a urine screen
16 was positive, a naloxone challenge test was performed.
17 A positive naloxone challenge test indicates that
18 patient had relapsed to physical opioid dependence.
19 Patients completed an opioid craving score on a visual
20 analog scale and self-reported opioid use was
21 collected using the timeline fallback method. In
22 addition, investigators and patients completed quality

1 of life assessments and health surveys.
2 The study was conducted according to the
3 principles of good clinical practice and per ICH
4 guidelines. Importantly, the study was independently
5 audited and the FDA conducted a site inspection, which
6 was successful and will be presented later this
7 morning.
8 The study enrolled primarily males, which is
9 consistent with a higher incidence of opioid
10 dependence among men and had a mean age of 30 years.
11 Enrolled patients were predominantly white. Patients
12 had a significant duration of opioid dependence, on
13 average a 10-year history. And the majority of
14 patients had been using heroin on a near daily basis,
15 although some patients reported a dependence to
16 methadone and other oral opioids. There was a high
17 rate of HIV positivity, and nearly all patients had a
18 history of hepatitis C, consistent with intravenous
19 drug abuse.
20 Looking at study completion, there was a
21 notable difference between the active and placebo
22 groups. Completion rates were substantially higher in

1 the Vivitrol arm of the study -- 53 percent compared
2 to 38 percent on placebo. And discontinuation due to
3 lack of efficacy and positive naloxone challenge test,
4 which also reflects lack of efficacy, are the primary
5 reasons for the higher discontinuation rate with
6 placebo. Taken together there were 51 patients
7 discontinued due to insufficient efficacy with placebo
8 compared to 23 on Vivitrol. And this difference was
9 highly significant.
10 Both treatment retention and naloxone
11 challenge were prespecified secondary endpoints, and I
12 will discuss them in greater detail in a few moments.
13 Importantly, there were no discontinuations for
14 adverse events on Vivitrol, and Dr. Silverman will
15 address this in his presentation.
16 Analysis of the study yielded results that
17 consistently favored Vivitrol. The primary pre-
18 specified analysis of the primary endpoint, opioid-
19 free weeks, was positive and statistically
20 significant. The study showed significant treatment
21 effects with all pre-specified secondary endpoints --
22 retention in treatment, opioid craving score, positive

1 naloxone challenge test, and self-reported opioid use.
2 And I think we have some technical
3 difficulties but I'll continue on.
4 The consistency across the endpoints
5 underscores the robustness of the demonstration of
6 efficacy. We'll start by reviewing the primary
7 endpoint. The primary analysis of the primary
8 endpoint was based on opioid-free weeks during Part A
9 of the study. And I'll run through the definition of
10 opioid-free weeks.
11 Between weeks 5 and 24 of Part A, there were
12 20 weekly visits. So for every patient, each visit
13 was scored as either opioid free or non-opioid free.
14 And a rigorous definition of opioid free was used.
15 For a visit to be considered opioid free, the
16 following three criteria had to be met. One, the
17 patient had to attend the clinic visit. Patients who
18 missed a scheduled clinic visit or discontinued the
19 trial, did not provide a urine, were scored as non-
20 opiate free. Two, the urine opiate screen had to show
21 no detectable opioids. And finally, three --
22 DR. SCHULTZ: Excuse me.

1 DR. EHRICH: -- patients had to confirm no
2 opioid use by self-report.
3 DR. SCHULTZ: Excuse me. I'm so sorry. At
4 this time we need to stop for a five-minute break to
5 correct the --
6 DR. EHRICH: Sure.
7 DR. SCHULTZ: Sorry about that. But just
8 five minutes and we'll resume your presentation at the
9 point where the AV went down.
10 DR. EHRICH: Okay.
11 DR. SCHULTZ: Okay.
12 (Recess.)
13 DR. SCHULTZ: The correct place. Thank you.
14 DR. EHRICH: Resuming with the slides.
15 Completion rates were substantially higher
16 in the Vivitrol arm of the study -- 53 percent
17 compared to 38 percent in placebo. And
18 discontinuation due to lack of efficacy and positive
19 naloxone challenge test, which also reflects lack of
20 efficacy are the primary reasons for the higher
21 discontinuation rate with placebo. Taken together
22 there were 51 patients discontinued due to

1 insufficient efficacy with placebo compared with 23 on
2 Vivitrol. And the difference was highly significant.
3 Both treatment retention and naloxone
4 challenge were prespecified secondary endpoints and
5 I'll discuss them in greater detail in a few moments.
6 Importantly, there were no discontinuations for
7 adverse events on Vivitrol, and Dr. Silverman will
8 address this in his presentation.
9 Analysis of the study yielded results that
10 consistently favored Vivitrol. The primary
11 prespecified analysis of the primary endpoint, opiate-
12 free weeks, was positive and statistically
13 significant. The study showed significant treatment
14 effects with all pre-specified secondary endpoints --
15 retention to treatment, opioid craving score, positive
16 naloxone challenge, and self-reported opioid use.
17 This consistency across endpoints underscores the
18 robustness of the demonstration of efficacy.
19 Let's start by reviewing the primary
20 endpoint. The primary analysis was based on opioid-
21 free weeks during Part A of the study. Between weeks
22 5 and 24 of Part A there were 20 weekly visits, and

1 each visit was scored for each patient as either
2 opioid free or non-opioid free. And a rigorous
3 definition of opioid free was used. For a visit to be
4 considered opiate free, the following three criteria
5 had to be met. The patient had to attend the clinic
6 visit. Patients who missed a scheduled clinic visit
7 or who had discontinued the trial were scored as non-
8 opioid free. Two, a urine opiate screen had to show
9 no detectible opioids. And finally, three, patients
10 had to confirm no opioid use by self-report. In other
11 words, patients who reported opioid use on the
12 timeline fallback session were not considered to be
13 opioid free for the week, even if urine testing did
14 not detective the presence of opioids.
15 The endpoint was originally entitled as
16 opiate-free urine tests, however, as we realized that
17 the analysis encompasses the domains of treatment
18 retention and opiate self-report, we've used the title
19 opiate-free weeks as it is more accurate. These data
20 were used to calculate the primary analysis. For each
21 patient, the percentage of opiate-free weeks was
22 calculated. For example, a patient with 20 of 20

1 opiate-free weeks had an opiate-free percentage of 100
2 percent. A patient with 18 opiate-free weeks out of
3 20 weeks had a percentage of 90 percent, et cetera.
4 And the primary pre-specified analysis of the primary
5 endpoint was a response profile comprised of the
6 continuous cumulative distribution of the percentage
7 of opiate-free weeks. And the distributions were
8 plotted for each treatment group and compared.
9 On the graphic, the X-axis is the percentage
10 of occurrence of opiate-free weeks during the
11 assessment period, ranging from 0 percent opiate free
12 weeks and 10 percent on the left to 90 percent and 100
13 percent opioid-free weeks on the right. The y-axis
14 ranges from 0 percent of patients on the bottom all
15 the way up to 100 percent of patients on the top.
16 Starting on the right are patients with 100
17 percent opiate-free weeks during the assessment
18 period. Twenty-three percent of patients on placebo
19 and 36 percent of patients on Vivitrol had 100 percent
20 opiate-free weeks. The difference in the percentage
21 of patients who were completely abstinent during the
22 six-month assessment period was statistically

1 significant.

2 As you move to the left, there were 32

3 percent of patients on placebo and 52 percent of

4 patients on Vivitrol who had 90 percent or greater

5 opiate-free weeks. The separation between Vivitrol

6 and placebo was maintained across the response

7 profile. The difference between Vivitrol and placebo

8 was highly significant with a p-value of 0.0002. The

9 median rate of opiate-free weeks was 90 percent with

10 Vivitrol, compared to 35 percent for the placebo

11 group. And this is a substantial difference.

12 Analysis of the primary endpoint showed a consistency

13 of treatment effects across pre-specified subgroups,

14 including sex, age, duration of opioid dependence, and

15 duration of pre-study detoxification.

16 And to give further perspective on the

17 primary analysis, here is a graph depicting the result

18 of all urine testing performed in the study. Each

19 horizontal line represents a single patient. The

20 patients in each treatment group are stacked according

21 to the number of urine samples provided. Patients

22 with the most urine samples are on the bottom, moving

1 to patients with the fewest samples on the top. The
2 white dots are opiate-free samples. The orange dots
3 are non-opiate free samples. And where the dot is
4 absent that indicates that no sample was provided,
5 either due to discontinuation or missed study visit.
6 The most prominent difference between
7 Vivitrol and placebo comes from fewer urine samples
8 provided by placebo-treated patients. This is due to
9 their lower retention in treatment with placebo.
10 Indeed, there were 40 percent more opiate-free weeks
11 with Vivitrol versus placebo-treated patients.
12 Now, a positive urine opioid test is not the
13 same thing as having relapsed to opioid dependence.
14 In other words, a slip or sampling of opioids does not
15 necessarily mean a relapse to physical dependence.
16 When a positive urine test was observed, a naloxone
17 challenge test was performed. A naloxone challenge
18 test assesses for symptoms of withdrawal and
19 highlights the distinction between opioid use and
20 relapse. Positive naloxone challenges are indicated
21 by the enlarged orange dots. There was a
22 significantly higher incidence of relapse with placebo

1 and compared to Vivitrol. Seventeen positive tests
2 were observed with placebo-treated patients compared
3 to only one with Vivitrol.
4 The naloxone challenge results are a
5 fundamental finding in the study that underlies a key
6 therapeutic benefit of Vivitrol. Continuous opioid
7 blockade prevented patients from relapsing to physical
8 dependence. These patients are then able to stay in
9 treatment and move forward in the recovery process.
10 According to the Department of Health and
11 Human Services, retention in a treatment program may
12 be the single most important indicator of medication
13 assisted treatment outcomes. Why is retention so
14 important in the context of opioid dependence?
15 Retention is what enables recovery. The longer
16 patients remain in treatment, the greater the
17 opportunity exists for patients and health care
18 providers to work together to engage in counseling,
19 stabilize abstinence, organize chaotic lifestyles,
20 diagnose and treat comorbid illness, and approve
21 family, work, and social relationships. These factors
22 move patients forward on the path to recovery.

1 Retention and treatment was prespecified as
2 a secondary outcome. Retention in Part A was
3 significantly greater with Vivitrol as compared to
4 placebo. The median duration was greater than 168
5 days for Vivitrol compared to 96 days with placebo.
6 For an opioid treatment trial, or even a trial in, for
7 example, schizophrenia, this degree of retention would
8 be considered to be very good. The retention curves
9 provide a useful way to benchmark the results in the
10 13 study with the U.S. studies.
11 Now, the 006 Study enrolled 101 opioid-
12 dependent patients in multiple centers across the
13 United States. Compared to the 13 study there were
14 more minorities represented and more than 50 percent
15 of patients had been dependent on oral opioid pain
16 medications.
17 This slide shows an overlay of treatment
18 retention from Vivitrol-treated patients from the 13
19 study and the 006 study. So these are separate
20 studies so the comparison needs to be interpreted with
21 caution. Nevertheless, there is a striking
22 correspondence. The retention rates are almost

1 identical, suggesting that the 13 results are
2 applicable to a U.S. population.
3 Another study that we can reference to
4 compare the retention rates is the 021 Health Care
5 Professional Study, which is underway in the United
6 States. Emerging results demonstrate high retention
7 as well; actually, greater than 50 percent retention
8 at six months. So as with the 006 study, the 021
9 Study provides additional bridging data to support the
10 use of Vivitrol in the treatment of opioid dependence
11 in the U.S.
12 Craving was a key secondary endpoint in the
13 13 study and results provide additional perspective
14 for the efficacy observed with the primary analysis.
15 Vivitrol yields a 50 percent reduction in opioid
16 craving scores compared to placebo where no reduction
17 was observed at all. And this difference was highly
18 significant and persisted throughout the treatment
19 period. We reviewed our results with experts in the
20 field. Many consider this finding to be both
21 fascinating from a mechanistic perspective and highly
22 relevant from the perspective of clinical utility.

1 We also explored several functional and
2 quality of life endpoints which served to support the
3 primary and secondary analyses. We saw significant
4 treatment effects with Vivitrol where one might expect
5 to see findings in the context of a six-month clinical
6 trial. A good example of a functional outcome are the
7 SF-36 results seen in the 13 study. At baseline,
8 patients recorded subnormal mental health-related
9 quality of life scores. With treatment, the mental
10 health component summary increased in both treatment
11 groups with Vivitrol and placebo, but the improvements
12 in Vivitrol-treated patients were significantly higher
13 than the placebo group.
14 On the other hand, baseline physical
15 component scores were normal. These patients were not
16 physically impaired. Following treatment, the
17 physical component scores remained normal. Overall,
18 the exploratory endpoints tell a coherent story that
19 further strengthens the efficacy observed and provide
20 evidence of the broader meaningfulness of the results.
21 In summary, the efficacy results show that
22 Vivitrol, in combination with counseling, was highly

1 effective in increasing opiate-free weeks, retaining
2 patients in treatment, reducing opioid craving, and
3 preventing relapse to physical opioid dependence. The
4 exploratory endpoints show evidence of a broader
5 health impact, particularly in mental health-related
6 quality of life, and results from U.S. studies, 004,
7 006 and 021, are consistent with the 013 study
8 findings and further indicate that Vivitrol is
9 applicable to the U.S. target population.
10 Now Dr. Silverman will review safety. Dr.
11 Silverman.
12 **Review of Safety**
13 DR. SILVERMAN: Good morning. I'm Bernie
14 Silverman, vice president of Clinical Science at
15 Alkermes.
16 I've been at Alkermes for nine years and
17 have been working on Vivitrol that whole time. My
18 medical training is in endocrinology and I've
19 participated in the care of thousands of people with
20 diabetes. I've been struck by the parallels between
21 Type 2 diabetes and addiction in terms of etiology,
22 yet marked differences in terms of public perception.

1 Both diseases represent a complex interplay between
2 genetics and behavior, yet diabetes is almost
3 universally viewed as a medical condition, whereas
4 addiction is often viewed as a failure of willpower.
5 One of the things I find most rewarding about working
6 at Alkermes is the opportunity to help change this
7 perception.
8 I will now continue with our safety data.
9 On the top portion of this slice is
10 displayed clinical trial exposure based on type of
11 dependence -- alcohol and opioid. The original NDA
12 for alcohol dependence included some patients with
13 opioid dependence. There is only one formulation of
14 Vivitrol. The currently marketed formulation is the
15 same one used in our alcohol and opioid clinical
16 trials.
17 In this presentation, data will be broken
18 out for the opioid patients from the original NDA for
19 purposes of comparison with the data from the pivotal
20 efficacy Study 013. The maximal exposures in clinical
21 trials are about four and a half years for alcohol
22 dependence and three years for opioid dependence.

1 This represents a total exposure of approximately 750
2 patient years. In addition, we have post-marketing
3 experience in a total of about 45,000 people over the
4 four years since approval.
5 The studies contributing the bulk of our
6 clinical trial safety experience in opioid dependence
7 are Study 006 and its extension study. Patients with
8 alcohol and/or opioid dependence were treated with
9 Vivitrol or oral naltrexone for 12 months, followed by
10 Vivitrol only treatment with a maximum exposure of
11 about three years. As presented earlier, Study 013
12 included patients with opioid dependence only and was
13 placebo-controlled through the initial six months,
14 followed by an open label extension which will yield a
15 maximum exposure of 18 months.
16 As this is a supplemental NDA, we've chosen
17 to highlight information relative to data obtained in
18 opioid-dependent patients. For analysis for adverse
19 events, Study 013 provides placebo-controlled data in
20 opioid-dependent patients from Study 006 reviews our
21 previous findings in opioid dependent patients from an
22 open label study conducted in the United States. For

1 analysis of issues specific to Vivitrol, we've pulled
2 from all opioid-dependent patients and all post-
3 marketing data to provide the most complete picture.
4 This slide highlights some of the
5 characteristics of the study population in Study 013
6 that have relevance for the interpretation of safety
7 data. Mean age was 30 years. Eighty-eight percent of
8 the patients were male. Forty-one percent were HIV
9 positive. However, patients with AIDS indicator
10 diseases, such as Kaposi's sarcoma were excluded from
11 participation. Eighty-nine percent of the patients
12 reported a history of hepatitis C. People with
13 greater than three-fold elevation and ALT and AST at
14 baseline or at screening were excluded from
15 participation.
16 Dr. Ehrich presented the longer attention of
17 treatment for Vivitrol patients. This results in a
18 differential time on study with placebo patients
19 contributing 34 patient years and Vivitrol patients
20 about 44 patient years. Thus, patients on Vivitrol
21 had a greater time period in which they could have
22 experienced adverse events.

1 There were no deaths in Study 013. There
2 were only a few serious adverse events, none of which
3 were deemed related to study drug and these will be
4 detailed on the next slide. The only patients who
5 discontinued due to serious adverse events were in the
6 placebo group. There were more adverse events and
7 more studies related adverse events with Vivitrol than
8 with placebo. No one discontinued due to a non-
9 serious adverse event. The seven patients with
10 serious adverse events had a total of nine events. No
11 events occurred in more than one patient and none of
12 these events were deemed related to study drug.
13 The three most common adverse events amongst
14 patients in the Vivitrol treatment group were nasal
15 pharyngitis, insomnia, and hypertension. The data
16 suggests the nasal pharyngitis, insomnia, and
17 injection site pain occurred more commonly with
18 Vivitrol.
19 Before discussing the laboratory findings
20 from Study 013, I'd like to show the adverse event
21 data from Study 006 to provide perspective from a
22 study done on a U.S. population.

1 Study 006 was a one-year, open label trial.
2 Phase 3 conducted in the U.S. There were 121 patients
3 with opioid or mixed opioid-alcohol dependence of whom
4 101 received Vivitrol. Key characteristics of this
5 opioid-dependent population were a mean age of 34
6 years, 66 percent were male, 84 percent white, 8
7 percent black. There were no HIV-positive subjects
8 and 8 percent had a history of hepatitis C. Data from
9 this study was submitted in the original NDA for the
10 alcohol dependence indication.
11 There were no deaths amongst the opioid-
12 dependent patients in Study 006. The only serious
13 adverse events reported by more than one patient were
14 drug dependence and overdose. A serious adverse event
15 of drug dependence represents someone hospitalized for
16 drug use. The overdose cases will be detailed later
17 in this presentation.
18 Here we see the most common adverse events
19 from the 006 open label U.S. study. Data from
20 patients who received oral naltrexone are also
21 included. Events are ordered by frequency of
22 occurrence in the Vivitrol column. The three most

1 common events seen in this population -- nasal
2 pharyngitis, insomnia, and headache -- were also among
3 the most common events in the 013 study. Overall,
4 there is a higher rate of adverse event reporting in
5 the 006 study relative to 013. This may relate to
6 cultural differences in patients' thresholds for
7 reporting subjective complaints.
8 We identified key safety topics potentially
9 related to Vivitrol use based on their inclusion in
10 the alcohol dependence package insert. The last two,
11 injection site reactions and liver safety I'll save
12 till the end so we can go into some detail. I'll also
13 explain key differences in the 006 and 013 populations
14 regarding these two topics. There are no new areas of
15 concern based on our opioid development program and
16 the four years of post-marketing surveillance.
17 This slide shows a number of events by
18 category from opioid clinical trials and from post-
19 marketing surveillance. Suicidality includes suicide
20 ideation, suicide attempt, and completed suicide.
21 This is a high risk population. It is estimated that
22 between 8 and 25 percent of people with alcohol or

1 opiate dependence die by suicide. Eosinophilic
2 pneumonia, though rare, is important as it would
3 rarely occur in the absence of drug exposure. As
4 expected, all patients recovered with corticosteroid
5 treatment.
6 A concern about giving opioid antagonists is
7 the ability to manage unexpected severe pain.
8 Surprisingly, no reported difficulties with pain
9 management were observed in clinical trials, despite
10 patients having injuries and occasional surgical
11 interventions. Guidance for pain management is
12 detailed in the current Vivitrol package insert. The
13 label includes guidelines for the override of blockade
14 on an inpatient basis. However, amongst the 11
15 reports related to pain management and the post-
16 marketing surveillance, there have been no reports
17 where inpatient admission was required.
18 Of the three cases of opioid overdose in
19 clinical trials, two occurred more than six weeks
20 after the most recent dose of Vivitrol. We have
21 received five post-marketing reports of opioid
22 overdose. Opioid overdose is an inherent risk in the

1 opioid-dependent population. Most of the reports of
2 withdrawal occurred at treatment initiation in
3 patients treated for alcohol dependence where the
4 physician was unaware of the patient's concomitant
5 opioid dependence. All of these risks can be
6 mitigated by physician and patient education.
7 Now I will talk about injection site
8 reactions.
9 Based on signals observed and post-marketing
10 surveillance, proposed label changes regarding
11 injection site reactions were submitted to the FDA.
12 This topic was the subject of an FDA alert in August
13 of 2008. Vivitrol injections may be followed by pain,
14 tenderness, induration, swelling, erythema, bruising,
15 or pruritis. Some cases required surgical
16 intervention. Most cases that underwent surgery began
17 as induration. Induration, a firmness involving skin
18 and subcutaneous tissue, usually spontaneously
19 resolves but can enlarge. We have gained an
20 understanding of risk factors related to injection
21 site reactions in general and induration in
22 particular. Inadvertent subcutaneous injection of

1 Vivitrol may increase the likelihood of severe
2 injection site reactions. Reported cases occurred
3 primarily in female patients with greater gluteal
4 subcutaneous fat occurs relative to men.
5 If injection site reactions are going to
6 occur, they tend to occur early in therapy. Focusing
7 on the most significant injection site reaction
8 induration during the initial six months of treatment
9 we saw a lower rate of injection site induration in
10 Study 013 compared to Study 006. However, in oral
11 instances, induration involves spontaneous -- resolves
12 spontaneously without surgery.
13 Several factors may contribute to this.
14 Patients in the 013 study have lower body mass indices
15 and were more often male. In addition, investigators
16 were well trained in injection technique. To allow
17 for successful intramuscular injection in patients
18 with a greater degree of subcutaneous fact, a two-inch
19 needle is provided in addition to the standard one and
20 a half-inch needle. In both the alcohol and opioid-
21 dependent patients, issues involving liver safety --
22 issues involving underlying liver disease warrant

1 careful attention to liver safety.
2 There is a box warning regarding
3 hepatotoxicity for oral naltrexone. The FDA asked us
4 to include a box warning in the package insert for
5 Vivitrol for alcohol dependence based on this
6 precedent. I've excerpted some key sections from the
7 Vivitrol box warning. Naltrexone has the capacity to
8 cause hepatocellular injury when given in excessive
9 doses. The margin of separation between the
10 apparently safe dose of naltrexone and a dose causing
11 hepatic injury appears to be only five-fold or less.
12 Vivitrol does not appear to be a hepatotoxin at the
13 recommended doses.
14 This concern regarding hepatotoxicity comes
15 primarily from studies using oral naltrexone for a
16 variety of indications, generally in doses greater
17 than 300 milligrams per day where a recommended dose
18 for alcohol dependence is 50 milligrams per day which
19 would give a total of 1400 milligrams over a four week
20 period of time.
21 Next we'll see the enzyme data from Study
22 013. This is a display of mean ALT, AST, and GGT

1 values at baseline and week 24. As can be seen, at
2 baseline, mean ALT values for placebo and Vivitrol are
3 similar but both are close to the upper limit of
4 normal. At week 24, the end of the double-blind
5 period, we again see little difference between
6 Vivitrol and placebo. For both groups there has been
7 minimal change from baseline. Similar findings are
8 seen with AST with no differences between treatment
9 groups. GGT is more variable with higher baseline
10 values in the placebo group, but both groups show a
11 decline over the 24-week treatment period.
12 Now I'll present our adverse event reporting
13 relative to liver enzymes from the 013 clinical trial.
14 Despite the similarity of mean laboratory values,
15 abnormal values were more frequently classified as
16 adverse events in the Vivitrol group relative to the
17 placebo group. However, only a minority of abnormal
18 lab tests were classified as AEs, and people on
19 Vivitrol did tend to stay in the study longer than
20 patients on Vivitrol. All patients with the above AEs
21 had a history of hepatitis C.
22 Next, let's look at an outlier analysis.

1 The ALT data from Study 013 are displayed here on a
2 shift table comparing placebo and Vivitrol-treated
3 patients at baseline and last reported value during
4 the 24-week double-blind period. Focusing on ALT, we
5 see similar numbers of patients entered with high
6 values -- 42 and 38 percent. Additionally, 38 percent
7 of placebo and 37 percent of Vivitrol-treated patients
8 had high values at last observation. And 5 percent of
9 placebo and 6 percent of Vivitrol-treated patients had
10 values greater than three times the upper limit of
11 normal.
12 On the next slide we'll see peak post-
13 baseline ALT versus peak post-baseline bilirubin
14 plotted for each patient. To the right of the
15 vertical line are patients with peak ALT more than
16 three times the upper limit of normal. Above the
17 horizontal line would be values of bilirubin greater
18 than two times the upper limit of normal. Some
19 patients never returned after the baseline assessments
20 and therefore cannot be plotted on this graph. So
21 what you see are data from the 107 Vivitrol patients
22 and 85 placebo patients. Most of the points are

1 clustered in the lower left-hand quadrant. Recall
2 that 89 percent of patients in this trial had a
3 history of hepatitis C. In more than 50 percent of
4 patients with hepatitis C, there can be fluctuations
5 in elevations of ALT. In patients with hepatitis C
6 and fluctuating ALT values, a longer observation
7 period will yield more opportunities for higher peak
8 values to be observed. Points in the upper right hand
9 quadrant would be indicative of drug-induced liver
10 injury. These have not been observed in this study.
11 So how has Alkermes managed risk and what do
12 we have planned for the future? In March of 2010, the
13 FDA approved a risk evaluation and mitigation
14 strategy, a REMS, for Vivitrol. As part of the REMS,
15 a medication guide is distributed to patients with
16 each dose of Vivitrol. The medication guide addresses
17 injection site reactions, overdose, withdrawal, and
18 pain management. Alkermes also makes available to
19 providers additional patient education materials for
20 distribution. A wild card is included, designed to
21 inform medical personnel that persons taking an opioid
22 antagonist with information about pain management.

1 To supplement the package insert, the field
2 sales force provides education regarding potential
3 risks. Education regarding injection technique is
4 emphasized and a DVD is in development to assist with
5 educational efforts. Educational material regarding
6 how to conduct an naloxone challenge is provided.
7 Recently approved by the FDA, the inclusion of a two-
8 inch needle in addition to the current one and a half-
9 inch needle will be available for intramuscular
10 injection, which providers may wish to use in patients
11 with greater subcutaneous gluteal fat. All of these
12 activities would continue with an opioid-dependence
13 indication.
14 In summary, there an established overall
15 safety profile of Vivitrol in patients with alcohol
16 dependence. Post-marketing data support this
17 understanding. No new safety signals have emerged
18 from clinical trials. No new risks have been
19 identified. The safety data we've collected in our
20 opioid development program are entirely consistent
21 with the current Vivitrol package insert. This data
22 will serve to effectively inform physicians on the

1 safe use of Vivitrol in this population.

2 Opioid dependence is a deadly disease --

3 devastating to patients, their families, and society

4 at large. Vivitrol will provide patients with opioid

5 dependence a new treatment modality with a well

6 understood safety profile.

7 I will now turn the podium over to Dr. Paul

8 Earley, who will describe his experience in treating

9 opioid dependence with Vivitrol.

10 **We Need Treatment Options**

11 DR. EARLEY: Good morning. I'm Dr. Paul

12 Earley. I'm the medical director of the Talbott

13 Recovery Campus in Atlanta, Georgia. We're the

14 largest and oldest program for treating addicted

15 health care professionals in the world. I've been

16 treating patients suffering from the disease of

17 addiction for 25 years and have been prescribing

18 Vivitrol for the past two and a half years.

19 I am here today because I feel strongly that

20 new therapeutic options are needed in the field of

21 addiction treatment. Addiction physicians have very

22 few effective tools and proven tools to treat the

1 tragic consequences of addiction on our loved ones and
2 society. My clinical experience is that Vivitrol is a
3 powerful and significant new tool in the nearly empty
4 toolbox of medications that have proven efficacy in
5 the treatment of addiction. Based on my clinical
6 experience I would like to share with you four key
7 areas that validate why Vivitrol is needed for the
8 treatment of opioid dependence.
9 The four areas are proven effectiveness;
10 this product is unique and it's fit for certain
11 patients; the benefits of once a month dosing; and why
12 labeling is important.
13 First, let me talk about the data presented
14 today and how it correlates with my own real world
15 experience. The data presented today shows a dramatic
16 reduction in opioid use when Vivitrol is used and is
17 entirely consistent with what I see in my practice
18 every day. Addiction is a brain disease with cultural
19 context. Despite these cultural differences, the
20 types of patients we see in the U.S. are similar to
21 those in Russia with our Russian colleagues, and this
22 is partially due to the fact that the intensity of

1 addiction swamps out more subtle cultural issues.
2 Despite this, the patient characteristics of those
3 enrolled in the 013 study are similar to the patients
4 I see in my practice. Both groups of patients are
5 motivated to treat their disease with an antagonist
6 medication.
7 Secondly, there are certain patients for
8 which long-acting antagonist stands out as uniquely
9 beneficial. Let me tell you about two types of
10 patients in my practice who fall into this category.
11 The first group is young adults between the ages of 18
12 and 28 who complete detoxification with us and are
13 subsequently started in Vivitrol. Young adults are
14 motivated to get better primarily because of family
15 support and a relatively short history of abuse. This
16 group reports a dramatic decrease in craving in our
17 experience. The mechanism of this is unknown but is
18 at least partially due to the drop in perceived drug
19 availability. Vivitrol blocks people from having a
20 perceived efficacy or effect from the drug and
21 therefore craving decreases.
22 Opioid-dependent young adults are excellent

1 candidates for Vivitrol to provide them with a choice
2 of abstinence rather than spending years or even a
3 lifetime on maintenance medication such as methadone
4 or buprenorphine. Vivitrol allows us to maintain a
5 non-using population of impulsive oxycodone in heroin-
6 dependent young adults in a sustained abstinent state.
7 This opens the door for addiction therapy to work. We
8 can maintain this cohort in long-term and less
9 expensive treatment due to this medication. Physical,
10 behavioral, and emotional treatment, including
11 learning new recovery skills, can only occur when
12 patients are in this abstinent state.
13 The second group in which I use Vivitrol is
14 in addicted professionals, such as doctors, lawyers,
15 pharmacists, and nurses. This group is best treated
16 without using agonist therapy. We've seen excellent
17 results in these groups using Vivitrol. For example,
18 in several state physician health programs located
19 across the United States, we've tracked scores of
20 physicians on Vivitrol. Provisional data from these
21 programs indicates zero opioid relapses in the
22 physicians who have remained on Vivitrol. It is our

1 belief that Vivitrol is now the standard of care for
2 opioid-dependent physicians who are in the earliest
3 phases of recovery.
4 Thirdly, a long-acting formulating offers a
5 new way to treat patients who struggle with their
6 addiction and are often unable to consistently adhere
7 to daily medication. For my patients, having the
8 injectable medication onboard for a full month offers
9 several benefits, the most important of these is only
10 needing to make a decision to commit to abstinence and
11 recovery once a month. This allows the patient time
12 to rebuild coping skills and new procedural memory is
13 required to maintain the recovery state.
14 Vivitrol ensures that the rewarding effects
15 of opioids are blocked for the entire month so if they
16 do try to go back and use the drugs they don't get
17 high. Participants can start to develop new memories
18 and experiences while remaining opioid free.
19 Having naltrexone onboard dramatically
20 reduces the likelihood that patients will abuse
21 opioids. Vivitrol as a once-a-month injection ensures
22 that patients are adherent for the full month. For

1 example, in the 013 study, a patient who slipped while
2 on Vivitrol was not likely to relapse back into opioid
3 dependence as compared to patients on placebo.
4 Patients who attempt to use narcotics while on
5 Vivitrol do not experience the powerful euphoria and
6 subsequent cascade into relapse. In this manner, we
7 have a safety net in place that prevents the
8 reestablishment of the physical dependence and
9 powerful addiction memories.
10 Additionally, others in the support systems,
11 whether they are the parent or even a physician health
12 monitor for an impaired or addicted professional can
13 be assured that the patient on Vivitrol is under
14 blockade. They don't have to worry about whether the
15 patient is using the drugs or not. Trust can be
16 rebuilt; families and lives repaired.
17 Despite the benefits that Vivitrol may
18 offer, right now it's difficult for addiction
19 physicians to use it for opioid dependence. Approving
20 this product is essential. Labeling will help inform
21 doctors on how to prescribe and monitor their
22 patients. New therapeutic options will benefit

1 physicians and their patients struggling with this
2 chronic life-threatening disease.
3 In summary, as a practicing physician who
4 treats patients with addiction every day, I can tell
5 you that Vivitrol works in this patient population.
6 Vivitrol is an important new tool for the treatment of
7 opioid dependence to help fight this growing brain
8 disease. Thank you.
9 **Closing Remarks**
10 DR. EHRICH: Thank you, Dr. Earley.
11 In closing, I'd like to review our
12 perspective on the questions that the FDA has brought
13 forward today. One relates to safety. Our safety
14 experience builds from oral naltrexone, Vivitrol
15 studies in opioid dependence, and four years of post-
16 market surveillance. In the trials of opioid
17 dependence, we did not have safety findings that have
18 not been previously observed. Now, we don't have
19 efficacy labeling for opioid dependence but safety
20 findings, such as overriding the blockade and loss of
21 opioid tolerance are well understood and very
22 explicitly described in the current labeling.

1 Another is our single pivotal study. It is
2 multi-center and the results are, as the guidance
3 states, statistically persuasive. The p-value is much
4 lower than p=0.01. The efficacy is consistent across
5 endpoints and subgroups. Importantly, the pivotal
6 study does not stand alone. It is supported by
7 pharmacodynamic studies and open label studies.
8 The third relates to the location of the 13
9 study. The study was conducted in Russia, yet the
10 context of the medical care provided by the study
11 centers resembles Vivitrol treatment setting in the
12 U.S. Patients enrolled in the study have motivation
13 and extrinsic support that parallels the target U.S.
14 population. Vivitrol is no stranger in the U.S. It
15 is approved, marketed, and used clinically here.
16 Studies in opioid dependence performed in the U.S.
17 provide pharmacodynamic, treatment retention, and
18 safety experience. The U.S. data serves as a bridge
19 to the pivotal efficacy study.
20 At the very core is the underlying disease
21 and associated pharmacology. As articulated by Dr.
22 Earley, opioid dependence is a severe brain disease

1 that transcends cultural factors. Opioid dependence
2 is endemic on all continents worldwide. The
3 fundamental, potent pharmacology of new opioid
4 antagonism that was tested in the 13 study is
5 operative, irrespective of country, culture, race,
6 ethnicity, or socioeconomic status. With Vivitrol we
7 have the opportunity to make a difference in the
8 treatment of opioid dependence in this country.
9 Thank you.
10 DR. SCHULTZ: Thank you. At this time we'll
11 move to clarifying questions. First, I'd like to
12 recognize Dr. Denisco is participating this morning
13 and give him an opportunity to introduce himself, if
14 you would.
15 DR. DENISCO: Good morning. I'm Richard
16 Denisco. I'm the medical officer at the National
17 Institute of Health. I apologize for being tardy.
18 **Clarifying Questions**
19 DR. SCHULTZ: Thank you. And we'll move to
20 clarifying questions. We'll keep a list. Yvette will
21 keep a list and give an opportunity to ask questions
22 in order. So if you'll identify yourselves we'll

1 move. Dr. Tai has a question. Dr. Michna has a
2 question. Dr. Walsh has a question. Dr. Denisco.
3 All right. We'll proceed. Oh, I'm sorry. Dr. --
4 DR. MICHNA: Yes. This question is for Dr.
5 Silverman in terms of some of the safety data. Do you
6 have any statistics on how many of these exposures
7 involve patients with chronic pain prior to their
8 addiction? And any data on pain levels post-exposure?
9 And if any kind of testing was done in terms of
10 increasing hyperalgesia, hypesthesia, or any
11 quantitative sensory testing done in these patients?
12 DR. EHRICH: Dr. Silverman?
13 DR. SILVERMAN: In the design of our
14 clinical trials and also our expectation for clinical
15 use, people with chronic pain to a degree that it
16 would likely require opiate use are not good
17 candidates for this therapy and ought to be managed by
18 another means. So that was an exclusion criteria
19 expectation for need of opiates.
20 We did not specifically measure pain levels
21 or look for hyperalgesia, but what's interesting is in
22 the current label are instructions for how to manage

1 pain detailing use of non-opiate analgesics and
2 progressing, if needed, to overriding the blockade on
3 inpatient basis for some with severe pain. And we've
4 used this in our clinical trials and it's in the
5 current label. And what's remarkable is that it's
6 worked quite well but that we've never -- we have no
7 reports from our clinical trials or post-marketing of
8 someone needing to override the blockade on an
9 inpatient basis with large doses of opioids.
10 DR. MICHNA: I mean, there's been a lot of
11 patient exposure. It's hard to believe that no more
12 than 11 people have had an issue with pain management.
13 I mean, statistically I think that's very unusual
14 given the population and the incidence of trauma,
15 fights. It's certainly not what I see.
16 DR. SILVERMAN: No. People do have their
17 pain managed. It's been effectively managed through a
18 combination of non-opioid analgesics. Some people
19 have taken opioid analgesics. The 11 post-marketing
20 reports that we have are -- 10 of them are from
21 consumers and they tend to follow a common thread,
22 which was, to quote from one, "Vicodin didn't work as

1 well as it usually does." And that's what we're
2 seeing. We have had patients in our alcohol trials
3 that went to surgery. Your point is well taken but
4 it's -- the results were surprising to me coming in
5 this field from the outside, is it's not been a
6 clinical problem either in the trials that we've
7 observed or in post-marketing surveillance.
8 DR. MICHNA: Yeah. It's hard to believe
9 that there weren't major surgery in any of these
10 patients and, you know, it's hard to believe as an
11 anesthesiologist that that would not be a rocky,
12 difficult, you know, therapeutic process, particularly
13 not so much inter-op but the immediate post-op,
14 certainly.
15 DR. SILVERMAN: Well, it can be managed
16 through, again, other means.
17 DR. MICHNA: Or morphine, but I doubt --
18 DR. SILVERMAN: Or by giving more Fentanyl.
19 You can override -- you always have the option to
20 override the blockade in a very carefully monitored
21 setting and, you know, a post-op unit would be a good
22 place where one would do that if need be.

1 DR. EHRICH: Thank you. One of the other
2 things that we do as part of our additional -- there's
3 a 24-hour pharmacist that is on-call in the context of
4 -- that can be contacted if additional information is
5 needed for pain treatment.
6 DR. SCHULTZ: I'd like to recognize Dr. Tai.
7 DR. TAI: Thank you. I have a couple points
8 begging for your clarification.
9 The first one is about the -- you did --
10 maybe I missed it but you did present the data
11 comparing the patient between the U.S. patient and
12 also the Russian patient. Do you have any data or
13 observation comparing the providers or the one who
14 treated patients in the U.S. versus the ones in
15 Russia?
16 That's the number one point. Do you want me
17 to get one each time or the other point? Okay. All
18 together. Okay.
19 The other two clarifications I'd like to
20 find out is from Dr. Earley, the real world
21 experience. Number one is that I think in the study -
22 - in the Russian study, the behavior intervention,

1 psychosocial support is provided for the trial. Do
2 you see that's necessary in the real world practice?
3 That's number one.
4 Number two is that where would you recommend
5 the medication being used? In what kind of medical
6 settings? That was my primary question. Thank you.
7 DR. SILVERMAN: I'll begin. Vivitrol is
8 used by -- is administered in about 400 treatment
9 settings or treatment centers in the U.S., and there
10 are about 130 physicians in the U.S. that prescribe
11 about 50 percent of Vivitrol prescriptions. These are
12 generally physicians who have experience and expertise
13 in the treatment of the medically-oriented treatment
14 of addiction. They have to have access or be able to
15 provide directly psychosocial therapy and they have to
16 have -- Vivitrol is a specialty injectable so there
17 are -- there's issues with, you know, acquiring it,
18 you've got to store it, administer it, all the
19 logistics involved. So that comprises -- that's sort
20 of a description that we have for our U.S. treatment
21 settings and physicians.
22 We've not done a formal analysis comparing

1 these treatment settings in the study centers, but I
2 think those key features are similar between the two.
3 The study centers in the network in Russia, these are
4 centers that they treat addiction from a medical
5 perspective. They're able to provide psychosocial
6 therapy. In this case it was with a standardized IDC.
7 And they do have the personnel and logistics to
8 reconstitute, to administer the IM gluteal injections.
9 From that perspective there's great similarity.
10 Dr. Earley, would you address some of your
11 perspectives on the psychosocial therapy?
12 DR. EARLEY: Paul Earley from Atlanta,
13 again. Thank you, Dr. Tai, for that question.
14 Our sense is, I mean, you know more about
15 this than probably I do sometimes in terms of your
16 research, but I can certainly say from a clinical
17 point of view that the retraining of goal directed
18 behavior of new memory circuits creating life skills
19 that are not drug centered, is the retraining of the
20 brain which is necessary for sustained recovery. I
21 see the use of Vivitrol as being a holding tank so
22 that that -- so that those methodologies will work.

1 And if an individual is consistently using narcotics,
2 any types of psychosocial therapies are weak to non-
3 effective because the effect of the drug on the brain
4 is so much more potent than my measly
5 psychotherapeutic interventions. However, if you have
6 the patient held in a recovery state, a lot of what we
7 do is retraining people to have normal lives, to seek
8 normal pleasure responses, to figure out how to rebond
9 with people and develop the kinds of skills that each
10 one of us use to cope with every day that drug addicts
11 have been totally circuited by the consistent drug use
12 over the years.
13 So how you do that is the $64,000 question
14 which again you know more about than I do, certainly
15 from a research perspective. But from the clinical
16 end, it requires being -- it requires being with one's
17 peers. It requires learning how to handle difficult
18 emotional states, learning how to deal with distressed
19 tolerance, learning how to not seek pleasure directly
20 but rather as a byproduct of living a well balanced
21 life -- the kinds of things that all of us learned as
22 adolescents that you almost have to retrain, whether

1 you're age 20 or age 65, if you are opioid dependent.
2 So that's been our experience. And we think
3 Vivitrol is a great drug to be used in combination
4 with the retraining process of long-term recovery,
5 intensive at first. Addiction is a chronic, life-long
6 disease that requires consistent attention over the
7 years. Because as I like to say, the illness kind of
8 will talk to you on your shoulder over time and 10, 15
9 years later will start whispering in your ear. And
10 unless you have some type of ability to -- skills to
11 overcome that you will relapse. So Vivitrol is a
12 great drug for holding -- it's a holding tank so that
13 the therapy works. And that's kind of how we view it.
14 Thank you.
15 DR. EHRICH: Thank you, Dr. Earley.
16 DR. SCHULTZ: Dr. Walsh.
17 DR. WALSH: My question is for Dr. Ehrich. I
18 actually just have some clarification -- I'm asking
19 for clarification about some of the study design
20 issues, and specifically in the 013 study.
21 Where patients were -- tested positive after
22 naloxone challenge, when you showed the stacked slide

1 later, no one ever reported back after that positive
2 challenge. I'm wondering whether or not a positive
3 challenge was the point at which the investigators
4 made the decision that someone would be excluded or
5 whether or not the patients truly dropped out because
6 it was their choice.
7 DR. EHRICH: A positive naloxone challenge,
8 as you say, means the patient had relapsed to physical
9 opioid dependence. And from the context of the trial,
10 from the context of receiving yet another dose of what
11 could have been an opiate antagonist, that patient
12 couldn't be treated because that next dose of
13 medication had the potential then to put the patient
14 into withdrawal. It doesn't mean that treatment is
15 over for that patient, and a number of these patients
16 did go on to have a further detoxicification, although
17 others were lost to follow up at that point.
18 DR. WALSH: But out of the context of the
19 trial.
20 DR. EHRICH: In the context -- in the
21 context of the trial that was a stopping out.
22 DR. WALSH: It was a stopping point. Okay.

1 I mean, because that difference accounts for the
2 difference in retention between the two groups. The
3 number of patients in the placebo group that had
4 positive naloxone challenge largely accounts for that
5 difference. And then the subsequent analyses, I
6 think, are dependent on retention because those who
7 are missing are counted as positive. Is that correct?
8 DR. EHRICH: It's a combination of the two
9 factors. It's a combination of the positive naloxone
10 challenge and the differential dropout rate due to
11 lack of efficacy.
12 DR. WALSH: Okay.
13 DR. EHRICH: Would you like to -- okay.
14 DR. WALSH: Yeah, I mean, the numbers are
15 shown in the table.
16 DR. EHRICH: Exactly. Exactly.
17 DR. WALSH: I think the difference was about
18 14 or 13 patients.
19 And then just one other very minor point of
20 clarification. In the in-patient laboratory challenge
21 study, in the materials that were provided it's not
22 clear what the route of administration was for the

1 hydromorphone challenge. Was that a parenteral
2 challenge or was it an oral challenge?
3 DR. EHRICH: That was parenteral.
4 DR. WALSH: It was parenteral. Thank you.
5 DR. SCHULTZ: Mr. Mullins?
6 MR. MULLINS: Yes. I had some questions
7 concerning study design and safety data. I wanted to
8 know if there were any studies done on
9 pharmacogenomics because it seems like when I look at
10 -- a couple things concern me. When I look at the
11 patient pool it seems to be rather homogeneous. And
12 we know that different subjects, patients, metabolize
13 substances differently. So it concerns me there was
14 not a diversity of data between severe to moderate
15 users, diversity of gender, diversity in culture,
16 ethnicity, in this Russian base. I would like you to
17 address that.
18 And please address slide 38 where in the
19 safety data for Study 013 you mention there is a
20 discontinuation rate for Vivitrol of 29 percent. I
21 think that's rather high and I would like some
22 explanation on that.

1 So, and then I had a question about
2 acquisition. So.
3 DR. EHRICH: Well, I would like to address
4 all these questions. And I'll start with your last
5 comment first and that is the discontinuation rate in
6 this -- in our studies. When you take a look at other
7 studies done in this indication, in opiate dependence,
8 other studies in addiction, and even in other related
9 CNS disorders, the treatment retention that we saw in
10 our program was quite good. And these are patients
11 again that are notoriously difficult to maintain in
12 studies and we are very pleased with the results that
13 we saw.
14 I'd like to ask --
15 MR. MULLINS: Do you have data on the
16 explanation to the 29 percent discontinuation rate?
17 Do you have details of that? Of why --
18 DR. EHRICH: In -- and I just want to make
19 sure I understand which study were you referring to?
20 MR. MULLINS: Study 013, slide 38. Do you
21 have data to explain?
22 DR. EHRICH: Slide up, please. So this

1 slide.

2 MR. MULLINS: Do you have extrapolation of

3 that category for other?

4 DR. EHRICH: For other, yes. We absolutely

5 do. Slide up, please.

6 So these are the -- this is a further

7 breakdown of those patients in the other category.

8 MR. MULLINS: So I have more questions about

9 -- when I had a question about acquisition. Subjects

10 withdrew with consent. Were these subjects paid or

11 how was it -- you mentioned the motivation level. So

12 would you comment on that?

13 DR. EHRICH: So patients received no

14 financial compensation to participate in the study.

15 And in terms of subject withdrew consent, sometimes

16 that category has a specific meaning in terms of

17 physically undergoing a consent withdrawal process.

18 That wasn't the case in our study. Our study, most of

19 the patients had a well-defined family member or

20 someone that we could contact to find out what had

21 occurred in the study. So there were patients that

22 did not return, that dropped out of the study, and we

1 were able to determine from the family member, the
2 spouse, the parent, that this patient had made a
3 decision that they did not want to return to the
4 study. So rather than say they were lost to follow-
5 up, we used the category of withdrew consent, although
6 that formally did not take place.
7 I'd like to ask -- to address your other
8 questions, I'd like to ask Dr. Turncliff to come up
9 and provide some perspective on the robustness of the
10 PK.
11 DR. TURNCLIFF: Good morning. Brian
12 Turncliff, translational medicine at Alkermes.
13 I think the root of your question does
14 relate to metabolism. If I could have XO slide 41,
15 please.
16 Just to reiterate, the metabolism -- slide
17 up, please.
18 The metabolism of naltrexone is not mediated
19 by cytochrome P450s. Cytochrome P450s are known as a
20 common mechanism of drug-drug interactions and
21 significant genomic variability. Naltrexone is
22 metabolized by an aldo-keto reductase enzyme, AK1C4.

1 This is a human cytosolic enzyme. It does have some
2 known polymorphisms, however, the population
3 distributions are not well understood. This may
4 explain some of the variability in oral naltrexone,
5 however, importantly, due to its route of
6 administration by IM injection and that the
7 formulation governs the release of naltrexone,
8 significant first pass metabolism is reduced.
9 We identified or conducted a population
10 pharmacokinetic analysis of 443 subjects that
11 contributed naltrexone concentrations across four
12 studies.
13 Could I have slide XO 33, please? Slide up.
14 In this study, a population pharmacokinetic
15 model was developed that looked at the co-variants of
16 age, sex, weight, race. Importantly, alcohol and/or
17 polysubstance dependence, as well as markers of renal
18 and hepatic function.
19 Just to address one of your questions
20 related to race. If I could have the distribution
21 slide of race. In this analysis, race was not
22 identified as a co-variant.

1 Slide up, please.

2 This slide displays the weighted residual

3 concentration data by race of all 3,821 concentration

4 data points. A weighted residual is the difference

5 between the predicted -- model predicted concentration

6 and the actual concentration. So this display shows

7 all concentration data in a box-and-whisker plot. The

8 green boxes reflect the 25th, 5th, and 75th percentile

9 of the concentration data with outliers indicated. As

10 you can see, all of these data are identified by a

11 zero weighted residual value indicating no significant

12 difference in race.

13 DR. EHRICH: Let me just finally -- thank

14 you, Dr. Turncliff.

15 And finally, I'd just like to underscore

16 that we did have differences in racial and ethnic make

17 ups of the study. The study in Russia was largely

18 white. The 006 study had -- was -- had approximately

19 16 percent non-white. And the 004 study, the

20 pharmacodynamic study actually was two-thirds African-

21 American.

22 MR. MULLINS: Were any of these subjects

1 pretreated with methadone in the Study 013?
2 DR. EHRICH: So all of the patients who had
3 initiation of therapy needed to be opiate free for a
4 minimum of seven days. A number of patients in the,
5 in particularly the 013 study, had been using
6 methadone prior to undergoing detoxification.
7 MR. MULLINS: Do we have any data on the
8 synergism between methadone and Vivitrol?
9 DR. EHRICH: Because methadone is an opioid
10 agonist and naltrexone is an opiate antagonist, they
11 oppose each other and are used together clinically.
12 So we do not -- we don't have any experience on co-
13 administration.
14 DR. SCHULTZ: Did you have further questions
15 on acquisition, Mr. Mullins?
16 MR. MULLINS: I think -- I think he answered
17 my question on acquisition.
18 DR. SCHULTZ: Okay. Thank you.
19 All right. Next we have Dr. Denisco.
20 DR. DENISCO: Thank you. I'd like to follow
21 up on the point of patients developing one time use of
22 narcotics and then those developing dependence.

1 Following up on the question about overriding the
2 mechanism of blockade when in severe pain. If the --
3 if patients in pain said the hydrocodone doesn't work
4 as well then that's telling me that the blockade
5 level, if it's working to some degree, even with
6 relatively weak opioid, they're getting -- still
7 getting some euphoric effect. And if that's the case
8 then, of course they could go on and become dependent
9 while still on -- still having the Vivitrol in their
10 system.
11 So I'm wondering if the dose of Vivitrol was
12 not high enough to create a total effective blockade.
13 I'm just -- I would think that it would be very hard
14 for a patient that had the injection to go ahead and
15 become physically dependent on an opioid unless they
16 were taking each dose was a very, very high override
17 of the blockade. So I'm just a little confused about
18 that point if one of you could help.
19 DR. EHRICH: I want to make sure I
20 understand the question. Could you, sir, just
21 rephrase the question? I want to make sure I address
22 what you're asking.

1 DR. DENISCO: Well, I'm wondering how a
2 patient that has the Vivitrol injection could still
3 feel some of the opioid effects of hydrocodone. That
4 was stated in the answer to the question on patients
5 having pain problems.
6 DR. EHRICH: Well, clearly Vivitrol will
7 block the effect of opiate analgesics. So we need to
8 make sure that physicians know how to understand and
9 how to treat pain in the context of Vivitrol treatment
10 should that occur.
11 And as Dr. Silverman indicated, we provide
12 information in our label, we provide education, and we
13 provide availability of a pharmacist to ensure that
14 that's -- that physicians understand that.
15 DR. POTTER: It's Bill Potter from industry.
16 Perhaps for further clarification here the
17 statement was made as I understand it that patients
18 didn't experience as much relief. I mean, but those
19 were anecdotal reports as I understand it. In other
20 words, was there no placebo control difference to show
21 that in the context of being on Vivitrol that you
22 could still observe under placebo-controlled

1 conditions some opiate-associated pain relief? I
2 would suspect that without that data the report of a
3 subject in the multiple pain studies we've done in the
4 field could be simply the well known placebo effect,
5 pain relief that you get with subjects.
6 So what would it take to provide scientific
7 evidence that you were actually getting pain-related
8 relief because of the opiate action versus the other
9 factors that feed into a subjective report?
10 DR. EHRICH: Dr. O'Brien, would you like to
11 address that?
12 DR. O'BRIEN: Well, I think Dr. Potter hit
13 the nail on the head because when you're dealing with
14 even strictly controlled studies involving pain there
15 is a huge placebo effect. And when naltrexone was
16 first discovered we did many, many studies of letting
17 people self-inject either opiate or placebo while they
18 were on naltrexone. And everything is relative when
19 you're dealing with competitive antagonism. So if you
20 have a high dose of naltrexone and a low dose of
21 opiate, you feel nothing. But the more you increase
22 the opiate, the more likely you are to feel a little

1 bit. And sometimes patients try very hard to overcome
2 the block and eventually you can. And we've had to do
3 this therapeutically in some medical emergency
4 situations. And it can be done. And it's perfectly
5 safe in the sense that you don't suddenly fall of a
6 cliff. If you keep increasing the dose you just
7 gradually start to feel the opiate effect. But I
8 suspect that the anecdote that Dr. Silverman mentioned
9 probably was more placebo effect than anything else.
10 But it theoretically would be possible. No
11 patient that I know of in the 40 years or so that I've
12 studied this drug -- no patient has ever become
13 dependent while they're on naltrexone. They would
14 have to spend a lot of money and use it on a regular
15 basis and be really, really difficult. It would be
16 much more expedient for them to just stop the
17 medication, wait till it goes away, and then go back
18 to their addiction.
19 But you have to keep in mind that this is
20 competitive antagonism. And so you can always
21 override, you know, the ligand binding of naltrexone
22 is not a permanent binding. It's constantly in

1 equilibrium depending on the concentration of the
2 agonist and the antagonist.
3 DR. DENISCO: If I may, so we can assume
4 that those patients that were on Vivitrol and had a
5 positive challenge test, then had used a large amount
6 of opiates to overcome their blockade?
7 DR. EHRICH: We only had one patient in the
8 study that had taken Vivitrol and had a positive
9 naloxone challenge test. And I didn't go into the
10 detail.
11 Slide up, please.
12 But if you take a look at that orange dot,
13 what you see on that one Vivitrol patient is that they
14 had actually missed a prior dose and had the
15 opportunity then to become readdicted.
16 DR. SCHULTZ: All right. We'll entertain a
17 question from Dr. Hwang at this time. We have
18 remaining questions from Maxwell, Woolson, White,
19 Baxter, and Montoya that we may need to hold until
20 either right before the lunch or after the open public
21 hearing. And Dr. --
22 DR. HWANG: (Off microphone.)

1 DR. SCHULTZ: All right. We have you next
2 on the list but we'll go with Dr. Hwang.
3 DR. HWANG: Thank you. Thank you very much.
4 I've learned a lot. I'm also a practicing
5 clinician over the years and especially dealing with
6 chronic mental illness, schizophrenic patients. And
7 substance abuse is -- especially cocaine, opiate-kind
8 of drugs -- are a very well known problem in curing
9 mental illness. So that's one question.
10 The other question is to follow up an
11 earlier question on ethnicity issues. So there will
12 be two parts here. The patients, especially
13 schizophrenic patients, bipolar patients who use drugs
14 and an increasing number of them are using opiate
15 drugs. And we do treat them but they are a lot more
16 challenging in many different ways -- compliance
17 issues, physiological issues, psychological issues. I
18 don't see much data on that, you know, co-morbidity
19 issues. So I would like to have some of that data
20 presented if you have them. And what the company's
21 plan is on labeling because it's likely that once it's
22 approved it's going to be marketed as a safe and easy

1 drug to use. And, you know, when you do that in a
2 clinical setting there will be lots of demand by the
3 patient and the physicians will be pressured to
4 prescribe this medication. And so what the company's
5 plan is for labeling in the dual diagnostic patient
6 population, especially the fact that these patients
7 also have a very high rate of suicide. I would like
8 to know that.
9 And number three is ethnic aspect. We do
10 know, especially in certain ethnic groups there is
11 significant, well-established polymorphism in P450. I
12 understand this drug doesn't work through P450 but the
13 dosage -- there is a significant difference in dosage
14 between ethnic groups. So I would like to know what
15 the company's plan is on that aspect.
16 DR. EHRICH: Well, first of all I'd say that
17 there are a number of studies that are ongoing in the
18 United States. These are being done largely in
19 academic centers looking at the use of Vivitrol. And
20 we've not done a study directly in patients who are
21 dual diagnosed. There was a study that was done by
22 Dr. Steven Batki at SUNY Buffalo. He's out at UCSF

1 now, I believe. And he did -- he performed a study in
2 patients with alcohol dependence and schizophrenia co-
3 occurring and showed a good treatment effect. But I
4 don't have that data with us here today.
5 And on issues, such as labeling, we will not
6 be describing Vivitrol as a drug that's safe -- well,
7 sorry. We believe we've got great safety but that
8 it's an easy drug to use. Vivitrol is a specialty
9 injectable so it really requires, you know, physicians
10 who have an understanding about how to use it, how to
11 reconstitute it, and how to work in that context. And
12 I think that experience is reflected in what we've
13 seen over the past number of years with Vivitrol in
14 the context of alcohol dependence that seems to find
15 its best home with physicians that know -- that know
16 what they're doing. And I would expect that there
17 will continue to be investigations with Vivitrol in
18 the post-approval setting.
19 DR. HWANG: (Off microphone.)
20 DR. EHRICH: The ethnic differences. So I'd
21 refer back to the -- to the data that Dr. Turncliff
22 presented. So we have substantial exposure, some from

1 the opioid program and then a much broader exposure in
2 the context of our alcohol dependent program where
3 we've done both individual PK, as well as population-
4 based PK. And it's that population PK data that
5 indicated -- as Dr. Turncliff showed that across
6 racial and ethnic groups we didn't see differences in
7 exposure. And I think that's quite consistent with
8 what we know about the metabolism. It's not
9 metabolized by the P450 system.
10 DR. SCHULTZ: Thank you. Unfortunately, we
11 are having -- running behind schedule. If we could go
12 ahead and move to a break just now, a quick five to
13 seven minute break. So if I could have everyone back
14 about 10:50 -- 10:50 or so. I'm sorry, 10:57. And we
15 will entertain -- and I apologize. The questions that
16 are remaining we do have noted and we will work those
17 in either before the lunch or after the open public
18 hearing. So thank you so much. We'll be back in
19 seven minutes.
20 (Recess.)
21 DR. SCHULTZ: If you could please return to
22 your seats we'll proceed with the FDA presentation.

1 Are we ready? I'd like to invite Dr.
2 Skeete.
3 **FDA Presentation:**
4 **Presentation of Safety of Vivitrol for Opiod**
5 **Dependence**
6 DR. SKEETE: Good morning. My name is
7 Rachel Skeete and I'm a clinical reviewer with the
8 Division of Anesthesia and Analgesia Products.
9 Today, I, along with Dr. Surya Nallani, who
10 is the clinical pharmacology reviewer, and Dr. Feng
11 Li, who is a statistics reviewer, will be discussing
12 the safety and efficacy data for Vivitrol for the
13 treatment of opioid dependence.
14 We'll provide background information on oral
15 naltrexone and on Vivitrol, which is a depo
16 formulation of naltrexone. We'll discuss efficacy
17 data provided by a placebo-controlled study and a dose
18 ranging proof of concept study providing supportive
19 evidence that Vivitrol blocks the effects of exogenous
20 opioids. Dr. Nallani will discuss the proof of
21 concepts study and Dr. Li will summarize the efficacy
22 findings.

1 Safety data will be focused on deaths,
2 serious adverse events or SAEs, discontinuations due
3 to adverse events or AEs, adverse events of special
4 interest, and common adverse events associated with
5 Vivitrol.
6 Vivitrol is an extended-release, injectable
7 formulation of naltrexone. Some of this will be
8 repetitive from the previous presentation but I'll
9 just point out some key points. Naltrexone is an
10 opiate antagonist with essentially no opiate agonist
11 properties. In 1984, oral naltrexone was first
12 "approved" for the blockade of effects of exogenously
13 administered opioids under the trade name Trexan.
14 This indication was approved after Advisory Committee
15 consultation when a program of clinical trials and
16 opioid addiction failed to demonstrate efficacy in
17 preventing relapse to opioid use. The pharmacologic
18 effect was well established, but as the applicant
19 described earlier in their presentation, the label
20 notes that there are no data that demonstrate an
21 unequivocally beneficial effect of truxan and rates of
22 recidivism among detoxified, formerly opioid-dependent

1 individuals who self-administered the drug. In 1994,
2 a supplemental application was approved to also add
3 the indication treatment of alcohol dependence. The
4 trade name was changed to Revia at the time of
5 approval of that efficacy supplement.
6 Again, Vivitrol is an extended-release,
7 injectable formulation of naltrexone with the
8 established name naltrexone for extended-release
9 injectable suspension. It was approved in 2006 for
10 alcohol dependence, relying in part of Agency efficacy
11 and safety data for review. Vivitrol is administered
12 as a 380 milligram dose given intramuscularly on a
13 monthly basis. When the original NDA application was
14 submitted, as you heard, it contained some safety data
15 in opioid-dependent and dually-dependent patients,
16 those who were dependent on both alcohol and opioids
17 as the potential for some off label use was
18 anticipated.
19 There were 121 opioid and dually-dependent
20 patients who contributed to safety data. One hundred
21 one received Vivitrol and 20 received oral naltrexone,
22 which was used as an active comparator. The original

1 application also included a dose-finding study which
2 demonstrated blockade of exogenously administered
3 opioids for at least 20 days. Shortly after approval
4 of the original application, Alkermes embarked on a
5 program to support a supplemental application for the
6 use of Vivitrol in the treatment of opioid dependence.
7 Alkermes sought Agency guidance on design of clinical
8 trials and on analytic methods.
9 The paradigm for clinical trials in
10 addiction treatment, however, was evolving at that
11 time and continues to evolve with a shift to a greater
12 focus on individual treatment response rather than
13 group means. Alkermes was informed that analyses
14 focused on group means, such as mean percent of weeks
15 abstinence would not be considered meaningful. This
16 is because these do not reflect the experience of
17 individual patients who might range from complete
18 responders to non-responders.
19 However, the applicant was concerned that
20 complete abstinence would be unattainable and
21 particularly in light of our asking for a study
22 duration of at minimum six months. There was also

1 lack of consensus on whether a drug use pattern could
2 be considered a treatment success.
3 Taking all of this into consideration, we
4 proposed a design in which various definitions of
5 treatment success, from complete abstinence through
6 other patterns of opioid use could be evaluated. In
7 this way, the distribution of responses could be
8 graphically displayed and the curves compared
9 statistically. We are calling this approach to
10 evaluating the distribution of individual responses a
11 response profile. We also informed the applicant that
12 there would be a need to evaluate the clinical
13 significance of the responses. We noted that the
14 emphasis should be on patients whose drug use patterns
15 were closer to abstinence. We communicated that the
16 application should be supplemented by safety data from
17 alcohol-dependent subjects and conveyed that a single
18 efficacy trial taken together with supportive evidence
19 from the pharmacodynamic study demonstrating
20 Vivitrol's blockade could suffice if the results were
21 compelling.
22 The studies to support clinical efficacy for

1 this application include study ALK21-013 and study
2 ALK21-014.
3 Throughout this talk we will be using the
4 full study name or shorthand of just the study number
5 interchangeably when discussing these studies. For
6 example, these efficacy studies will be referred to as
7 ALK21-013 and -014 -- and -004, or Study 13 and Study
8 4.
9 Study 13 is a double-blind, placebo-
10 controlled efficacy study. Study 4 was a dose
11 finding, proof of concept, pharmacodynamic study which
12 provided initial evidence that Vivitrol could work in
13 this indication.
14 I will now turn the discussion over to Dr.
15 Nallani, who will discuss the clinical pharmacology
16 data submitted for Vivitrol.
17 **Summary of Clinical Pharmacology of Vivitrol**
18 DR. NALLANI: Thank you, Dr. Skeete. Good
19 morning. I'm Srikanth Nallani, senior clinical
20 pharmacologist supporting the Division of Anesthesia
21 and Analgesia products.
22 I'll be presenting Agency's perspective on

1 clinical pharmacology aspects of Vivitrol supporting
2 its investigation for the proposed indication.
3 Specifically, I'll be describing the clinical
4 pharmacology of naltrexone released from Vivitrol and
5 the findings of dose response with a view to provide a
6 mechanistic basis for the investigated dose and the
7 dosing frequency investigated in the Phase 3 clinical
8 trial.
9 As mentioned before, naltrexone is a high
10 affinity, μ-opioid receptor antagonist. It's primary
11 pharmacological actions are elicited by blocking the
12 effects of exogenously administered opioids. In this
13 regard, oral naltrexone is commonly used in healthy
14 volunteer pharmacokinetic studies to block opioid
15 effects of opioid drug formulations. Now, use of
16 naltrexone in the treatment of alcohol dependence is
17 thought possibly due to blockade of endogenous peptide
18 effects.
19 It is important to note some of Agency's
20 perspectives on Revia that would apply to the current
21 discussion. Specifically, Agency had noted that oral
22 naltrexone will produce effective opioid blockade when

1 administered by means that enforce compliance. Agency
2 also noted that failure of the drug to show benefits
3 in terms of recidivism rates appears due to poor
4 compliance. So today, clinical pharmacology
5 presentation will provide Agency's perspective on
6 proposed product characteristics that might indicate
7 improved compliance.
8 Here on this slide shows the profile of
9 naltrexone on the y-axis and time on x-axis.
10 Pharmacokinetic profile of Vivitrol shown here is
11 following the first dose administration, unlike what
12 the sponsor has shown in slide number CC-21, which is
13 a study state profile or after the fourth dose
14 administration in a healthy volunteer PK study.
15 A closer examination is needed to understand
16 the PK profile if naltrexone over the first week after
17 intramuscular injection. Naltrexone pharmacokinetic
18 profile is characterized by a transient peak which
19 happens within a couple of hours after injection. As
20 previously noted in slide CC-21 from Sponsors, this
21 initial peak is also thereafter at study state. And
22 plasma levels dropped significantly within 12 hours.

1 And at study state, this drop is not so dramatic as
2 after the first dose. And hence, it may not be
3 relevant when it comes to practice.
4 Recovery in plasma levels, in the form of a
5 second peak is noted about two to three days after
6 administration. Now, beginning 14 days after dosing,
7 naltrexone concentrations slowly decline with
8 measurable concentrations noted up to 28 days. As
9 described by the PK, the release of drug from
10 microspheres happens in stages. And as such, release
11 of naltrexone from microspheres is the major
12 determinant of pharmacokinetic disposition of
13 Vivitrol. Now, we did note that decreased naltrexone
14 exposure in terms of the area under the curve was
15 noted in subjects with higher body weight; however,
16 Dr. Feng Li noted that there was no effect of body
17 weight on clinical efficacy.
18 Pharmacokinetics of Vivitrol were not
19 affected by several intrinsic factors, such as age,
20 race, sex, mild and moderate hepatic impairment, and
21 as such, as the Sponsor has indicated, naltrexone is
22 extensively metabolized by hepatic and extrahepatic

1 metabolic enzyme allocator reductase. And hence,
2 renal impairment may not significantly affect
3 naltrexone pharmacokinetics. In addition, because of
4 the non-SET mediated metabolism of naltrexone we do
5 not anticipate any major drug-drug interactions with
6 SIP inhibitors or in users.
7 Alkermes conducted a dose-finding study, No.
8 004, findings of which form the basis for dose
9 selection and the duration of use of Vivitrol in the
10 Phase 3 clinical trial No. 13. Briefly, the dose-
11 finding study No. 4 was a randomized, single-dose,
12 opioid challenge study conducted in highly non-
13 dependent opioid-experienced adult subjects. As this
14 is a dose-finding study, the 380 milligram dose is not
15 evaluated in this particular study. The subject was
16 to assess the presence, duration, and the degree of
17 opioid blockade and also simultaneously assess safety
18 and tolerability of Vivitrol.
19 I'll present the details of the study design
20 using a schematic. Upon enrollment, hydromorphone
21 challenge test was administered to different subjects
22 and those who were able to tolerate that several days

1 later received a naloxone challenge test. And during
2 the hydromorphone challenge test, increasing dose of
3 intramuscular hydromorphone injections were
4 administered at one hour intervals. A dose of 0
5 milligrams hydromorphone or placebo was administered
6 at times 0. An hour later, 3 milligrams hydromorphone
7 was administered, and thereafter on an hourly basis up
8 to 6 milligrams hydromorphone was administered
9 intramuscularly.
10 Drug effects. In terms of both subjective
11 measures and objective measures were collected in 15-
12 minute intervals throughout the hour after
13 hydromorphone administration. Subjects who were able
14 to tolerate hydromorphone up to 4.5 milligrams and
15 also passed the naloxone challenge test were then
16 randomized to receive 75, 150, and 300 milligrams of
17 Vivitrol on day one. They returned on several other
18 days as indicated here and the hydromorphone challenge
19 test was repeated with the same scheme of
20 hydromorphone injections and the pharmacodynamic
21 assessments. Additionally, a pharmacokinetic
22 assessment of one single blood sample, a pre-

1 hydromorphone challenge test was collected for mainly
2 assessing naltrexone and placebo IM.
3 I'll take a few minutes to describe the
4 figure showing results of the dose-finding study.
5 Response to the question, do you feel any drug
6 effect? as indicated by subjects on 100 millimeter
7 visual analog scale is plotted on the y-axis with the
8 time indicated in minutes, following the hydromorphone
9 challenge is noted on the x-axis. For reference, I
10 have added a gray line at 10 millimeters on the visual
11 analog scale response. Intramuscular hydromorphone
12 injection during challenge session is indicated by
13 upward arrows and the dose adjacent to it indicates
14 the amount of hydromorphone injected.
15 I will first present hydromorphone challenge
16 test results from the cohort of subjects receiving 75
17 milligrams and then overlay the results of cohorts of
18 subjects receiving 150 or 300 milligrams of Vivitrol.
19 Data are indicated as box plots where the median of
20 observations is indicated as a square. Entire range
21 of data is indicated as a tick bar or a thin whisker.
22 And data points that are standing outside the range,

1 in other words, outliers, are indicated as plus
2 symbols.
3 During screening visit as shown by the
4 median data are boxes. Subjects did not experience
5 drug effects when they received a placebo at times 0.
6 However, upon administration of 3 and 4.5 milligrams
7 of hydromorphone, one hour apart, a dose-related
8 increase in hydromorphone effects was noted. And on
9 day 7, when the plasma levels of naltrexone were
10 substantially higher, a complete blockade of opioid
11 effects was noted in most subjects.
12 I'd like to indicate an important
13 observation here. During screening session, the
14 majority of subjects received only up to 4.5
15 milligrams hydromorphone. However, during day 7 and
16 day 14, because of maintaining certain levels of
17 naltrexone, these subjects were able to receive up to
18 6 milligrams of hydromorphone. And this observation
19 was noted before both day 7 and day 14, which is not
20 indicated here for the purpose of showing the most
21 meaningful information. By day 28, shown here,
22 recovery of opioid effects became apparent in most of

1 the subjects receiving 75 milligrams Vivitrol.
2 I will now present results of cohort
3 receiving 150 milligrams.
4 DR. SCHULTZ: It looks like we might need to
5 take five minutes to have the slide problems
6 corrected. If you could please stay available to the
7 room that may be helpful. We'll start as soon as the
8 problem is addressed. Thank you.
9 (Recess.)
10 **Clarifying Questions**
11 DR. SCHULTZ: What we'd like to do at this
12 time is give an opportunity for the committee members
13 who had clarifying questions, if there is one that
14 does not require a slide from the sponsor we will move
15 through the group and I think Dr. Maxwell was next and
16 give them an opportunity to ask clarifying questions.
17 DR. MAXWELL: Okay. I have a question but I
18 want to clarify a statement that was made.
19 I think in response to Mr. Mullins there was
20 some comment about, oh, a lot of these clients had
21 been on methadone before. My question is I did not
22 think methadone was available for use or allowed to be

1 used in Russia.

2 SPEAKER: Not legally.

3 DR. EHRICH: Do you want to -- would you

4 like to address that, Dr. Krupitsky?

5 DR. KRUPITSKY: Good morning. My name is

6 Evgeny Krupitsky. I'm from Saint Petersburg

7 State/Pavlov Medical University and Bekhterev Research

8 Psychoneurological Institute.

9 That's true. Methadone is not available in

10 Russia as medicine for substitution therapy. However,

11 it is available as a street drug in an injectable

12 formulation.

13 DR. MAXWELL: Okay. I just wanted to

14 clarify that. Now, my question -- to get back to what

15 really concerned me, the data shows that in this trial

16 013, 88 -- 86 percent of the subjects were male. I'm

17 concerned about what data have we got on females? And

18 I see part of it would be in the FDA presentation.

19 But what are the effects -- what do you do when a

20 woman becomes pregnant -- what are the effects on the

21 fetus? Because this is such -- and particularly in

22 terms of the other opiates where right now the

1 majority of clients entering treatment with a
2 dependence on other opiates in the U.S. are female, so
3 what's the impact on females?
4 DR. EHRICH: So we have a substantial safety
5 experience in women as part of our U.S. studies and as
6 part of the U.S. clinical program. Dr. Deaver, would
7 you like to address the question regarding our
8 recommendations?
9 DR. DEAVER: My name is Dan Deaver. I'm the
10 vice president for Non-Clinical R&D at Alkermes.
11 Naltrexone is a class -- pregnancy Class C
12 drug. It is not recommended for use during pregnancy.
13 It has shown teratogenic effects in animal studies
14 early in gestation.
15 DR. MAXWELL: Okay. Thank you.
16 DR. SCHULTZ: Okay. We'll proceed with Dr.
17 Woolson had a question.
18 DR. WOOLSON: Sure. I'm not sure if this
19 will require a slide but this is really a follow up to
20 the retention question that's come up in a number of
21 different -- from a number of other questioners.
22 Retention is regarded as something good -- a good

1 outcome, and it's been stated as such with some of the
2 presentations here today. And failure to retain has
3 been implied to be a bad outcome. And in fact, has
4 been imputed as a bad outcome in some of the primary
5 analyses that have been done.
6 So my question is more of a general one.
7 Since retention is such a key component of the primary
8 analysis, what criteria were used to ensure that we
9 were assessing this in an objective way, that is
10 reasons for discontinuation with our plans in place,
11 for example, to contact the family if individuals
12 dropped out to see whether the individual was using
13 opioids or not? I guess my question is really the
14 degree to which we have information on this incomplete
15 group of individuals over and above us just implying
16 that they dropped out and therefore their outcome is
17 bad.
18 MR. EHRICH: One of the features, as Dr.
19 Krupitsky describes of the patients, is that the
20 patients generally had a family member involved,
21 typically a parent. And so we were able to use that
22 information to help get a further assessment of what

1 indeed was transpiring after discontinuation. And we
2 used all of that information in terms of making that
3 assessment that you saw in terms of patient
4 disposition.
5 MR. WOOLSON: Can I follow up with that?
6 There are a very large fraction of
7 individuals in the placebo group who dropped out
8 before week 5, which week 5 is really the first time
9 we're going to use information for the primary
10 endpoint. And like 36 percent, as I recall, dropped
11 out before week 5. And 13 percent in the Vivitrol
12 group. Yet, those individuals that were all then
13 assessed to have a bad outcome for the remaining 20
14 weeks. Can you just give us what your rationale was
15 for doing so? In fact, a bad outcome uniformly for
16 those 20 weeks.
17 DR. EHRICH: So, what the data highlight is
18 that the effect of Vivitrol occurs quite early in
19 terms of being able to retain patients in treatment.
20 And Dr. Ling, this is an analytic approach that's been
21 used now more and more consistently within opiate
22 dependence and Dr. Ling also pioneered this in his use

1 in the NIDA clinical trial of multi-center study of
2 bupinorphine. Would you like to comment on that?
3 DR. LING: Walter Ling from UCLA.
4 I think your question is a very good one and
5 for many years we struggled with this. Traditionally,
6 we used to argue about what happens. A patient
7 doesn't come in and you can't tell whether or not
8 they're using or not using, although in general almost
9 all the fallout data we know about opiate addicts who
10 get out of treatment, the news is not good. Relapse
11 is very common.
12 In this study and a number of other studies
13 we did, you could turn the situation around. Instead
14 of looking for a bad outcome or positive urine as an
15 indication of bad outcome, what the study did was turn
16 things around using clean urine as an indicator of
17 good outcome. It's pretty much like a teacher
18 teaching a class and giving the whole class a test.
19 Even though you're counting the points that you earn,
20 but the concept is actually broader. It does imply a
21 certain degree of treatment adherence. You have to go
22 to the clinic to be able to give urine. And the urine

1 you give has to be negative to earn a point. So
2 everybody can earn a number of points. And the number
3 of urine that can collect over the whole period is
4 then the denominator.
5 And so everyone -- the number of clean
6 urines is how well you perform in this. And you can
7 think of the whole treatment experience as your
8 attempt to do well by earning urine clean samples.
9 And if you look at it that way then there is no need
10 for imputing missing data or if you're not there you
11 obviously couldn't give a urine sample. You're not at
12 the clinic. And if you couldn't give a sample you're
13 not going to have a negative test. That's the way
14 this study looks at things.
15 DR. WOOLSON: Well, I guess I still have a
16 question because effectively those individuals who
17 dropped out during the first four weeks -- and there
18 are some 48 of the 124 in the placebo group -- they
19 have -- they're being considered in the next 20 weeks
20 as having used opioids. And so therefore, they're in
21 the denominator of the calculation that we do. For
22 example, the percentage of individuals who are opioid

1 free over those 20 weeks.
2 So to me I'm still struggling with the issue
3 that that information has been imputed rather than
4 observed. I'm just trying to sort out what's been
5 observed versus what's been imputed in terms of
6 interpreting these results.
7 DR. EHRICH: Well, you are -- so you're
8 correct. Treatment retention was a key factor in
9 driving the primary outcome. And I think just the
10 perspective that has been applied is that imputation
11 implies that we're sort of making something up. And
12 the basis of -- the basis of success in the trial is
13 that in order to be successful you need to stay in
14 treatment. And that's because -- I think maybe as Dr.
15 Earley put it earlier -- earlier this morning. The
16 point of, you know, what Vivitrol is doing is it's
17 preventing patients from relapsing to physical opioid
18 dependence.
19 It's preventing -- it's permitting them to
20 stay in treatment. It's permitting them to have an
21 occasional slip and still be able to stay in
22 treatment. And that's what permits patients to then

1 get into -- get these additional support to work on
2 the additional problems, improve family relationships,
3 et cetera, as we discussed, and draw people towards
4 recovery.
5 And I think that the way the efficacy of
6 Vivitrol has been articulated as prevention of
7 relapse, I think it reflects that factor. But, you
8 know, there is -- there's always going to be an
9 uncertainty in terms of what precisely is occurring,
10 you know, following discontinuation, but our
11 definition of success -- our pre-specified definition
12 of success for the study was that they had to show up,
13 and if you were going to be considered to be opiate
14 free you have to show up and you have to give us a
15 clean urine.
16 DR. SCHULTZ: Dr. White had a question that
17 doesn't require a slide.
18 DR. WHITE: It does require a slide but I
19 could try.
20 DR. SCHULTZ: Go ahead and try.
21 DR. WHITE: It's related to the key
22 secondary endpoint of treatment retention. And the

1 question -- I did have a question about the first
2 month also but I think you answered that.
3 The second is it hasn't -- the curves have
4 not reached an asymptote after six months. So do you
5 feel that six months -- I know that there's an open
6 label study and I'm interested to know if you have
7 data -- does it actually reach an asymptote? That's
8 one question.
9 Then the second question is since treatment
10 retention is included in your other graph, for those
11 patients who come in every month, I'd be interested to
12 know what the graphs look like for those who receive
13 the injections. So, you know, this is -- I think it's
14 more difficult without a slide. But --
15 DR. EHRICH: There are some slides that we
16 could show you and we do have information on what
17 occurred during Part B of the study. Would it be
18 worthwhile to address that at a point when we have AV
19 available?
20 DR. SCHULTZ: We'll follow up on that point.
21 DR. WHITE: Okay.
22 DR. SCHULTZ: Once we have slides available,

1 whether it's after the open public hearing or before.
2 Thank you.
3 So I think Dr. Baxter had a question.
4 DR. BAXTER: Yes, thank you. I have a
5 couple of things.
6 One, I think that it's important to know
7 that in that study group 021 with health care
8 professionals that there may have been some other
9 incentives to keep them in, like their licenses. So
10 we should be aware that that is a very powerful
11 incentive that we see among that group.
12 I'm interested -- I think it was Dr. O'Brien
13 that mentioned that there was a subgroup of alcoholics
14 that this medication was not efficacious.
15 DR. EHRICH: It is efficacious.
16 DR. BAXTER: Okay. But did you infer that
17 there is a subgroup that this medication is not
18 efficacious?
19 DR. EHRICH: (Off microphone.)
20 DR. BAXTER: In alcoholics, yes.
21 DR. O'BRIEN: The official FDA package
22 insert says that it's -- I've forgotten the exact

1 words but it's efficacious in alcoholism. And this
2 came directly from our own research which eventually
3 got replicated by others.
4 But since that time we have tried to figure
5 out which alcoholics it is especially effective for.
6 Because if you look at the effect slides you'll see
7 that some alcoholics get no response whatsoever and
8 others it turns their life around. It makes a really
9 big impact. And since I'm the first person to give it
10 to alcoholics I've really seen some people over the
11 years that it's made a huge difference for. In the
12 oral form even. I think it's even better in the depo
13 form.
14 But so we have a gene that we found where
15 the key aspect of this genetic variant is that when
16 these people drink alcohol they get a large increase
17 of endogenous opioids. So they get more euphoria from
18 alcohol than other people. And as I say to my
19 patients, which is I think at least partly true, when
20 you drink alcohol, it's as though you've taken a shot
21 of heroin. So this drug that was developed for heroin
22 works for you. And it's a way of explaining to

1 people. And the big effect is that it doesn't stop
2 them from drinking but it does stop them from getting
3 the big high, and therefore it's most effective in
4 reducing heavy drinking. Also abstinence, but more
5 it's reduction of heavy drinking. So that's why I
6 said that it's -- it's effective for some alcoholics
7 but it's effective for all opiate addicts. That's the
8 part that's really important because all it can do is
9 block opiate receptors.
10 And that's why when you look at the data in
11 the opiate group, some of them still have positive
12 urines because they do over time try some opiates.
13 This is what they've done for years and they don't
14 just stop it because the drug doesn't, you know, the
15 naltrexone doesn't stop them from taking a drink or
16 taking a host of heroin, but it does stop them from
17 getting high from it.
18 DR. BAXTER: Thanks. I really wanted to --
19 I actually threw that up there to you because I
20 thought that that was a very important point. And
21 that's something that we all need to understand
22 regarding this medication.

1 I also wanted to ask, you know, what is the
2 optimal dose that will provide blockade out at 28
3 days?
4 DR. SCHULTZ: Thank you so much.
5 Unfortunately, and I appreciate your flexibility, if
6 you could hold that question we'll pick that up later.
7 And I do appreciate everyone being good about this.
8 We'll go back to the FDA presentation now
9 that the AV is up, but Dr. Baxter, please keep that in
10 mind.
11 We'll go back to Dr. Nallani.
12 **FDA Presentation Continued After Technical Difficulty**
13 **Summary of Clinical Pharmacology of Vivitrol**
14 **(Continued)**
15 DR. NALLANI: Okay. To recap quickly,
16 during the screening when subjects receive increasing
17 doses of hydromorphone intramuscularly there is a
18 dose-related increase in drug effect perceived by
19 individuals. A week after administration of Vivitrol
20 and thereafter up to 14 days, those that are receiving
21 75 milligrams of Vivitrol have -- the majority of them
22 have their opioid effects blocked because there are

1 some outliers. And with the 75 milligrams cohort,
2 return of these opioid effects is noted by day 28.
3 Now, I'll overlay the results of 150
4 milligrams receiving cohort. Again, they had
5 increased doses -- drug effects following increasing
6 doses of hydromorphone during screening. And on day 7
7 and day 14, the majority of them had the opioid
8 effects blocked, although some -- one or two
9 individuals had return of opioid effects by day 28.
10 The majority of them had the opioid effects blocked.
11 And as shown here, by day 42 the majority of the
12 opioid blockade is lost.
13 And I'll now overlay the results of the 300
14 milligrams cohort on the backdrop of 75 milligrams
15 cohort. Again, during screening, most of these
16 subjects had increased drug effects with increased
17 hydromorphone dosing, and the majority of them had
18 blockade of opioid effects on day 7 and 14. And this
19 continued for a majority of them for up to day 28.
20 And the opioid blockade was lost by day 42. And the
21 sponsors presented results from the observations only
22 on day 28.

1 So in summary, hydromorphone challenge results
2 indicate most subjects were able to tolerate up to 4.5
3 milligrams of hydromorphone injection at screening.
4 And there is a dose-related increase in drug effect
5 reported by all subjects. On day 7 and day 14, most
6 of the subjects -- all of the subjects, in fact,
7 received up to 6 milligrams hydromorphone
8 intramuscularly and complete opioid blockade is noted
9 in most subjects in all dose groups up to day 14.
10 Recovery of opioid effects is noted in
11 several subjects receiving 75 milligrams dose group
12 and opioid effect blockade continued for up to 6
13 milligrams hydromorphone dose in the 300 milligrams
14 receiving cohort. And as the sponsor showed in their
15 bar graph, 83 percent of the subjects received 300
16 milligrams of Vivitrol, had received up to 6
17 milligrams hydromorphone, and still had opioid effects
18 blocked. Recovery of opioid effects was noted in most
19 subjects by day 42.
20 Several subjects in cohorts receiving 75 and
21 150 milligrams Vivitrol had undetectable plasma
22 levels, possibly providing explanation to the loss of

1 opioid blockade effect. However, sustained plasma
2 levels of naltrexone up to 28 days were confirmed in
3 this dose-finding study that 300 milligrams Vivitrol
4 and also in a single dose and multiple dose PK study,
5 day 28 levels were detectible when 380 milligrams
6 Vivitrol was administered.
7 Systemic naltrexone levels in terms of the
8 area under the curve increased with dose up to 300
9 milligrams in this dose-finding study, and also up to
10 380 milligram dose in another dose proportionality
11 study. And then based on maintaining the plasma
12 concentrations by day 22 as high as possible, the
13 sponsor selected the 380 milligram dose for dose
14 selection for investigation in Phase 3 clinical trial
15 No. 13. In addition, as previously pointed out by the
16 sponsor, plasma levels of naltrexone were assessed
17 pre-dose upon return for medication on every visit.
18 And plasma levels were maintained in the majority of
19 these subjects.
20 And in summary, clinical pharmacology
21 information submitted for 380 milligram Vivitrol is
22 adequate in terms of relative viability, dose

1 proportionality, and factors that affect
2 pharmacokinetics of naltrexone. And drug release from
3 Vivitrol microspheres in itself is the major
4 determinant of pharmacokinetics of naltrexone. And
5 the Phase 2 opioid blockade study supports the
6 evaluation of Vivitrol for the treatment of opioid
7 dependence, both in terms of the dose selected and
8 also the once a month administration by providing
9 sustained plasma levels and also sustained blockade of
10 opioid effects for a majority of subjects.
11 Thank you very much. Now I'll turn it back
12 to Dr. Skeete.
13 DR. SKEETE: I believe we'll move forward in
14 the agenda to Dr. O'Neill at this time.
15 **Dealing with Foreign Clinical Trial Data in the Review**
16 DR. O'NEILL: Good morning. I'm Bob
17 O'Neill. I don't know where my slide are here. Can
18 somebody get these up for me? Thanks.
19 I've been asked to -- I'm the director of
20 the Office of Biostatistics in CDER, and I've been
21 asked to talk about a topic that is sort of a generic
22 topic that's relevant to, I believe, a conversation

1 I'll have later on in the day with regard to maybe the
2 safety profile of this product as it has been
3 evaluated in a foreign study. And the topic that --
4 let me see if I can get this down.
5 Am I to use this? I'm sorry if I'm -- what
6 am I not doing here? I just want to sequence this
7 guy. There we go. Did I sequence the matter of
8 existence? All right. I'm going to talk from over
9 here then. I apologize for that.
10 This is what I'm going to cover here. Some
11 of our -- I thought there might be a screen up here,
12 but all right.
13 Some of the experience we've had with
14 foreign clinical data, and particularly the ICH E5
15 document, which I believe is in the material available
16 to everybody. I happen to be the ICH E5 topic leader,
17 and for those of you who don't know about ICH, it's
18 the International Conference for Harmonization which
19 began in early 1990 and it was the pharmaceutical
20 industry and the regulators in Japan, the European
21 Union, and the United States coming together to come
22 up with common standards for how we would look at this

1 particular problem.

2 But in general, we're receiving an

3 increasing number of clinical trials, including data

4 that is outside of the United States. And some of you

5 may be aware, this is a report that's only a month or

6 so old that was an evaluation by the Inspector General

7 of challenges to FDA's ability to monitor and inspect

8 foreign clinical trials. It's not necessarily bedtime

9 reading and it doesn't go through analysis or design

10 issues. It's essentially more about FDA's ability to

11 monitor and get access to foreign clinical trial

12 sites. And it's got some recommendations.

13 It's hard to read what those recommendations

14 are. But one of the interesting recommendations is

15 that in the electronic submission of data to us, we

16 need to have the information specified at the site

17 level so that we can look at results at a site by site

18 level to see what the source of heterogeneity might

19 be. And it also has a lot to do with the inspection

20 strategies in terms of how we might look at the data

21 to be able to decide how to inspect clinical trials.

22 But as far as our review process, we -- my

1 shop supports the 15 medical review division in the
2 Office of New Drug Evaluation. And this is generally
3 the way we look at the data. We look at -- we look at
4 clinical trials with regard to the results inside and
5 outside the United States. And I'm going to give you
6 a couple of examples of what we've found here. The --
7 the results of looking at studies of safety and
8 efficacy outcomes inside the United States are not
9 always very easy to interpret.
10 And the kinds of things that we might look
11 at is not just the treatment effect itself but what's
12 the dropout pattern, differences in response rates,
13 concomitant medication, whether the primary and
14 secondary variables are going in the right direction,
15 whether the exposure and follow up is the same or
16 different in different regions. So those are the
17 kinds of things. And we might actually go in on
18 individual patient profiles and look at what's
19 happening longitudinally with individuals.
20 So if you conceptually look at a clinical
21 trial, this is more a schematic for a multiregional,
22 multi-center trial. What you're talking about right

1 now is a trial totally done within Russia. But what
2 we're seeing a lot of is multiregional trials. Part
3 of it's done in North America. Part of it's done in
4 Europe. Part of it's done maybe even in South
5 America. So when you look at parsing out the sources
6 of noise and variation and what not, this is a
7 conceptual framework. And certainly, if you were
8 thinking about auditing a trial or quality assurance
9 of a trial, that's what you might be thinking about.
10 But here's some experience of our office.
11 It's not all that current, but over the last seven
12 years – this study probably was done up till 2008 –
13 I'm going to tell you about what we found in terms of
14 the clinical studies that we've reviewed. And then
15 there are a few examples in 22 of the NDA submissions
16 that we've evaluated in terms of what the decision was
17 by the medical reviewing division as to what to do in
18 the face of sub-heterogeneous results.
19 This is just a brief summary. We've
20 reviewed about 2,000 clinical – Phase 3 clinical
21 trials during FY01 to FY07 in terms of – and about 41
22 percent of those trials were domestic only, 50 percent

1 were sort of combined domestic-foreign studies, and
2 the rest were totally foreign studies. So it gives
3 you a sense of the number of patients. And this is
4 only increasing. And this was also reflected in the
5 report – the Inspector General's report. This is not
6 an uncommon finding.
7 So when you're looking at the treatment
8 effects, safety or efficacy, by region or by country
9 or by inside the United States or outside the United
10 States and you find – you should expect some
11 differences in heterogeneity but too much is too much.
12 And then you have to decide what you're dealing with
13 and whether these are real or whether it's just a play
14 of chance. And this is an example of one of my
15 colleagues who supports the cardio renal division.
16 Went back and looked at the last outcome. They do
17 very large outcome trials in the cardio renal area.
18 Maybe 2,000, 3,000, 4,000, 5,000, 10,000 patient
19 trials for large outcomes.
20 And we've been finding an interesting
21 pattern in this area. I don't think it's been
22 confirmed but these are 16 independent studies, large

1 outcome studies. And what you're seeing here is the
2 difference between the treatment effect inside the
3 United States and the treatment effect outside the
4 United States. And this is in terms of the log-hazard
5 ratio, which is normally what you might be looking at
6 in time to event trials. But this is an effect size.
7 And the interesting message here is in about 13 out of
8 the 16 trials, the effect size in the United States
9 was smaller than the effect size outside of the United
10 States on the efficacy side.
11 So, what to make of it, don't know. But I
12 have another interesting example that's coming up in a
13 few minutes. So what the review division might be
14 struggling with is what I would do about it. Let's
15 say if I only have a single study. And in some
16 situations, in four situations, the drug was not
17 approved because of this heterogeneity and another
18 study was asked for, maybe with a certain design. Or
19 maybe the labeling was done in such a way as to inform
20 about it. And I'm going to get into that.
21 This is an example of merit. This is
22 Toprol. And this is the labeling. This is straight

1 from the labeling. This is based upon a clinical
2 trial where the primary endpoints were all-cause
3 mortality plus all-cause hospitalizations. And
4 essentially, this is – this is the figure that is in
5 the labeling. And this is your typical sort of forest
6 plot for the results for the endpoint of interest. In
7 this case it's mortality and some of the other non-
8 fatal events. And it's by a lot of different
9 subgroups. And subgroups can fool you, but
10 nonetheless, the arrow that is there is the result in
11 the U.S. and the non-U.S. And this was not an easy
12 decision for the medical review division when the
13 effect on mortality was virtually all outside of the
14 United States and what to make of it. But it was put
15 in the label and that's the way it was labeled.
16 So not only that, but there was a discussion
17 of this particular trial because this, interestingly
18 enough, this trial had significant findings and it was
19 stopped early for a significant mortality finding.
20 But nonetheless, you would have thought that maybe
21 during the course of the monitoring this might have
22 been identified that there was a U.S. versus a non-

1 U.S. issue but it wasn't. Anyway, there's been an
2 article about it and this is not necessarily – a lot
3 of people don't agree on how to deal with this and
4 it's a very difficult problem.
5 But just three weeks ago we had an advisory
6 committee on this particular topic. Some of you may
7 or may not have heard about this, but this is a
8 Clopidogrel competitor. And there was a study that
9 was published in the New England Journal of Medicine.
10 It was a multiregional study. And we went to the
11 advisory committee – Cardio Renal Advisory Committee
12 on July 28th, a few weeks ago, and essentially these
13 were the results for the comparison of clopidogrel
14 versus ticagrelor. And, you know, it looked like this
15 was a slam dunk with regard to the efficacy results.
16 But the question that we put to the advisory committee
17 was do you believe the difference in clinical outcomes
18 between the U.S. and the rest of the world was
19 attributable to the play of chance or a lot of other
20 reasons? And essentially, that's what the question to
21 the committee was.
22 And this study was called PLATO. A large

1 study, as you can see, 17,000 patients or so outside
2 the United States. About 1,400 patients inside the
3 United States. And these were what the effect sizes
4 were. And the committee kicked this around and
5 struggled with this. And one of the big issues was
6 concomitant onboard aspirin as a confounder, and
7 whether it was essentially being used differentially
8 in the different regions. And this is just a funnel
9 plot of the results of the various centers and who's
10 on the edge. Those boundaries, essentially, once
11 you're outside those boundaries this is not likely to
12 be a chance finding. It's more the chance finding.
13 So you can see where USA and Hungary and Poland and
14 Turkey are sort of around the boundaries. But
15 obviously, U.S. is the largest sample size here.
16 So the question given to the advisory
17 committee was what do you think? Do you think this
18 difference is the play of chance? Concurrent use of
19 aspirin or some other reason? And they didn't think
20 it was the concurrent use of aspirin. So they sort of
21 said you guys have a tough problem. Go deal with it.
22 And so they did not necessarily give us a bottom-line

1 on this.

2 And so that's only to say these are not easy

3 issues, interpreting foreign data where there's

4 heterogeneity in both effect size and on the safety

5 and the efficacy side. I believe a few years ago

6 coming to this committee was our anti-epileptics and

7 suicidality. And one of my colleagues presented the

8 medDRA analysis that we did, but interestingly enough

9 there was a suggestion that outside the United States

10 the suicidality was higher. The risk was higher

11 outside the United States. And coming after that

12 there was an article by Tom Loughren, Judy Racoosin

13 and Tariq Hamid – three other colleagues, Tom's

14 division director. And again, a similar message that

15 the side effect profile risk might be different inside

16 and outside the United States.

17 So this is not an unusual thing. What to

18 make of it and what not is – requires a lot of subject

19 matter specialty thought and whatnot. But it's just

20 to give you some idea of what's going on in other

21 areas and how it's being dealt with and thought about.

22 So here we are with ICH E5. Now, I believe

1 this background of paper guidance is in your – it's
2 available. I believe it's in the packet that was
3 given to the committee. But this thing was, like I
4 say, a joint effort of Japan, the United States, and
5 European Union. It was published in 1998 and it was
6 primarily motivated by the fact that how many times do
7 I have to duplicate a drug development program in your
8 region. It was essentially can we do one drug
9 development program and have the results apply to
10 Japan and the United States and Europe. And that was
11 the idea behind this. In terms of limiting the amount
12 of duplicative drug development.
13 And so this document was put out there and
14 essentially the key features of it was to establish a
15 framework so that you could use the results from
16 another regions and extrapolate those results to your
17 region. And there was the concept of bridging data.
18 So short of doing another clinical trial, could you do
19 something like pharmacokinetic, pharmacodynamic
20 studies or something on a surrogate that might bridge
21 the data from one region to another. So that was the
22 idea behind that.

1 And in this particular document was the idea
2 of classification of intrinsic and extrinsic factors.
3 The intrinsic factors essentially are those things
4 that go with the patient, and it could be their
5 genetic profile, their maleness, their femaleness, or
6 whatever; whether you have differential effects with
7 regard to the intrinsic factors that are related to an
8 individual. And then there was the extrinsic factors
9 associated with where the trial is done. In the
10 milieu, in the medical environment, or whatnot. And
11 what might heterogeneity be due to? It could be due
12 to any or both or some combination of these. So it
13 laid that out as a general framework.
14 But it also put a cap on how much additional
15 data a regulator could ask of a sponsor given that the
16 data was virtually all outside the United States and
17 you were still not comfortable with either believing
18 the result or you had no experience with that region
19 or that country or whatever. So it asked it out loud
20 for another clinical study to be requested, primarily
21 focused on the efficacy side, not on the safety side.
22 So, and I'll return to that in a moment.

1 So, at the time of its development back 10
2 years or so ago, it was trying to look at all the drug
3 development programs that had gone on in the past and
4 that somebody was trying to get into Japan or trying
5 to get into the United States after a program that had
6 been completed for Europe, what more did they have to
7 do short of doing a full drug development program?
8 But now in the future it's no more – it's no longer a
9 bridging. If I have a prospective plan, how do I
10 develop in 2010 the collection of studies that will be
11 acceptable to multiple regions? So it's more the idea
12 of multiregional studies that is coming in. And
13 that's what I'll get into because then about five or
14 six years after this guidance was on the street, then
15 there was a supplement called Questions and Answers.
16 And it clarified some of the points of ambiguity that
17 were in the original document. And it introduced the
18 idea of a multiregional trial for bridging.
19 And it also started to, but not really,
20 touch on the whole pharmacogenomic issue because
21 originally it was very interesting. ICH E5 began as a
22 – began as the Japanese saying we metabolize drugs

1 differently than the rest of the world so we need
2 different doses. And that was sort of the idea behind
3 that original sort of ethnic factors and the
4 acceptability of foreign clinical data. A review of
5 the study said it was more a difference in the study
6 designs result that were responsible for that
7 differential interpretation rather than intrinsic
8 factors itself. But nonetheless, here we are in a
9 pharmacogenomic world where some of that is actually
10 relatively relevant, particularly in terms of
11 metabolism of drugs and whatnot.
12 So E5 allows every region, meaning Europe,
13 the United States, Japan, and everybody who is not at
14 the table - Canada. We're getting into, you know,
15 India and Asia and other regulatory agencies. And the
16 general concept of if you feel the evidence is pretty
17 good except for the fact that there's some uncertainty
18 still left, you have the right to ask for another
19 study. And this has been asked for in psychiatry and
20 neurology. Tom Loughren's area and Russ Katz's area
21 has asked for additional studies, particularly on the
22 efficacy side. That's sort of because we didn't have

1 much experience with the trials being done in those
2 regions or those investigators or something along
3 those lines.
4 But so the question and answer piece of the
5 ICH E5 essentially laid out can I bridge my data in
6 another way? And the idea of this multiregional
7 clinical trial was introduced. And I'm not going to
8 go through it. You can read it yourself, but
9 essentially it says a multiregional trial for the
10 purpose of bridging could be conducted in the context
11 of a global development program designed for near
12 simultaneous worldwide registration. The objectives
13 would be to show that the drug is effective in the
14 region, meaning the United States or in Europe, and to
15 compare the results of the study between the regions
16 with the intent of establishing that the drug is not
17 sensitive to ethnic factors, whether they be intrinsic
18 or extrinsic factors. And the primary endpoint could
19 be maybe even defined somewhat differently in the
20 different regions depending on what their focus might
21 be.
22 And so from - this is still part of the

1 Question and Answer section of ICH E5. It sort of
2 says it could either be a standalone result. So if
3 you had a multiregional study and all the action as in
4 your region and you felt you believe that, that might
5 be good enough for you. But it may not be good enough
6 for another region if there was no action in their
7 region. On the other hand, if it is all, you might be
8 able to draw strings, if you will, from the treatment
9 effects in three different regions. They are all
10 reasonably the same and they all reinforce each other.
11 And that would be good enough also in other words. So
12 those were the two scenarios.
13 So, how have we applied this? Mostly in the
14 evaluation of multiregional studies. Not so much in
15 the evaluation of a single trial done in Russia, which
16 is not a multiregional trial, but there – there is
17 obviously a routine assessment now of the results
18 inside and outside the United States. And sometimes
19 after that evaluation is done we may request
20 additional study or additional data if the results are
21 in question. And that's actually addressed in the
22 original ICH E5. And it's primarily related to

1 safety. Not so much efficacy.
2 So let's say this is not a problem about
3 efficacy; it's a problem about having some concern
4 that the safety profile is not essentially
5 characterized well enough. And it may be that there
6 was some concern earlier on when this document was
7 being written that safety studies coming from Japan
8 were less useful to us because patients were not -
9 they would not volunteer that they were having an
10 adverse event. So you're underestimating the safety
11 profile. Or there may be other things that are going
12 on that might be some concern.
13 So the bottom-line here is additional
14 studies to meet the region's regulatory requirements
15 may be necessary, not a full blown development program
16 but another study. And it could be an open label
17 study. It could be a single cohort study. It could
18 be a safety study specifically addressing some
19 concerns. So this is the Section 3.24 that speaks to
20 the issue of under what circumstances might I want or
21 could I ask for another safety study. And it's
22 relevant to what you folks will probably talk about

1 this afternoon. So I'm not going to go through it.
2 Again, this is just saying if there is no efficacy
3 bridging study needed or if the efficacy bridging
4 study is too small of insufficient, you can ask for
5 some other stuff.
6 So anyway, I'm not going to - this is more
7 about what do we do in the future. And as we think
8 about how with the amount of foreign data that's
9 coming our way and everybody's way, this is a design
10 issue. How do you design your study so you think
11 about this prospectively rather than dealing with it
12 when you've been dealt the hand you've been dealt.
13 So my concluding remarks are the new areas
14 of clinical investigation that we have less experience
15 with will continue to be scrutinized closely and that
16 has a lot to do with our inspection strategies, how
17 comfortable we are with the investigative population,
18 the training, how the companies have trained these
19 folks the ability to be able to comply with protocols
20 and whatnot. So this is natural for studies in
21 regions where we have less experience to be
22 scrutinized a little more. And the options exist to

1 approve and ask for a safety study in the U.S. or to
2 label, as we did with metoprolol and some of the
3 others, label with results that may not be applicable
4 but put your hands up and say I don't know what to
5 make of it but I'm just informing you about these
6 results being somewhat different.
7 And that's it for me. So I'd be willing to
8 take some questions if you have some.
9 **Clarifying Questions**
10 MR. MULLINS: I have a question.
11 DR. SCHULTZ: Dr. Mullins?
12 MR. MULLINS: Does the FDA have any
13 standards for third-party reporting overseas?
14 DR. O'NEILL: What do you mean by third-
15 party?
16 MR. MULLINS: Third-party reporting. In
17 essence, we had a statement made earlier by the
18 sponsor that for discontinuations, family members were
19 reporting on the rationale for discontinuation.
20 DR. O'NEILL: Well, you know, that's part of
21 the protocol. It's not a requirement. I mean, that's
22 part of the protocol and who's given the

1 responsibility for, let's say, follow-up. One of the
2 larger issues in any clinical trial is what do you do
3 with someone who withdraws from a clinical trial and
4 how do you follow them up? That's a big ticket item.
5 It's a big ticket item in the neuropharm area. It's a
6 big ticket item in a lot of areas where what does the
7 protocol say about after you go off of exposure. Did
8 you sign up for six months? And is there a mechanism
9 to go and find out something about you while you've
10 gone off of exposure? So that's a problem in this
11 country.
12 In fact, we just had a -- the short answer
13 to your question is there's no -- there's no law.
14 There's no guidance. There's no place we can go and
15 say thou shall do this.
16 MR. MULLINS: Well, there's a lot of
17 subjectivity. The reason I asked that, with third-
18 party reporting there's a possibility for bias of
19 inaccuracies as far as reporting of adverse events or,
20 you know, while discontinuation --
21 DR. O'NEILL: Well, yes and no. I mean, we
22 could probably talk about this. Third-party might be

1 a CRO. And if you were in a blinded study versus an
2 unblended study that might be an issue. There was a
3 recent large public discussion about the record study
4 for Avandia for which that was an open label study and
5 the concern was whether some events were being sent to
6 an adjudication committee because investigators knew -
7 - because it was an unblinded study they might
8 differentially send forward an outcome to be
9 adjudicated by a blinded committee.
10 So there are many different variations on
11 this theme. And I don't know this data. I don't know
12 this protocol well enough to address this question
13 down in the weeds. But all I'm saying is that's part
14 of what you need to be thinking about in terms of the
15 believability or the credibility of the study or the
16 processes that were put in place to do that kind of
17 collection.
18 MR. MULLINS: Thank you.
19 DR. SCHULTZ: I think at this time we'll
20 proceed with the FDA presentation. Dr. Li.
21 DR. WAPLES: Actually, since there's only
22 about five minutes left, do we want to maybe break for

1 lunch and then just continue with the FDA after the
2 Open Public Hearing?
3 MS. SCHULTZ: That would be fine. At this
4 point we'll break for lunch. The members are reminded
5 not to discuss any information about today's meeting
6 during the lunchtime. And we'll reconvene at 1
7 o'clock. Should we try 1 o'clock instead of 1:15?
8 DR. WAPLES: Yes, please.
9 MS. SCHULTZ: We'll reconvene at 1 p.m.
10 (Whereupon, at 12:10 p.m., a luncheon recess
11 was taken.)
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2 A F T E R N O O N S E S S I O N

3 (1:11 PM)

4 **Open Public Hearing**

5 DR. SCHULTZ: All right. Thank you. If

6 everyone could take your places we'll begin the

7 afternoon.

8 What we'd like to do now is proceed with the

9 Open Public Hearing.

10 Both the Food and Drug Administration and

11 the public believe in a transparent process for

12 information gathering and decision-making. To ensure

13 such transparency at the Open Public Hearing session

14 of the Advisory Committee meeting, the FDA believes

15 it's important to understand the context of an

16 individual's presentation. For this reason, FDA

17 encourages you, the open public hearing speaker, at

18 the beginning of your written or oral statement, to

19 advise the Committee of any financial relationship

20 that you may have with the sponsor, its product, and

21 if known, its direct competitors. For example, this

22 financial information may include the sponsor's

1 payment of your travel, lodging, or other expenses in
2 connection with your attendance at this meeting.
3 Likewise, FDA encourages you at the
4 beginning of your statement to advise the Committee if
5 you do not have any such financial relationships. If
6 you choose not to address this issue of financial
7 relationships at the beginning of your statement, it
8 will preclude you from speaking.
9 The FDA and this committee place great
10 importance in the open hearing public process. The
11 insights and comments provided can help the agency and
12 this committee in their consideration of the issues
13 before them. That said, in many instances and for
14 many topics there will be a variety of opinions. One
15 of our goals today is for this open public hearing to
16 be conducted in a fair and open way where every
17 participant is listened to carefully and treated with
18 dignity, courtesy, and respect. Therefore, please
19 speak only when recognized by the chair. Thank you
20 for your cooperation.
21 At this time we'll invite the first open
22 public hearing speaker.

1 (Whereupon, a technical difficulty occurred
2 and continued throughout the Open Public Hearing due
3 to sound system problems.)
4 DR. WAPLES: OPH number two.
5 MS. SHAFFER: Good afternoon. My name is
6 Terry Shaffer from St. Louis, Missouri. If it was not
7 for Vivitrol I would not be here today at this
8 hearing. I feel that I would have lost my son to
9 heroin addiction. I have attended (inaudible)
10 friends' funerals from overdosing. Young men under
11 (inaudible) their parents (inaudible) after my son
12 overdosed on heroin, he was placed on Vivitrol for 13
13 months. He is now high on life.
14 He will graduate from college with a
15 bachelor of science in construction management in
16 December of this year. This is (inaudible) today
17 (inaudible) he was given (inaudible) heroin. Without
18 this form of medication I do not feel that I
19 (inaudible) would not be able to get high. Time was
20 needed. Protection is needed. He received this month
21 by month. I am a nurse and I gave him these
22 injections monthly.

1 I was able to travel to his college every
2 four weeks. I (inaudible) each injection (inaudible)
3 insurance policy he was able to (inaudible) we were
4 very fortunate that our insurance (inaudible)
5 Vivitrol; it was not easy. I continue to push
6 (inaudible) covered. Our (inaudible) offered nothing.
7 My son thought Vivitrol was a tool to give the patient
8 time to achieve and maintain addiction remission. He
9 is now able to think and make (inaudible) choices. He
10 felt (inaudible) cravings and created a safety net to
11 protect him. Vivitrol made it possible (inaudible)
12 receive treatment, participation without jeopardizing
13 his schooling or his job (inaudible) first time in
14 years that he knows the sun is shining (inaudible) my
15 son is truly an addiction survivor
16 DR. WAPLES: Thank you. OPH number three.
17 MR. VOLLER: Good afternoon, ladies and
18 gentlemen. My name is T.J. Voller. My travel
19 accommodations were provided by (inaudible). I am an
20 addiction survivor. Today I would like to tell you
21 about Vivitrol (inaudible) saved my life. To give a
22 bit of background on myself, I'm 29 years old from

1 (inaudible) Massachusetts. I come from a stable, two-
2 parent family home (inaudible) at the age of 22 I
3 became a full-time opiate (inaudible) $300 a day
4 heroin habit.
5 I was very lucky to be successful in my
6 profession at a very young age (inaudible) because
7 (inaudible) five years (inaudible) habit. On October
8 13, 2006, my life was forever irrevocably changed. My
9 father, who was also my best friend (inaudible) my
10 successful career (inaudible) I had no savings
11 (inaudible) I don't like talking about this, but I
12 need to illustrate (inaudible).
13 In October of 2007, I went to my first detox
14 (inaudible) process in and out of detox and rehabs
15 until December of 2009. I tried every imaginable
16 (inaudible) but the result was always the same. I
17 will admit my disease (inaudible) under the control
18 for two to three months and then I would relapse.
19 In December of 2009, after spending
20 approximately $15,000 in treatments, I found myself in
21 a familiar situation, broke and (inaudible) while I
22 was in (inaudible) I really didn't know much about

1 Vivitrol (inaudible) so in the first week of January
2 of this year, I received my first injection of
3 Vivitrol and have been addiction free ever since.
4 I'd like to tell you how my life has changed
5 (inaudible) saved my life. I can tell you now I have
6 life. I firmly believe that I have a life because of
7 Vivitrol (inaudible) my success (inaudible) crippling
8 cravings stopped me from doing anything, stopped me
9 from being a son, stopped me from being a brother
10 (inaudible) I'm full time enrolled in college. I have
11 a full-time job and I believe if it weren't for
12 Vivitrol, I would still be stuck in that same viscous
13 cycle over and over and over again.
14 I truly believe this drug saves lives. I
15 believe it saved my life. I've seen it save other
16 people's lives. I really -- I appreciate having these
17 hearings (inaudible) I'm a living, breathing example
18 that this drug works. Thank you very much.
19 DR. WAPLES: Thank you. OPH number four.
20 MS. SIMPSON: My name is Kimberly and I am
21 19 years old. I live just outside of St. Louis and I
22 am really excited to be here to share my story. I

1 actually (inaudible) to be here (inaudible) my father
2 and grandfather used heroin together. My grandfather
3 had a heroin overdose in his early forties. At 15 I
4 tried drinking alcohol and hanging around with a guy
5 in my neighborhood who introduced me to heroin
6 (inaudible) my life spun out of control. My family
7 (inaudible) seeing in me so I left home (inaudible)
8 overdose (inaudible) I got pregnant at 16 and begged
9 my mother and grandmother to take me back. I was
10 scared and didn't have anywhere to go.
11 They took me back if only I did not use
12 heroin (inaudible) two months after my daughter was
13 born. I then (inaudible) after that my mother
14 (inaudible) she had found a treatment center that
15 (inaudible) I had never heard of this medication
16 (inaudible) I wasn't sure about taking medicine to
17 treat my addiction (inaudible) heroin and after a few
18 weeks (inaudible) an entire month. I didn't have to
19 take a pill every day.
20 While on Vivitrol, I did not take heroin no
21 matter what kind of (inaudible) I was exposed to. I
22 know I was protected and my mother and her mother felt

1 very reassured that they did not need to watch me
2 swallow the pill (inaudible) told (inaudible) I am now
3 (inaudible) my mother, who was very faithful
4 (inaudible) day in and day out even on days when she
5 got very few hours of sleep between shifts. My
6 insurance company paid for it and now I am getting
7 ready for the fourth shot. I have been on Vivitrol
8 for a whole year. I (inaudible) twice a week for
9 counseling and random drug testing.
10 Thanks to Vivitrol (inaudible) my life has
11 changed. I am back in school. My legal problems
12 appear (inaudible) my progress (inaudible) next few
13 months I will be (inaudible) get my 15-month-old
14 daughter, Kailyn, back (inaudible) a mother that she
15 would be proud of (inaudible) heroin overdose
16 (inaudible) that could have been my life.
17 I am grateful for the opportunity to share
18 my story (inaudible) and I hope that many young people
19 will (inaudible) for addiction (inaudible).
20 DR. WAPLES: Thank you. OPH number five.
21 MR. COFFEY: Thank you for the opportunity
22 to speak here today on behalf of Faces and Voices of

1 Recovery. My name is Bob Coffey (inaudible) long-term
2 recovery. Long-term recovery for me means that I've
3 been drug and alcohol free for almost 20 years
4 (inaudible) friends and allies (inaudible) pathways to
5 recovery, including medication -- including
6 medication-assisted recovery.
7 We're a national organization of individuals
8 and organizations (inaudible) individuals, families
9 and society. However, left untreated (inaudible)
10 catastrophic in terms of loss of employment, failure
11 at personal relationships, multi-generational
12 (inaudible) trauma, healthcare costs, death and
13 (inaudible) system. Addiction (inaudible)
14 prescription drugs (inaudible) public health crisis
15 (inaudible) increase over 10 years (inaudible)
16 prescription pain medications.
17 In 2008, prescription pain medications was
18 the second most common type of illicit drug use in the
19 United States for people seeking recovery from pain
20 medicine (inaudible) help them address their addiction
21 to (inaudible) all pathways (inaudible) pathways
22 (inaudible) medications (inaudible) recovery

1 (inaudible) doctors and other healthcare professionals
2 (inaudible) work with individuals to create a
3 treatment and recovery plan that's (inaudible) person.
4 These plans (inaudible) individuals
5 (inaudible) recovery. More -- more medications are
6 needed to effectively treat addiction in the growing
7 public health crisis (inaudible) today there are only
8 four FDA-approved medications on market to treat
9 alcohol dependence and (inaudible) patients to treat
10 opioid dependence.
11 In contrast, there are more than (inaudible)
12 medications for HIV/AIDS. We know that this product
13 will be the only agonist or non-addictive therapy
14 (inaudible) recovery since there is a such a low level
15 of (inaudible) therapies (inaudible) recovery
16 (inaudible) on the market (inaudible) medication
17 (inaudible) multiple options. Patients (inaudible)
18 should be able to select the (inaudible) for example,
19 agonist or non-agonist, injection or oral (inaudible)
20 medications available (inaudible) for care (inaudible)
21 of the lives of individuals, their families and
22 communities.

1 Thank you again for the opportunity to be
2 here today. Many Americans like me are living
3 productive lives in long-term recovery (inaudible)
4 policy makers to make it possible for every American
5 to recover from addiction and alcohol(inaudible) thank
6 you.
7 DR. WAPLES: Thank you. OPH number six.
8 MR. MENZIES: My name is Percy Menzies. I'm
9 the president (inaudible) Assisted Recovery Center
10 (inaudible) I have received funding from (inaudible)
11 and my travel was paid by (inaudible) because of my
12 vast experience in having (inaudible) I have worked
13 for a pharmaceutical company (inaudible) 1984
14 (inaudible) heroin addiction (inaudible) passion for
15 this medication because the pharmacies are very
16 intrigued (inaudible) brain (inaudible) medication and
17 10 years ago I left the pharmaceutical industry,
18 opened a clinic (inaudible) great medication
19 (inaudible) medications (inaudible) significant
20 (inaudible) made a huge difference.
21 For the first time the issue of compliance
22 (inaudible) in the country to use it and great success

1 (inaudible) very important because(inaudible) for
2 healthcare professionals and other professional
3 (inaudible) people who are (inaudible) and Vivitrol,
4 the results have been amazing (inaudible) first time
5 (inaudible) medication for (inaudible) patients with
6 (inaudible) using medications that are (inaudible) 40
7 patients right now (inaudible) makes a lot of sense
8 because (inaudible) opioids (inaudible) I think we
9 need something desperately (inaudible) significantly
10 enhances the outcomes (inaudible) this medication
11 (inaudible). Thank you (inaudible) thank you.
12 DR. WAPLES: Thank you. Next, OPH number
13 eight.
14 MS. MACK: My name is Christine Mack
15 (inaudible) son Brandon. Brandon was intelligent
16 (inaudible) man. Brandon was severely addicted to
17 heroin. He had an (inaudible) from his first
18 injection at 16 years old. We've been through various
19 treatment options over the years, including Methodone
20 Suboxone (inaudible) in October 2008, I placed Brandon
21 in an inpatient rehab facility. I had to take a loan
22 against my 401k (inaudible) to do so (inaudible) post-

1 rehab he was placed in halfway house in Bloomington,
2 North Carolina (inaudible) that house and several
3 others.
4 I learned more about halfway houses and
5 rehab facilities (inaudible) the short story is that
6 Brandon ended up on (inaudible) Vermont. Brandon is
7 six foot, three inches tall (inaudible) six months of
8 strung out (inaudible) and he weighed less than 120
9 pounds. Brandon (inaudible) last summer (inaudible)
10 Brandon agreed to take Vivitrol injections monthly.
11 Vivitrol has been a turning point in Brandon's life,
12 my life and the life of our family.
13 Very simply put, it works. Brandon has held
14 a full-time job since September 2009 in an
15 installation program that repairs life-saving systems
16 in Richmond hospitals, schools and commercial
17 buildings. He's been recognized with a skill
18 (inaudible) and is living in his own apartment. He
19 takes public transportation daily. He works
20 (inaudible) court costs. His goal is to earn his
21 driver's license again. He's gone from being homeless
22 on the streets, on the short track to an early death

1 from heroin, malnutrition and illness to being a
2 (inaudible) member of U.S. society.
3 He feels good about himself (inaudible)
4 years. He took injections for one year and Vivitrol
5 has given me my son back. Vivitrol works (inaudible)
6 Brandon was invited here today and he (inaudible)
7 come. I'm delighted to tell you he couldn't get off
8 work. He would want you to know that he lives one day
9 at a time. So do I. So do his brothers, his
10 employers, his friends (inaudible) I'm not naïve. I
11 have finally got some hope though (inaudible) I will
12 do everything in my power (inaudible) my son.
13 I ask you to consider (inaudible) United
14 States. I can't give you statistics or percentages and
15 (inaudible) but I ask you to think about drugs as a
16 foundation for crime. Obviously there's an illegal
17 drug trade. There's also armed robbery (inaudible)
18 auto theft, prostitution, kidnapping (inaudible)
19 domestic violence, child and elder abuse (inaudible)
20 50 percent of (inaudible) court system, overcrowding
21 in our prisons and more importantly (inaudible) huge
22 portion of (inaudible) abuse and addiction. You

1 already know, you already know that substance abuse
2 affects all society (inaudible) socio-economic levels
3 (inaudible) physicians, our attorneys, judges,
4 politicians, entertainers.
5 Drugs are present and pervasive (inaudible)
6 every minute of every day (inaudible) Vivitrol
7 (inaudible) insurance companies don't have feelings.
8 Most of them do not cover this valuable treatment.
9 That's been our experience. Injections are expensive
10 and cost-prohibitive for most families. We need your
11 support. We need your help. Please make this
12 medication available (inaudible) there is so little
13 support for (inaudible) in the United States and it's
14 a giant (inaudible) we cannot continue to ignore this
15 giant (inaudible) please don't (inaudible) this is
16 (inaudible).
17 DR. WAPLES: Thank you.
18 MS. MACK: Thank you for the opportunity.
19 DR. WAPLES: Thank you. OPH number nine.
20 DR. FISHMAN: Hello, my name is Dr. Michael
21 Fishman. I'm from Atlanta, Georgia. I'm the director
22 of Talbot Recovery (inaudible) in Atlanta. I have

1 (inaudible) financial (inaudible) paid for my travel.
2 I also have 21 years (inaudible) I've been practicing
3 addiction medicine for the past 20 years (inaudible)
4 overdose is common. In my whole experience Vivitrol
5 has helped to save many lives.
6 I have treated at least 100 patients with
7 Vivitrol over the past four years (inaudible) program
8 (inaudible) the opioid cravings (inaudible) many of
9 the young adults don't think or they react.
10 Unfortunately, in the Atlanta area it's very easy to
11 get heroin (inaudible) I have seen patients call their
12 dealers, come on campus. I have been in a program
13 where a boyfriend bought a girlfriend a shot of heroin
14 and she overdosed (inaudible) I have seen people
15 impulsively run off without thinking (inaudible) it's
16 incredible to watch in your own front lines
17 (inaudible) with Vivitrol on board, these patients
18 (inaudible) my experience, most of them (inaudible)
19 second to think before they run off (inaudible) many
20 of these patients are at high risk for overdose
21 because their tolerance has decreased and they
22 (inaudible) want to use the same dose they did before

1 treatment.
2 I can’t tell you how many funerals I’ve gone
3 to with grieving parents (inaudible) 18, 19, 20-year-
4 old (inaudible) in my experience Vivitrol (inaudible)
5 increase the cravings. I have seen people (inaudible)
6 get better exponentially. I firmly believe that it
7 helps (inaudible) over time. I also have experience
8 treating professionals. Many professionals
9 (inaudible) especially in anesthesia or (inaudible)
10 I’ve seen (inaudible) I have seen many people addicted
11 (inaudible) including alcohol. If the drug of choice
12 is available, I’ve seen people use that drug
13 (inaudible) to get out of withdrawal. With Vivitrol
14 you don’t have that problem.
15 Also with professionals, and especially
16 anesthesiologists (inaudible) specialty (inaudible)
17 opioid addicts, Vivitrol is a great way to help them
18 get back into medicine (inaudible) professionals use
19 (inaudible) none of that with Vivitrol. I’ve seen
20 (inaudible) DIGITAL AUDIO STARTS HERE effects from
21 Vivitrol, the most common is some pain at the
22 injection site. Otherwise, in my experience with it

1 it's well tolerated and the patients are able to
2 settle down into treatment and do the work that they
3 need instead of focusing and obsessing on using
4 opiates.
5 I strongly urge this committee to consider
6 Vivitrol as an indication for opiate addiction. It's
7 a valuable tool in our field. It's saving lives. I
8 hope you hear the passion in my voice. I don't like
9 to go to these funerals, and Vivitrol is absolutely
10 saving lives.
11 Thank you.
12 DR. WAPLES: Thank you. OPH number 11.
13 DR. BERGER: Good afternoon, Madam Chair and
14 distinguished members of this FDA Committee. My name
15 is Dr. Tom Berger. I'm executive director of the
16 Veterans Health Council for Vietnam Veterans of
17 America. I have absolutely no financial relationship
18 of any sort with Alkermes or any other pharmaceutical
19 company.
20 Just last week the popular news magazine,
21 Time, reminded the American people that our country
22 faces a new drug crisis. Addiction prescription

1 painkillers. However, I'd like to remind everyone
2 sitting in this room that 2010 marks the ninth
3 straight year of America at war, concerns with
4 military and veterans' health issues, another
5 addiction challenge is beginning to resurface as our
6 military tries to curb the volume of narcotics given
7 to troops. As the number of prescriptions for
8 painkillers and instances of drug abuse continue to
9 soar according to Pentagon data and recent
10 congressional testimony. Military doctors wrote
11 almost 3.8 million prescriptions for pain relief for
12 service members last year. That's more than four
13 times the 866,773 doses handed out in 2001 according
14 to Pentagon data.
15 Here are some of the resulting issues that
16 face our soldiers and veterans related to addiction
17 and abuse of pain medications. One in four soldiers
18 admitted using prescribed drugs, mostly pain
19 relievers, in the 12 months prior to a Pentagon survey
20 in 2008. Fifteen percent said they'd abused drugs in
21 the 30 days before that survey. Pentagon records also
22 the abuse of prescription drugs is higher in the

1 military than among civilians. Five percent of
2 civilians reported abusing prescription drugs in a 30-
3 day period in 2007 compared to 11 percent of military
4 personnel.
5 Military officials and analysts say the
6 increase in the use of narcotic pain medication
7 reflects the continuing toll on ground troops fighting
8 in Iraq and Afghanistan, often through more than one
9 combat deployment. In addition to those that are
10 wounded, large numbers of soldiers and marines develop
11 aches and strains carrying heavy packs, body armor,
12 and weapons over rugged and mountainous terrain.
13 Furthermore, our veterans seek relief from the chronic
14 pain that accompanies their war wounds and opioid
15 addiction, as in prescription drug addiction to pain
16 killers, such as oxycontin, Demerol, Dilaudid,
17 Vicodin, and codeine. And they're available to our
18 veterans at virtually no cost through the VA.
19 (Inaudible.) for just a second the issue of
20 pain with (inaudible) of mental illness among our
21 veterans. Among 100,000 RIF/OEF troops first seen at
22 VHA facilities between 2001 and 2005, 25 percent

1 received mental health diagnoses -- excuse me -- and
2 substance use disorder including opioids.
3 The medication being considered here today
4 is very important for the veterans in our military
5 communities. The drug has already been tested in
6 opioid-dependent parolees and probationers in clinical
7 trials. Based on the results seen to date I'd like to
8 make these key observations. I think it's fair to
9 expect that the impact on reducing opioid use could
10 have significant economic outcomes for everyone
11 involved in terms of the cost of recidivism. And one
12 of the key points about naltrexone is that it is not a
13 substitution of one addictive substance for another.
14 I'd like to make it clear that veterans with
15 substance abuse disorders face significant barriers
16 for treatment. Now, I hope that you will consider
17 seriously the drug that's before you for your
18 consideration today. I'm here today to say that our
19 veterans with substance abuse disorders need more
20 treatment options.
21 Thank you very much.
22 DR. WAPLES: Thank you. Would the last OPH

1 presenter please come forward.

2 MS. GALLBREATH: Good afternoon. My name is

3 Laura Gallbreath, director of Integrated Health and

4 Wellness Promotion at the National Council for

5 Community Behavioral Health Care. I received no

6 financial support from Alkermes and no support for

7 travel here today.

8 The National Council, we are a non-profit

9 organization representing about 1,600 community

10 behavioral health provider organizations across the

11 country providing treatment and rehabilitation to

12 individuals with mental illnesses and addictive

13 disorders. The National Council and our members

14 represent the public sector safety net for millions of

15 individuals with severe and persistent mental illness

16 and addictions, and we provide a wide array of

17 recovery and person-centered support services and

18 treatment. The National Council feels strongly that

19 pharmaceutical treatments for opioid dependence is an

20 important area of research and development for the

21 FDA.

22 Earlier today, the Substance Abuse and

1 Mental Health Services Administration unveiled the
2 results of the latest national survey on drug use and
3 health survey. This annual survey, as you may know,
4 is the largest of its kind and it's the government's
5 primary vehicle for determining how many people are
6 abusing illegal drugs, pharmaceuticals, alcohol, and
7 tobacco.
8 While we are pleased to hear that the use of
9 cocaine among those aged 12 and older has declined by
10 about 30 percent since 2006, the sad news is that non-
11 medical use of prescription drugs, including opioids,
12 has risen in the past year. Medication assisted
13 treatment is an increasingly vital option that
14 includes the use of medication along with counseling
15 and other supports. We believe that treatment which
16 includes medication are of high value for opioid
17 addiction as medication allows individuals to regain a
18 normal state of mind free of highs and lows and can
19 help really reduce problems of withdrawals and
20 cravings.
21 And we believe medication-assisted treatment
22 gives patients and their providers a chance to manage

1 their addiction and focus on the work needed to
2 support long-term recovery.
3 This morning's study also showed that a vast
4 disparity exists between the number of people needing
5 specialized treatment for substance abuse problems and
6 the number of people who actually receive it. It was
7 startling that according to the survey, 23.5 million
8 Americans aged 12 or older -- that's about 9 percent
9 of the population -- needs special treatment for a
10 substance abuse problem, but only 2.6 or roughly l1
11 percent of them receive treatment. The addition of
12 pharmacotherapy treatments creates a solution likely
13 to bring more patients in for treatment. Since more
14 patients are presenting for treatment, not only is
15 there an advantage from the direct benefits of the
16 drug, but the advantage of being able to treat
17 patients who otherwise wouldn't have been seen.
18 Opioid dependence carries a very powerful
19 stigma, and removing the stigma of opioid dependence
20 is critical to helping people receive proper care. A
21 key part of achieving that goal is wider recognition
22 that opioid dependence is a medical issue and that a

1 variety of FDA approved treatments are available.
2 Lastly, I want to stress the co-morbidity of
3 opioid addiction and mental illness. Drug addiction
4 is a complex brain disease and occur in some of the
5 same brain areas as other mental disorders, such as
6 depression, anxiety, and schizophrenia, and is really
7 an area that could use more attention by the FDA in
8 terms of exploring some of the co-morbidities between
9 addiction and mental health conditions.
10 Lastly, I just want to thank you for the
11 valuable role that you play in evaluating drug safety
12 and efficacy, and we believe that as health care
13 reform creates more opportunities in terms of access
14 to specialty substance abuse treatment, that we want
15 to be able to assure that a broad array of treatment
16 options are available to patients.
17 Thank you very much.
18 DR. WAPLES: Thank you.
19 DR. SCHULTZ: The open public hearing
20 portion of this meeting has now concluded and we will
21 no longer take comments from the audience.
22 The Committee will now turn its attention to

1 address the task at hand -- the careful consideration
2 of the data before the committee, as well as the
3 public comments.
4 First, we'll need to finish up some of the
5 FDA presentations that we were not able to complete
6 this morning. So I'd like to invite Dr. Skeete to
7 finish up.
8 DR. SKEETE: Hello, again. My name is
9 Rachel Skeete. I'll just remind you. I'm a clinical
10 reviewer with the Division of Anesthesia and Analgesia
11 Products.
12 When we left off, we left off at the end of
13 the discussion of the clinical pharmacology data by
14 Dr. Nallani. Dr. Nallani, thank you for your
15 presentation.
16 We'll now focus on Study 13, the placebo-
17 controlled efficacy trial. Since much of the study
18 design was described already, I'll simply point out
19 that it was conducted in two parts. Part A was a
20 double-blind placebo-controlled portion, and Part B is
21 ongoing and is an open label 12-month extension of
22 Study 13. The submission contains only efficacy data

1 from Part A which has been completed.
2 The naloxone challenge test was described by
3 Dr. Ehrich earlier today. I'll give a little more
4 information on the test in brief for those who might
5 not be familiar with it. It consists of injecting a
6 low dose of naloxone, which is another opioid
7 antagonist, either subcutaneously or intravenously.
8 In a person with physical dependence on opioids, this
9 results in a precipitation of detectible signs and
10 symptoms of withdrawal. If someone has a positive
11 naloxone challenge, they are considered physically
12 dependent on opioids. So for the study it serves as
13 both a safety and efficacy measure.
14 In terms of safety, it is an attempt to
15 avoid giving a long-acting opioid antagonist to
16 someone on opioids and potentially precipitating
17 withdrawal. For efficacy, it is a measure of
18 physiologic dependence so that when the test is
19 positive the patient is considered to have relapsed or
20 to have failed the study.
21 The primary efficacy outcome was a response
22 profile based on each patient's rate of opioid-free

1 weeks during the last 20 weeks of a 24 week double
2 treatment -- double-blind treatment period. A one-
3 month grace period was incorporated during which
4 opioid use, if it occurred, was not considered in the
5 analysis. This was to allow time for patients to
6 engage in treatment and with the understanding that
7 some patients might test the blockade early on in
8 treatment.
9 We are asking the Committee to consider the
10 applicability of the efficacy findings to the U.S.
11 opioid-dependent population and here are describing
12 key baseline characteristics for the Russian opioid-
13 dependent clinical trial population. I'll also make
14 note of data for the U.S. opioid-dependent population
15 at large when data are available. There were 250
16 subjects enrolled in the study -- 126 in the Vivitrol
17 arm and 124 in placebo. The population was young,
18 about 30 years of age on average. They were
19 predominantly male, about 90 percent in each arm were
20 male, and almost exclusively white; save for two Asian
21 subjects in the Vivitrol arm, all other participants
22 were white. The U.S. opioid-dependent population is

1 more varied with respect to ethnicity and gender.
2 In this table our selected baseline
3 characteristics related to opioid dependence.
4 Subjects in the Vivitrol arm overall had a shorter
5 history of opioid dependence. When you look at the
6 less than five year category you can see that more
7 subjects in the Vivitrol arm fall into the shortest
8 duration category. In contrast, more placebo patients
9 are represented in the category of longest duration;
10 that is a more than 15 year opioid-dependence history.
11 We did explore the impact of this characteristic
12 through subgroup analysis and found that it did not
13 have an impact on the efficacy results.
14 In both the Vivitrol and placebo arms, the
15 majority of patients received inpatient detoxification
16 for more than 14 days. And the majority,
17 approximately 90 percent in each arm, used heroin in
18 the 30 days prior to the baseline assessment. As Dr.
19 O'Brien described earlier, the U.S. opioid-dependent
20 population on the other hand is more likely to meet
21 criteria for dependence on narcotic analgesics.
22 According to 2008 data from the National

1 Survey on Drug Use and Health, which I'll also refer
2 to as NSDUH data, approximately 1.7 million people met
3 criteria for dependence on narcotic analgesics, and
4 about 300,000 met criteria for dependence on heroin.
5 This table shows a disposition for patients
6 in the study. And this has already been described
7 earlier in Alkermes' presentation. Dr. Li will now
8 present the primary efficacy results from Study 13.
9 **Presentation of Efficacy of Vivitrol for Opioid**
10 **Dependence**
11 DR. LI: Thank you, Dr. Skeete.
12 As Dr. Skeete has mentioned, the primary
13 efficacy outcome was the response profile based on
14 each patient's rate of opioid-free weeks from week 5
15 to week 24. A patient had an opioid-free week only if
16 the urine drug test was negative and there was no
17 self-reported opioid use in the past week. All
18 missing drug tests, including those due to patients
19 dropping out of the study were imputed as positive for
20 the efficacy analysis. The response profile was
21 generated for each treatment group by calculating the
22 cumulative percent of patients achieving each rate of

1 opioid-free weeks. The response profiles were
2 compared using the lender written test.
3 This graph shows cumulative percent of
4 patients who dropped out before each weekly visit from
5 baseline to week 24 for each treatment group. The
6 horizontal axis denotes the Vivitrol week. The
7 vertical axis denotes the cumulative percent of
8 patients who dropped out before each weekly visit.
9 Patients received their first dose at baseline and
10 then the second dose at week four. We say that
11 patients in the placebo group dropped out much faster
12 than the Vivitrol group during the first four weeks
13 before receiving the second dose. Approximately, 36
14 percent of the patients in the placebo group and 13
15 percent of the patients in the Vivitrol group dropped
16 out before week 5. The dropout pattern was similar
17 between the two groups after week 4. The primary
18 analysis was based on data from week 5 to week 24.
19 For patients who dropped out before week 5, all the
20 urine tests in the last 20 weeks were considered as
21 positive.
22 The response profiles are displayed in this

1 figure. The applicant has discussed it in detail and
2 we don't disagree with their results. Of great
3 interest to the Division is a percentage of patients
4 who achieved complete abstinence from opioid use. The
5 right end of the graph shows that the Vivitrol group
6 had a larger percent of patients who achieved the 100
7 percent opioid-free weeks than the placebo group. The
8 percentage of patients who achieved complete
9 abstinence from opioid use during the last 20 weeks
10 are showing in the table. Twenty-three percent of the
11 patients in the placebo group and 36 percent of the
12 patients in the Vivitrol group achieved complete
13 abstinence. The difference was significant as
14 evaluated using a Chi-Square Test.
15 The treatment effect was consistent for
16 subgroups of sex, age, durations of opioid dependence,
17 and the pre-study detoxification.
18 Now I'm returning the podium to Dr. Skeete.
19 DR. SKEETE: Thank you, Dr. Li.
20 To close out the efficacy discussion I'll
21 briefly mention that the applicant also evaluated
22 secondary endpoints, including study retention,

1 opioid-craving score, and percent of self-reported
2 opioid-free days, which were discussed during
3 Alkermes' presentation. Note that the Study Endpoints
4 and Labeling Development team (SEALD) has raised
5 concerns about the validity of the instruments used in
6 the craving assessments. And secondly, that self-
7 reported opioid-free days have been folded into the
8 primary analysis.
9 The safety data will be the focus of the
10 remainder of the talk. Safety data were provided and
11 opioid-dependent subjects who were in Study 13
12 represented in the -- your left-most circle of the
13 diagram. Opioid-dependent subjects also come from
14 Study 6 and the extension study of Study 6, the area
15 of overlap in the diagram. These are the opioid- and
16 dually-dependent subjects who I mentioned were
17 included in the original application. Safety data
18 were submitted for the alcohol-dependent population,
19 which is represented in the larger gray circle. Most
20 of these data were reviewed in the original NDA.
21 These were data from Study 2 and Study 3, and the two
22 extensions of Study 3, as well as data again from

1 Study 6, which primarily enrolled alcohol-dependent
2 subjects.
3 Alcohol-dependent subjects represent the
4 majority of the patients in the safety database.
5 Taken together, all these studies make up the combined
6 population. Finally, available post-marketing data
7 for adverse events of special interests were also
8 submitted.
9 The framework that we use for the review of
10 safety centered on three questions. The first was,
11 what new safety information can be garnered from this
12 expanded safety database resulting from the addition
13 of opioid-dependent subjects. In other words, are
14 there perhaps new adverse events that we may be able
15 to identify with this larger pool safety database?
16 Secondly, what are the indication-specific
17 findings of interest? Meaning that the safety profile
18 for the alcohol-dependent population is considered to
19 be fairly well characterized, but what might be
20 findings that are specific to opioid-dependent
21 subjects?
22 And thirdly, what do we learn from comparing

1 U.S. versus Russian opioid-dependent subjects on
2 Vivitrol? It has become evident that the rate of
3 adverse event reporting was distinctly lower in the
4 Russian study. So what can we learn from comparing
5 the safety data available in the opioid-dependent and
6 dually-dependent U.S. clinical trial population
7 available from Study 6?
8 This table provides a description of studies
9 included in a safety database, and these have already
10 been described earlier today.
11 These are the safety assessments that were
12 used during the studies.
13 This table represents the extent of exposure
14 to Vivitrol. Eight hundred fifty patients in the
15 safety database received at least one dose of
16 Vivitrol. Two hundred eighty eight had at least one
17 year of exposure to Vivitrol and maximum exposure was
18 reached by 46 patients who received Vivitrol for more
19 than three years. Overall, this represents adequate
20 chronic exposure to Vivitrol from the Agency's
21 perspective.
22 The next two tables illustrate some of the

1 demographic features of the clinical trial populations
2 which include, again, alcohol-dependent patients
3 studied in trials in the U.S. and opioid-dependent
4 patients studied in U.S. study ALK21-006 and Russian
5 study ALK21-013
6 The tables also include some data from the
7 National Survey on Drug Use and Health or NSDUH,
8 pertinent to the demographics of the opioid-dependent
9 population in the U.S.
10 I'd like to point out that in looking at the
11 safety population, we are pooling data which has some
12 limitations, namely that these data are from different
13 studies with populations that are not identical and
14 with study designs that are not equivalent. However,
15 it does offer an opportunity to compare across
16 studies. It provides us with a larger sample size to
17 identify safety events and helps us to determine how
18 readily we can extrapolate the data.
19 From the table you can see that the opioid-
20 dependent population is overall younger than the
21 alcohol dependence, with the Russian population being
22 the youngest on average. According to NSDUH data,

1 about two-thirds of the U.S. opioid-dependent
2 population is under 35 years of age. So the opioid-
3 dependent clinical trial populations overall then are
4 a reasonable match in terms of the age of the target
5 population.
6 In terms of gender, the U.S. alcohol and
7 opioid-dependent clinical trial populations are
8 primarily male but still include a number of women.
9 NSDUH data on gender are provided in the last column
10 for the U.S. population. Data are provided for those
11 meeting criteria for heroin dependence and for those
12 meeting criteria for narcotic analgesic dependence.
13 Based on NSDUH data, these are two distinct
14 populations.
15 The U.S. heroin-dependent population is
16 primarily male and, like the U.S. clinical trial
17 population, is 66 percent male. On the other hand,
18 the narcotic analgesic-dependent population in the
19 U.S. is about evenly divided between males and
20 females. And finally in comparison, in the clinical
21 trials, the Russian opioid-dependent population as
22 almost entirely -- that is 88 percent -- male.

1 As mentioned earlier, the Russian study
2 population was almost all white, except for two
3 Asians. All the clinical trial populations are
4 majority white but there is more racial and ethnic
5 diversity seen among the U.S. study populations. The
6 NSDUH data show that the narcotic analgesic dependent
7 population in the U.S. is about 84 percent white,
8 which lines up with the clinical trial population for
9 Study 6. However, the heroin-dependent population is
10 less than 60 percent white. But again, we've heard
11 this morning that there were no pharmacokinetic
12 differences based on race.
13 With respect to the type of opioid used,
14 patients in the Russian opioid-dependent clinical
15 trial population were primarily heroin users. As
16 compared with the U.S. opioid-dependent population,
17 who according to NSDUH data are primarily dependent
18 upon narcotic analgesics. The U.S. clinical trial
19 population uses heroin and narcotic analgesics
20 approximately equally, but only about half of the
21 patients in the study population provided data on the
22 type of opioids they use primarily. Most patients in

1 the Russian study population carried a diagnosis of
2 hepatitis C, and a number of the patients, 41 percent,
3 were HIV positive.
4 Safety findings related to fatal outcomes
5 have been described by Dr. Silverman earlier today.
6 This table shows a number of serious adverse events
7 that occurred for subjects included in the safety
8 database during their first six months of study
9 participation. This is the time period during which
10 there were subjects on placebo, allowing for
11 comparison between placebo and treatment arms.
12 Studies 2, 3, and 13 had a placebo arm. Patients who
13 were on placebo on these studies were grouped together
14 and are represented in the first column. Patients who
15 were on Vivitrol in these studies are grouped together
16 and represented in the neighboring column.
17 When comparing the pool data for subjects on
18 placebo and subjects on Vivitrol and placebo-
19 controlled studies, the percentage of serious adverse
20 events was slightly higher in the placebo arm than in
21 the Vivitrol arm -- 6 versus 4 percent.
22 SAEs for the alcohol-0dependnet population

1 were seen in patients in Study 3 and Study 6. They
2 were reviewed during the original NDA review. The
3 SAEs that were considered at that time to be drug-
4 related were depression and suicide, eosinophilic
5 pneumonia, and injection site necrosis. For the
6 opioid-dependent population, SAEs were seen in
7 patients in Studies 13 and 6.
8 In reviewing the data in opioid-dependent
9 patients for the efficacy supplement, we looked
10 specifically for those SAEs that I mentioned were seen
11 among the alcohol-dependent subjects. And also to
12 look to determine if other types of drug-related SAEs
13 would be seen in the opioid-dependent population.
14 Study 6 was a year-long study. So while the
15 SAE table summarizes the data for the first six months
16 of study participation, the SAEs described here
17 occurred among patients for up to a year
18 participation. In other words, for the duration of
19 that study. Among the American opioid-dependent
20 subjects there were six SAEs of depression and events
21 of suicidal nature thought to be drug-related.
22 Because the mechanism of action is opioid antagonist

1 or blockade, we reason that it is possible that
2 endogenous opioids in addition to exogenous opioids
3 could also be blocked and in turn lead to adverse
4 events of depression and suicidality.
5 There were three cases of opioid overdose.
6 An accidental overdose is seen as a risk for patients
7 who attempt to overcome the blockade using large
8 quantities of opioids and also for patients who use
9 opioids after missing a dose of Vivitrol or dropping
10 out of treatment. These patients often have reduced
11 tolerance compared to pretreatment levels and may
12 misjudge the dose of opioid used.
13 Among the Russian opioid-dependent subjects
14 there were few SAEs overall. Four subjects on placebo
15 and three subjects on Vivitrol had an SAE. The study
16 enrolled again a number of subjects with HIV. In this
17 trial, SAEs that occurred in more than one subject
18 were of infections ideology. All three of the
19 Vivitrol patients had infection SAEs and some had
20 progression of their underlying HIV AIDS disease. In
21 the placebo arm, two of the SAEs were related to
22 hospitalizations associated with relapse, and one of

1 the infection SAEs in the placebo group was diagnosed
2 during a hospitalization.
3 While these events in the HIV-positive
4 patients on Vivitrol may be an effect of longer time
5 on study, we cannot say for certain. There were no
6 SAEs of depression, suicide, or overdose in the
7 Russian clinical trial population. And there were no
8 new cases of eosinophilic pneumonia or injection site
9 reactions requiring surgery in both the American and
10 Russian opioid-dependent study populations included in
11 the safety database.
12 Dr. Silverman described the discontinuations
13 due to adverse events in the opioid-dependent clinical
14 trial population, but I will be describing these
15 events in a pooled fashion. Discontinuations due to
16 adverse events provide us some insight into the types
17 of adverse events that represent dose limiting
18 toxicities or those adverse events that make the drug
19 difficult for patients to take.
20 Premature discontinuations by study and
21 treatment arm are shown in this table, and the focus
22 is on those premature discontinuations that are due to

1 adverse events. When comparing the pooled data from
2 those on placebo and those on Vivitrol and placebo-
3 controlled trials which are represented in the first
4 two columns, we can see that more patients in the
5 placebo arm discontinued prematurely but more, nearly
6 two times more patients on Vivitrol discontinued due
7 to AEs.
8 Most discontinuations actually occurred in
9 the Vivitrol arm of the placebo controlled study and
10 alcohol-dependent subjects at Study 3. And there
11 appear to be zero discontinuations among patients on
12 Vivitrol in Study 13, the placebo-controlled efficacy
13 trial in opioid-dependent subjects. However, this
14 remains under review.
15 Finally, 9 percent of all patients on
16 Vivitrol had discontinuations due to AEs. AS we saw
17 from the table, no Vivitrol-treated subjects in ALK21-
18 013 discontinued due to an adverse event. Ten percent
19 of alcohol-dependent subjects on Vivitrol and 7
20 percent on placebo discontinued because of an adverse
21 event. In the U.S. opioid-dependent clinical trial
22 population, events that led to treatment

1 discontinuation in more than one patient included
2 pregnancy, which occurred in four patients.
3 There were also three to four suicide
4 attempts. We are saying three to four because based
5 on the narratives there was one patient who appeared
6 to have discontinued due to a suicide attempt;
7 however, the event was not coded as such.
8 We focused on seven adverse events of
9 special interest. These were of special interest
10 because they were safety concerns identified during
11 the original NDA review for the alcohol dependence
12 indication and in the post-marketing setting. And
13 also based on the mechanism of action of naltrexone,
14 special attention was given to AEs of serious
15 injection site reactions eosinophilic pneumonia,
16 severe allergic reactions, hepatic effects, depression
17 and suicidality, accidental overdose, and
18 precipitation of opioid withdrawal.
19 Of these seven adverse events, we will focus
20 on the AEs that we consider important in this
21 indication. For the first three, there were no new
22 findings with respect to serious injection site

1 reactions in eosinophilic pneumonia and the combined
2 population and the AEs of allergic reaction are under
3 review.
4 For each of the events of interest, when a
5 standardized medDRA was available it was performed for
6 the AEs and in this case it was performed for the AEs
7 related to hepatic effects and depression and
8 suicidality.
9 These standardized medDRA queries or SMQs
10 represent a search strategy, in our case a broad one,
11 to identify terms that may relate to signs, symptoms,
12 diagnoses, and other findings associated with a given
13 medical condition or an event of interest. These
14 SMQs, because of their broad strokes, provide a wide
15 ranging view of an event of interest associated with a
16 particular therapy. As mentioned, SMQs were performed
17 for hepatic effects and depression and suicidality.
18 Vivitrol carries a warning because of risk
19 of hepatic effects seen with oral naltrexone. In
20 reviewing the hepatic effects for this efficacy
21 supplement, a number of strategies were used to try to
22 fully characterize these effects. An SMQ, namely the

1 possible drug-related hepatic disorder's SMQ was
2 performed. The clinical trial database was reviewed
3 by the applicant for terms related to liver injury and
4 lab values were reviewed with a focus on shifts and
5 lab values over time and measures of central tendency.
6 No serious hepatic events related to
7 Vivitrol were seen premarketing. There were few
8 patients with viral hepatitis in those studies, though
9 patients with some degree of alcohol-related injury
10 were included. In contrast to the pre-marketing
11 population, 89 percent of Study 13 patients had viral
12 hepatitis, and we are afforded an opportunity to see
13 the effects of Vivitrol in patients with viral
14 hepatitis, which is highly prevalent among injection
15 drug users.
16 Based on the data from the applicant's
17 review and SMQ, the only pattern of adverse event
18 suggesting a role of Vivitrol was in the case of
19 hepatic laboratory abnormalities that were reported as
20 adverse events. Labs were drawn monthly in Study 13,
21 and if a patient had a potentially clinically
22 significant lab abnormality, this was entered into the

1 case report form as an adverse event. These events
2 were more common in Vivitrol-treated than placebo-
3 treated patients in this study which you have heard
4 earlier.
5 Alkermes attributes the difference in rates
6 of hepatic laboratory abnormality AEs to general
7 fluctuations and hepatic enzymes that could occur in a
8 population where a large number of subjects have
9 hepatitis C. Because of the differential rate of
10 dropout among the Vivitrol and placebo arm, Alkermes
11 believes that this difference in hepatic enzyme
12 abnormality AEs is an effect of simply more
13 opportunity to observe these fluctuations in the
14 Vivitrol arm who had more study completers.
15 In their presentation, Alkermes remarked
16 about this, noting that the patients in the Vivitrol
17 arm had a longer time on study. To explore this
18 possibility we performed a person-time analysis which
19 is an attempt to account for differential time on
20 study. In this analysis, any patient in Study 13 who
21 had a laboratory abnormality of ALT, AST, GGT, or
22 total bilirubin that was recorded as an adverse event

1 was included once. Patients could have had more than
2 one abnormality or could have had an abnormality on
3 more than one occasion, but this is the number of
4 patients who had any of these abnormalities at any
5 time.
6 There were 26 subjects in the Vivitrol arm
7 and 10 on placebo who had one of these events
8 identified by the SMQ. These included events that
9 fell under both hepatic and hepatobilliary disorders,
10 as well as a hepatobilliary investigations groupings,
11 with the latter representing the majority of the
12 events. During this time period, which was the first
13 six months of study participation, patients in the
14 Vivitrol arm contributed a total of 46.6 person years
15 and the placebo group contributed 35.8 person years.
16 With the person years contributed as a denominator and
17 the number of patients with an AE as a numerator,
18 results from the analysis are .558 for the Vivitrol
19 arm and .279 for the placebo arm.
20 As you can see the person-time analysis
21 which corrects for differing length of time at risk
22 does not completely account for the difference in

1 rates of potentially clinically significant enzyme
2 abnormalities. We did not see a drug-related effect
3 on liver function test abnormalities coded as adverse
4 events in the alcohol-dependent population.
5 We also reviewed lab data for Study 13. In
6 this first table we looked at shifts to higher lab
7 values over time. Subjects who had an ALT or AST
8 value that was more than three times the upper limit
9 of normal were excluded from participation in Study
10 13.
11 So we looked to see how many patients had
12 shifts to more than three times the upper limit of
13 normal at any point during the study, knowing that all
14 patients enrolled were less than three times the upper
15 limit of normal at baseline. As we did with the
16 hepatic laboratory abnormality AEs, we counted
17 patients only once if they had lab values greater than
18 three times the upper limit of normal on more than one
19 occasion. We found that for ALT values, 21 Vivitrol
20 patients versus 11 placebo patients shifted to more
21 than three times the upper limit of normal, and for
22 AST, 15 Vivitrol versus 9 placebo patients shifted to

1 above three times the upper limit of normal on one of
2 their post line -- post-baseline values throughout
3 their participation in the study.
4 This table is different -- a little
5 different from the shift table that you saw this
6 morning because we were looking at peak post-baseline
7 value rather than the last post-baseline value. In
8 this second table, we looked at the mean change from
9 baseline to the peak post-baseline value and found
10 that for both liver function tests the Vivitrol arm
11 had a slightly greater mean change on average than the
12 placebo arm.
13 In another analysis not shown here, we also
14 found that these differences between Vivitrol and
15 placebo for shifts as in the first table and for
16 measures of central tendency as in the second table
17 were consistent when examining the number of AEs per
18 number of laboratory tests drawn per group.
19 Overall, for AST there were only two
20 patients who had shifts to more than 10 times the
21 upper limit of normal, one in each arm and only a
22 single placebo patient experienced a shift to more

1 than 10 times the upper limit of normal for ALT.
2 There were no cases of liver failure and no laboratory
3 pattern suggestive of severe drug-induced liver injury
4 as was reported by Alkermes earlier in their
5 presentation. However, taken together with the
6 hepatic lab abnormality AEs data, these lab data
7 demonstrate that there do appear to be some hepatic
8 effects but we are not seeing evidence of severe drug-
9 induced liver injury. Vivitrol already carries a
10 warning about hepatic effects, and based on the data
11 the warning appears to be fitting.
12 As mentioned, because of the potential for
13 blockade of opioid receptors to interfere with
14 endogenous opioids, the mechanism of a naltrexone
15 raises concern about dysphoria and depression. In the
16 pre-marketing safety database, it was observed that
17 adverse events of a suicidal nature -- that is
18 suicidal ideation, suicide attempts, and completed
19 suicides -- were infrequent overall but were more
20 common in patients treated with Vivitrol than in
21 patients treated with placebo -- 1 percent versus
22 zero.

1 For the opioid-dependent population, a
2 depression and suicide self-injury SMQ was performed
3 for this event of interest. These two tables
4 represent the results of that SMQ for the first six
5 months of study participation and for beyond six
6 months. In the first table, for the patients in Study
7 13, 2 percent of placebo versus 1 percent of Vivitrol-
8 treated patients had an adverse event identified by
9 this SMQ. In Study 6, 18 percent of the Vivitrol-
10 treated patients and 15 percent of the oral
11 naltrexone-treated patients had an AE identified by
12 the depression and suicidality SMQ.
13 In the second table representing events that
14 occurred beyond 24 weeks of participation, 20 percent
15 of the patients continuing on Vivitrol had an AE
16 identified by the SMQ and half of those were AEs of
17 depression and depressed mood. Additionally, 23
18 percent of those on oral naltrexone had an AE
19 identified during this time period. The data indicate
20 that naltrexone is associated with depression and
21 suicidality and this risk is reflected in the label.
22 As discussed earlier today, patients who are

1 physically dependent on opioids at the time of dosing
2 with Vivitrol are likely to experience precipitated
3 opioid withdrawal. In Study 13, measures were put in
4 place to try to ensure that subjects were not
5 physically dependent at the time of Vivitrol
6 administration, including the naloxone challenge test
7 which has been discussed many times today. And in
8 this setting, no ALK21-013 subjects had events coded
9 to withdrawal syndrome. In Study 6, there were three
10 opioid-dependent patients who had events coded to
11 terms of withdrawal symptom or withdrawal syndrome.
12 These occurred in two patients on Vivitrol and one
13 patient on oral naltrexone.
14 There were no cases seen in the alcohol-
15 dependent patients but 32 cases were reported in post-
16 marketing suggesting that this could occur more
17 frequently if the product is marketed for the new
18 indication and if efforts are not made to ensure that
19 a patient is not physically dependent on opioids at
20 the time of administration of the drug. This risk is
21 also addressed in the label.
22 As mentioned earlier, accidental opioid

1 overdose is a risk for patients who attempt to
2 overcome the blockade using large quantities of
3 opioids and for patients who use opioids after missing
4 a dose of Vivitrol or dropping out of treatment.
5 Again, these patients often have reduced tolerance
6 compared to pre-treatment levels and may misjudge a
7 dose of opioid use.
8 This is one that we consider to be an
9 indication-specific concern that is not expected to
10 apply to patients using the product for the currently
11 approved indication but is likely to occur more
12 frequently if the product is marketed for the new
13 indication.
14 In Study 6, there were four opioid
15 overdoses, with two requiring hospitalization. None
16 were fatal, and all occurred in opioid-dependent
17 subjects. The events occurred at the end of the
18 interdose interval or when a dose was missed. None
19 occurred among the Russian opioid-dependent patients
20 in Study 13. In the post-marketing setting there were
21 four cases, three of which were fatal. Three of the
22 cases occurred approximately one month following the

1 last Vivitrol injection.

2 The risk of accidental opioid overdose is

3 described in the label. The label, however,

4 emphasizes events of accidental overdose in a setting

5 of trying to overcome the blockade using large doses.

6 These data suggest that loss of tolerance and opioid

7 use at the end of a dosing interval are also of

8 concern.

9 These are the last set of safety findings

10 that we'll discuss. The adverse event profile of

11 Vivitrol in U.S. patients has been described earlier

12 but also including some patients with opioid

13 dependence in addition to the alcohol-dependent

14 patients was characterized based on a safety database

15 reviewed in the original NDA submission.

16 The opioid-dependent patients participating

17 in the U.S. trial Study 6 had an adverse event profile

18 that was similar to the established profile. For

19 example, nausea, abdominal pain and injection site

20 pain were common in Study 6 and in the alcohol-

21 dependent population. However, there were some

22 events, for example, hepatic enzyme abnormalities and

1 infections that were not among the most common adverse
2 events in the alcohol-dependent population.
3 A grouped adverse event analysis was used
4 for Study 13 because of the overall low rate of
5 adverse event reporting. This table represents the
6 common adverse events found through analysis of events
7 at the high level group team or HLGT level occurring
8 in 5 percent or more of patients in the Vivitrol arm.
9 The table shows that adverse events in the
10 hepatobilliary investigations, HLGT, are common and
11 more frequent in the Vivitrol arm. And this has
12 already been discussed in detail.
13 Adverse events in the sleep disorders and
14 disturbance and administration site reactions, HLGTs,
15 were adverse events that we had already seen in the
16 alcohol-dependent population. However, while we saw
17 infection-related adverse events at a similar rate for
18 the Vivitrol-treated and placebo-treated alcohol
19 dependent patients, here in Study 13 we're seeing
20 infections at a higher rate in the Vivitrol arm.
21 Infections were also a commonly reported event in the
22 opioid-dependent patients in Study 6, but we didn't

1 have a placebo arm in that study for comparison.
2 Because Vivitrol-treated patients were in
3 the study longer and there's a possibility that this
4 explains a difference, another person-time analysis
5 was performed. In this analysis, any patient who had
6 an adverse event in a system organ class or SOC,
7 infections and infestations, was counted once.
8 Patients could have had more than one kind of
9 infection or could have had the same type of infection
10 on more than one occasion but this is the number of
11 patients who had any adverse event in the SOC at any
12 one time. Twenty-four, or 19 percent of Vivitrol-
13 treated patients had an AE in infections and
14 infections SOC versus 14 or 11 percent on placebo.
15 You'll recall from the previous analysis
16 that the person years contributed by the Vivitrol
17 patients was 46.6 and for the placebo arm it was 35.8.
18 With the person years contributed as a denominator,
19 the result is 0.515 for the Vivitrol arm and .391 for
20 placebo. As you can see, the person-time analysis
21 which corrects for differing length of time at risk
22 partially but not completely accounts for the

1 difference in risk of infection -- on rates of
2 infection. This may be the result of increased
3 contact with the health care system for the Vivitrol
4 patients who had longer time in study but an effect of
5 treatment remains another plausible explanation.
6 That ends the discussion of the safety
7 findings. Throughout this talk we have summarized our
8 efficacy and safety findings from our review of the
9 efficacy supplement to date. In conclusion, for
10 efficacy, the pharmacodynamic study demonstrates
11 Vivitrol's opioid blockade effects. The efficacy
12 study provides evidence that Vivitrol prevents relapse
13 to opioid use in recently detoxified opioid-dependent
14 patients in a single study. The study was conducted
15 in Russia and there may be demographic, cultural, and
16 societal differences that may impact our ability to
17 extrapolate the data to the U.S. opioid-dependent
18 population.
19 In terms of safety, we saw that the overall
20 safety profile in opioid-dependent patients is similar
21 to the established safety profile in the Vivitrol
22 label but that the rate of AE reporting was distinctly

1 lower in the Russian population.
2 We also saw some indication-specific
3 observations, namely that among the alcohol-dependent
4 patients there were no opioid overdose events and
5 while the events were uncommon in the opioid-dependent
6 population, clinical trial data and post-marketing
7 data confirmed that accidental overdose may occur in
8 particular at the end of a dosing interview.
9 Opioid-dependent patients may be more
10 vulnerable to the hepatic effects of naltrexone,
11 particularly those patients with viral hepatitis. And
12 we also saw that Vivitrol-treated opioid-dependent
13 patients reported more infections of all types,
14 including viral, fungal, and bacterial infections,
15 than patients treated with placebo.
16 This concludes our discussion of the safety
17 and efficacy data for Vivitrol for the treatment of
18 opioid dependence.
19 And with that I'd like to thank all those
20 who contributed to the efficacy and safety review for
21 this application, and I'd like to thank all of you for
22 the present this information and gain the Committee's

1 perspective on the efficacy and safety data submitted
2 in this application.
3 Thank you.
4 DR. SCHULTZ: Thank you. I believe there's
5 one more presentation from the FDA.
6 **Summary of Clinical Site Inspections**
7 DR. PUROHIT-SHETH: Good afternoon,
8 everyone. And thank you for allowing me the
9 opportunity to present.
10 I'm the brand chief in the Division of
11 Scientific Investigations for Good Clinical Practice
12 Branch II. And my branch is responsible for all of
13 the good clinical practice inspections that are
14 conducted in support of marketing applications for all
15 of the review divisions.
16 What I would like to cover today is I will
17 provide an overview of CDERs bioresearch monitoring
18 program and then I will give you some metrics on the
19 domestic and international inspections that we conduct
20 in our bioresearch monitoring program, followed by our
21 experience with oversight over Russian clinical sites.
22 And then I will end with a summary of our inspection

1 results -- the inspections that were conducted in
2 support of the marketing application that is currently
3 under evaluation.
4 So what is FDA's bioresearch monitoring
5 program? Our program is a comprehensive program of
6 onsite inspections and data audits that are designed
7 to monitor all aspects of the conduct and reporting of
8 FDA-regulated research. And our objectives are three-
9 fold. We want to verify that the data that was
10 collected in support of the marketing application is
11 reliable; that the rights, safety, and welfare of
12 human subjects are protected; and to ensure that FDA-
13 regulated research is conducted in accordance with our
14 regulations.
15 Our program responsibilities include
16 adherence to applicable regulations with respect to
17 studies of good laboratory practice, bioequivalent
18 studies, as well as good clinical practice. And we
19 have oversight over institutional review boards,
20 clinical investigators, sponsors, monitors, and
21 contract research organizations.
22 Our GCP regulations cover clinical and

1 nonclinical research and the applicable regulations
2 are 21 CFR Part 50, 54, 56, 312, and 314, which cover
3 informed consent procedures, financial disclosure, IRB
4 approval and continuing review, as well as our
5 investigation of new drugs and new drug application
6 regulations.
7 Our inspections are facilitated and
8 conducted through our Office of Regulatory Affairs.
9 DSR reviewers assign and facilitate the conduct of
10 these clinical inspections. On occasion, when
11 scientific or medical expertise is warranted, our
12 reviewers may also participate.
13 So we perform and assign these inspections
14 through ORA. We also investigate allegations of
15 regulatory noncompliance. We provide scientific and
16 medical reviews of the establishment inspection
17 reports generated by our field investigators. We make
18 recommendations regarding data reliability to the
19 product review divisions, and we take appropriate
20 regulatory action when warranted. So if we find
21 significant issues of noncompliance that would impact
22 data reliability or human subject protection -- for

1 example, we may submit a warning letter, or for
2 clinical investigators domestically we may initiate
3 disqualification procedures if we find that the
4 findings are very significant.
5 So how many inspections does our center
6 conduct annually? This shows you from Fiscal Year
7 2002 through Fiscal Year 2009. And generally we're
8 about 700 inspections annually. Last year we had
9 close to 800 inspections. The measure -- the majority
10 of the inspections are of clinical investigators. And
11 our clinical investigator inspections, last year we
12 conducted 458. We're about -- generally about 400
13 annually. And this encompasses both domestic and
14 international inspections of clinical investigator
15 sites.
16 And of the clinical investigator inspections
17 we conduct, approximately a third of them -- a quarter
18 to a third in any given year are overseeing clinical
19 investigator sites overseas. Last year we conducted a
20 total of 119 international inspections in support of
21 marketing applications.
22 Where are we going to conduct these

1 inspections? Well, as you can see, 60 percent of
2 inspections that we conducted last year were in
3 Europe, followed by 21 percent in Asia and Pacific,
4 and then 7 percent each Africa, South America, and
5 then we had Canada and Australia.
6 So, when do we conduct these inspections?
7 Well, inspections can be conducted at any time during
8 product development. So bioresearch inspections can
9 be conducted during the IND phase or the NDA phase.
10 And the inspections that are conducted during the IND
11 phase are generally for cause as a result of a
12 complaint where we have allegations of significant
13 issues of good clinical practice noncompliance.
14 Inspections that are conducted in support of marketing
15 applications are conducted routine, but there may be
16 significant issues that may have been identified
17 during the preliminary review of the application early
18 on that would also be considered for cause if there
19 are significant issues that we need to evaluate with
20 onsite inspections.
21 And as we discussed earlier, our oversight
22 is -- extends to IRBs, clinical investigators,

1 sponsors, monitors, and contract research
2 organizations.
3 So when a marketing application is submitted
4 to the Agency, what factors are taken into
5 consideration in the determination of sites to
6 inspect? Well, first of all, we're looking, number
7 one, if we're going to inspect the application, we
8 want to see the relevance and importance of the study
9 to the application. Is it a new molecular entity? Is
10 the supplement intended to support an indication of
11 vulnerable population? Is it a new indication? A new
12 formulation? Et cetera.
13 Once we decide to inspect the application,
14 we're looking at the contribution of the clinical
15 investigator sites to the data as a whole. We're
16 looking at outlier data with respect to safety and
17 efficacy, looking at the statistical impact of the
18 data from the site, and we're also evaluating the
19 history of the clinical investigator with respect to
20 prior inspections, as well as findings of previous
21 clinical inspections.
22 When we receive an application with data

1 that comes from overseas, as well as domestic, what
2 are the factors that we like to evaluate? If we get
3 an application and it has insufficient domestic data,
4 we are more likely to inspect. Especially if the data
5 is solely coming from foreign sites, we are more than
6 likely to inspect that as well.
7 And Dr. O'Neill discussed earlier this
8 morning about looking at regional differences in the
9 evaluation of the data, and if analyses have been
10 conducted and are domestic and international data have
11 conflicting results, we'd also like to do a handful of
12 domestic as well as foreign inspections to evaluate
13 the discrepancy. And if there are serious issues that
14 need resolution -- if there are complaints or if there
15 is suspicion of fraud, scientific misconduct, or
16 issues that would denote significant human subject
17 protection violations, then we are more than likely to
18 inspect these as well.
19 The goals of our inspections are to assess
20 many different aspects of the conduct of clinical
21 trials to include the qualifications of the clinical
22 investigator, the oversight of the clinical

1 investigator, the adequacy of the clinical setting of
2 care where the study is being conducted, the quality
3 of informed consent procedures as well as informed
4 consent documents, IRB approval or in the case of
5 international inspections, their ethics committee's
6 oversight. We're looking at the adequacy of urine
7 study protocol. We're looking at test article
8 accountability, as well as the adequacy and accuracy
9 of the records that are maintained during the conduct
10 of the clinical trial.
11 So what do we look at during these
12 inspections? FDA field investigators will evaluate
13 the source documents that are available, to include
14 medical record data, which would be compared to case
15 report forms, as well as data listings that have been
16 submitted by the applicant in support of the marketing
17 application. Our investigators verify whether
18 subjects existed.
19 Did the subjects have the disease under
20 study? Did they meet the eligibility criteria as
21 specified in the protocol? Was IRB or an independent
22 ethics committee approval obtained? Was consent

1 obtained appropriately? Did the clinical
2 investigators in study site staff adhere to the
3 protocol? Did they verify primary efficacy endpoints
4 as well as key secondary endpoints? Did they evaluate
5 adverse event reporting -- actually, collection and
6 reporting of adverse events to include SAEs and
7 deaths? Did they also evaluate any safety data that
8 may have been collected in the conduct of the clinical
9 trial? And did they evaluate drug accountability and
10 the adequacy of finding?
11 And once the inspections have been
12 conducted, the reports are submitted back to my
13 division and my staff will review the establishment
14 inspection report of the EIR and the pertinent
15 documents that have been collected by the field
16 investigators to support any violations that have been
17 noted. We then will provide a summary of our
18 inspectional findings and we will provide our
19 recommendation to the review division as to the
20 adequacy and reliability of the data that was
21 collected in support of the marketing application.
22 If violations have been observed, we

1 evaluate these in the context of how significant were
2 these violations. Were they isolated in occurrence,
3 unlikely to impact the total outcome of the study? Or
4 were these pervasive findings where we have
5 significant concern that the study may not have been
6 conducted adequately at a given site such that the
7 data are not considered reliable?
8 And then DSI makes final classifications of
9 the inspections -- NAI, VAI or OAI. And I will cover
10 this in a couple slides. And we prepare a post-
11 inspectional correspondence to the inspectional
12 entity.
13 What types of issues or violations are
14 typically noted? In Fiscal Year 2009, this graph will
15 show you that approximately 50 percent of our
16 inspections did not have any significant findings.
17 They were NAI, denoting that no action was indicated
18 and no significant problems were identified.
19 When problems did occur, as you can see in
20 yellow, which denotes our foreign inspection
21 deficiencies, and in blue, which denotes our domestic
22 inspection deficiencies, they're pretty comparable.

1 There's not many significant differences between the
2 types of deficiencies that are noted during
3 inspections conducted domestically versus
4 internationally. But the most common deficiencies
5 noted are failure or not adhering to the protocol, not
6 maintaining accurate or adequate case records of study
7 conduct, issues with drug accountability, issues with
8 informed consent, and under reporting of AEs, which
9 was the least common deficiency noted.
10 So what are our compliance classifications?
11 What does an NAI, VAI, or OAI denote? NAI means no
12 action indicated. It means that during the inspection
13 no significant issues were identified; that the study
14 in general was conducted adequately and the data is
15 considered reliable.
16 When a VAI classification is made, it
17 denotes that there were some issues that were noted
18 and voluntary action is indicated, but the types of
19 violations and the scope of violations noted are
20 unlikely to impact reliability of the data as a whole
21 from that site.
22 When an inspection is classified as OAI or

1 official action indicated, it denotes that significant
2 issues of good clinical practice noncompliance were
3 noted during the inspection such that the reliability
4 of the data is in question. And/or we noted
5 significant issues with protection of the rights,
6 safety, or welfare of human subjects. And when we
7 have a classification of OAI, it denotes some
8 regulatory action on our part or administrative action
9 by the Agency.
10 So what percentage of our inspections are
11 OAI? So for all clinical investigator inspections, to
12 include domestic and foreign, you can see the majority
13 by far, 94 percent, are -- the data is considered
14 reliable and no significant issues that would impact
15 data reliability are noted. Last year, Fiscal Year
16 2009, we had about 6 percent of our inspections
17 resulting in a classification of OAI.
18 How does this compare with our international
19 inspections? As you can see, again, the majority, and
20 in this case 99 percent of inspections are classified
21 as NAI or VAI. Again, no significant issues were
22 noted. One percent in the international realm were

1 classified as official action indicated.
2 So what has our Russian experience been?
3 Our center has inspected 71 clinical sites from Fiscal
4 Year 99 through Fiscal Year 2009. And this graph will
5 show you on an annual basis the number of clinical
6 investigator inspections that have been conducted in
7 Russia.
8 The most common good clinical practice
9 deficiencies are violations that have been noted
10 during FDA inspections in Russia are very similar to
11 what has been our experience with domestic inspections
12 and other international inspections, mainly failure to
13 follow the protocol, inaccurate or inadequate records,
14 inadequate drug accountability, failure to report
15 adverse drug reactions, and informed consent issues.
16 And the classifications for the Russian
17 inspections are comparable to what we've noted in
18 other international inspections. And the majority, 64
19 percent of these were classified as NAI; VAI, 35
20 percent; and only 1 percent of the inspections to date
21 that have been conducted in Russia of clinical
22 investigator sites have been classified as official

1 action indicated.

2 So now I'd like to end, provide a brief

3 summary of the inspections that have been conducted in

4 support of this efficacy supplement related to

5 Vivitrol. Our division submitted assignments for four

6 clinical investigator sites in Russia; three were in

7 St. Petersburg and one was in Leningrad region in

8 Russia. And these four out of 13 sites were

9 inspected.

10 So that's approximately 30 percent of the

11 clinical investigator sites that were inspected. As

12 you saw in Dr. O'Neill's talk, typically it's about 1

13 to 2 percent of clinical sites that are inspected for

14 any given application, so we did certainly a

15 considerable number more inspections for this

16 application. And also top point out, total number of

17 patients in Study 13 were 250, and these four sites

18 accounted for 159 or approximately 60 percent of the

19 subjects for this study.

20 And the scope of the Russian site

21 inspections was similar to what I described earlier as

22 the scope of our general inspections. We evaluated

1 subject eligibility; evaluated variants to study
2 blinding and randomization procedures; evaluated
3 documentation of concomitant medications; variants to
4 protocol and the specific assessments that were
5 warranted at any given visit; completion of required
6 study questionnaires, as well as completion of the
7 diagnostic and bio specimen testing; maintenance or
8 the adequacy of the records that were maintained for
9 the study.
10 We also evaluated the consistency of the
11 data that was noted in the source documents versus
12 what was submitted in the application; evaluated drug
13 accountability; looked at monitoring visit logs,
14 monitoring reports. We evaluated document and
15 protocol violations and their informed consent
16 procedures, as well as their independent ethics
17 committee approvals.
18 And of specific interest during these four
19 inspections was the evaluation of the adequacy of
20 adverse event and serious adverse event collection and
21 reporting. As Dr. Skeete mentioned earlier, one of
22 the concerns with Study 13 was that there was a

1 decreased reporting of adverse events in this study
2 that was conducted in Russia.
3 And the results of our inspections were that
4 no significant issues were identified during our
5 inspections and a comprehensive inspection were
6 conducted at all four sites. We found the adverse
7 event and serious adverse event reporting was
8 adequate. There was no evidence that there was
9 underreporting of adverse events or serious adverse
10 events at any of the sites that were inspected. And
11 our recommendations to the Review Division said the
12 data is considered reliable in support of the
13 marketing application.
14 So in summary, our center's bioresearch
15 monitoring program oversees inspections related to
16 clinical trial data in support of FDA-regulated
17 products. Our inspections are conducted worldwide.
18 Our previous inspectional history at Russian sites has
19 not identified any specific concerns to clinical trial
20 data that has been generated in Russia. And with
21 respect to the current marketing supplemental
22 application that is in-house, inspections at four

1 Russian sites did not identify any significant
2 deficiencies, and the data is considered reliable in
3 support of the application.
4 Thank you for your attention.
5 **Clarifying Questions**
6 DR. SCHULTZ: Well, that concludes the FDA
7 presentations. We'll try to return to some questions.
8 I know we have a couple remaining sponsor questions
9 but if we could start -- for any clarifying questions
10 for the FDA presentations, we'd like to -- and please
11 try to be succinct and answer the questions in a
12 direct manner so that we can be very productive in our
13 questions. Are there any questions for the FDA at
14 this time?
15 Dr. Woolson?
16 DR. WOOLSON: Brief question. I think for
17 Dr. Li. You mentioned that the individuals who
18 dropped out before week 5 of Study 13, that they were
19 considered to have -- to be opioid positive for the
20 remaining 20 visits for the remaining 20 weeks and the
21 analysis is similar to what the sponsor had done. Did
22 you do any additional sensitivity analyses to see how

1 sensitive the analysis results were to that
2 assumption? I mean, were there -- did you -- I mean,
3 I think it's reasonable to expect that those that
4 dropped out would have a higher probability of being
5 opioid positive for those remaining weeks but I'm
6 still struggling with the issue of us assuming that
7 they're positive every single week and every single
8 person is positive for the balance.
9 DR. LI: Yeah. For patients who dropped
10 out, no, primarily the reason is lack of efficacy or
11 relapse to opioid. So it's reasonable to impute them
12 as positive. So I haven't tried the other ways to
13 impute the results.
14 DR. SCHULTZ: Dr. Tai?
15 DR. TAI: This is a question just curious
16 about when you do the GCP international audit, what
17 about the consent process and the consent form? Are
18 they -- the international one, are they comparable to
19 domestic consent in terms of its content and the
20 questions?
21 DR. PUROHIT-SHETH: Sure. And when we
22 inspect international sites, we actually inspect to

1 our regulations. So we are evaluating the adequacy
2 informed consent to the regulations that are in Part
3 50. So we look. There's eight elements that need to
4 be present, you know. And when we find a deficiency,
5 it denotes that the informed consent procedures and
6 the documents were applicable and they were in
7 compliance with the regulations that are domestically.
8 DR. MONTOYA: I have a question about the
9 hepatic effects -- if there was any analysis looking
10 at patients -- 89 percent of the patients were
11 positive for hepatitis C. Was there any difference in
12 terms of response to naltrexone in patients with
13 hepatitis C?
14 DR. WINCHELL: When you say difference in
15 response, do you mean likelihood --
16 DR. MONTOYA: Between naltrexone and
17 placebo?
18 DR. WINCHELL: Sorry. Difference in
19 efficacy or difference in the likelihood of having a
20 hepatic abnormality?
21 DR. MONTOYA: Hepatic abnormality.
22 DR. WINCHELL: If I understand correctly,

1 all of the patients who had the adverse events
2 reported in the hepatobilliary investigations, SOC,
3 were in the subset that were -- that had viral
4 hepatitis.
5 DR. MONTOYA: I would be interested in
6 knowing if a patient who has hepatitis C, what is the
7 safety of naltrexone here?
8 DR. WINCHELL: Well, what we noted was
9 although there was -- there were a number of patients
10 who had elevations to three times upper limit of
11 normal, almost no one who had more extreme elevations,
12 and there were no serious hepatic events, no what we
13 call High's Law cases, which is the concurrent
14 occurrence of transaminase abnormality with elevation
15 in bilirubin, so we don't disagree with Alkermes that
16 there's not -- there doesn't seem to be, even in the
17 population with viral hepatitis, an indication of
18 serious hepatic injury.
19 We think there's an indication that it does
20 cause some elevation in transaminases which is
21 something that's been long established. But despite
22 the population having a high prevalence of viral

1 hepatitis, we did not see serious hepatic injury.
2 DR. SCHULTZ: Mr. Mullins?
3 MR. MULLINS: Yes. I had a question about
4 the reporting level of SAEs between the Russian
5 population the U.S. population, did you do any further
6 analysis on the difference in reporting of SAEs and
7 was it based on study design, adherence to protocol or
8 -- there seemed to be a difference between the report
9 of those adverse events.
10 DR. PUROHIT-SHETH: So during the
11 inspection, because we already were aware of the
12 decreased reporting, we had tasked our field
13 investigators to specifically evaluate the adequacy of
14 AE and SAE reporting.
15 And based on extensive interview, not only
16 to clinical investigators and the study stuff, then
17 information that was relayed back to us was that the
18 Russian population -- it appears to be some sort of
19 cultural difference in reporting of these. That they
20 do not tend to report minor issues or minor health
21 concerns or any type of health concerns to the
22 frequency as do the American population. They're

1 rather stoic in the reporting of these adverse events.
2 MR. MULLINS: So in self-reporting they seem
3 to report less than U.S. subjects?
4 DR. PUROHIT-SHETH: That is apparent from
5 our interviews.
6 DR. SCHULTZ: Dr. Covington?
7 DR. COVINGTON: Yeah. In the Russian study
8 with all these HIV-positive patients, were there any
9 T-cell count following or any other studies designed
10 to see if there were any adverse immunological effects
11 from the naltrexone?
12 DR. WINCHELL: We looked at general
13 hematology that was reported but maybe Alkermes could
14 comment on whether there were specific immunological
15 evaluations.
16 DR. SILVERMAN: Yes. Our intent wasn't to
17 do an in-depth study of HIV, so we did not do T-cell
18 counts in this population. We did excluded people
19 with more severe HIV. Again, any AIDS indicators of
20 the disease, like Karposi's sarcoma, did not
21 participate in the study.
22 DR. SCHULTZ: Dr. White?

1 DR. WHITE: Just a question about the
2 underreporting. Is that known from other studies --
3 from other -- is that something that's common among
4 the population and known from other studies?
5 DR. PUROHIT-SHETH: That -- I don't have
6 that information. This was the first time in our
7 inspections that such an issue had arose and we had
8 done our inspections and found out that it's just a
9 cultural -- it appears to be a cultural difference.
10 DR. SCHULTZ: Just as a follow on to Dr.
11 Montoya's question, can you just tell us what the
12 enrollment requirement was for liver enzyme levels so
13 we can see what the differential change is in the two
14 groups. But what was the requirement for people
15 coming in? Did they have to be less than two times
16 normal? Did they have to be within normal limits?
17 DR. WINCHELL: Patients -- patients were
18 excluded if their AST or ALT exceeded three times the
19 upper limit of normal. I don't believe there was
20 exclusion criteria based on GGT. And I can't recall
21 the exclusion criteria based on bilirubin. Maybe Dr.
22 Silverman can recall.

1 DR. SILVERMAN: We excluded people with
2 bilirubin over 10 percent the upper limit of normal.
3 And Dr. Winchell is correct -- that we did not have
4 specific criteria for GGT. That's why when it showed
5 the baselines you'll see they were significantly
6 higher than the relativity between ALT and AST.
7 Dr. SCHULTZ: Dr. Hwang?
8 DR. HWANG: My question is on the rate of
9 dropout the first four weeks. Vivitrol obviously has
10 a much greater dropout rate than -- the placebo has a
11 much greater dropout rate than Vivitrol, sorry. But
12 after four weeks, the dropout between the treatment
13 group and the placebo group are very comparable. Now,
14 usually what happens is when patients realize they're
15 on placebo they don't want to continue and they
16 dropout from the study. So I was wondering if this
17 was a true blind -- double-blind study?
18 DR. WINCHELL: Certainly, the point has been
19 raised that patients who would sample opiates would be
20 able to discern whether they could sense the
21 subjective effects of opiates or not. So there may
22 have been some patients who sampled opiates in that

1 first month or even the first couple of weeks. But
2 what's interesting is that the dropout actually looks
3 like it happens more between weeks -- it's not the
4 first week. It's after that. So, could it be because
5 they figured out that what treatment arm they're in?
6 Possibly. But what about the rest of those guys?
7 Were they just dumb? It's hard to say.
8 There's -- I don't think anybody knew what
9 injection they got at the time that they got it. And
10 it also was surprising to us that if you looked at the
11 data from the first four weeks in the patients who did
12 come back, a lot of people never samples opiates. So
13 there may have been quite a few patients for whom the
14 blind was maintained.
15 DR. RAPPAPORT: I would just add that for
16 symptomatic disorders we rarely do active controls so,
17 you know, who knows what the real rates of unblinding
18 are. In any disorders, in psychiatry or pain or
19 addiction, it's really hard to know.
20 DR. SCHULTZ: Did Dr. Maxwell have a
21 question?
22 DR. MAXWELL: Let me add one little piece.

1 I'm not sure it's a question. But given that there is
2 no legal methadone treatment programs in Russia,
3 there's a dearth. Other than just forced residential
4 or -- residential is the only game in town. So I
5 think there's probably some effects from the fact that
6 this was a program you could go to. Perhaps you could
7 get much better counseling than you'd get in a regular
8 state-run program. If I was in that and my only other
9 option was to dropout and go -- and if I complained
10 and thought that might get me thrown out, I think that
11 could affect part of the response right there. That
12 you don't have the methadone. You don't have the
13 suboxone and all these other comparisons, which is a
14 problem.
15 Also, I'm a little concerned because we're
16 looking at people using southwest Asian heroin versus
17 the kinds of heroin here which I wonder does it have a
18 different effect based on what kind of footprint is on
19 the heroin? I don't know. I mean, there's a whole
20 lot of other stuff going on or not going on in Russia
21 that makes this -- could make this program much more
22 attractive than treatment as usual.

1 DR. SCHULTZ: I think Dr. Montoya had a
2 question.
3 DR. MONTOYA: Was there any difference in
4 recruitment rates across the different study sites?
5 And also was there any difference in terms of
6 treatment success and the primary outcome measure that
7 may -- one site may account for a larger difference or
8 something like that?
9 DR. HWANG: The treatment effect was
10 consistent across the different sites.
11 DR. WINCHELL: We can't really --
12 DR. MONTOYA: And recruitment?
13 DR. WINCHELL: We can't really comment on
14 the recruitment but perhaps someone from Alkermes can
15 answer that.
16 DR. EHRICH: Beyond the 250 patients that
17 were enrolled in the study there were an additional 87
18 patients that were screened. So actually, the screen
19 failure rate was very low. We don't -- I don't have
20 here with me today specific information about that
21 rate from site to site.
22 DR. SCHULTZ: Mr. Mullins?

1 MR. MULLINS: I had two quick questions. I
2 want to understand if there was any explanation, any
3 psychological examinations done to understand the
4 higher suicidality rate. And secondly, I want to know
5 if there was an explanation for the difference -- if
6 there was any MedDRA analysis done or other studies
7 that we could look at as far as safety is concerned.
8 Because we're just looking at one. And there seems to
9 be a direct correlation between time and increase in
10 toxicity and SAE. So I wanted to know are there any
11 longitudinal studies that we could look at or any
12 other analysis -- MedDRA analysis -- whether anything
13 done that we could look at safety? Because it seems
14 like long-term use led to greater exacerbations.
15 I'm concerned about the U.S. population in
16 particular because if this -- if this treatment
17 affects liver toxicity, a larger number of the U.S.
18 patients have hepatitis C and they have HIV, which
19 makes them more vulnerable. So I wanted to speak to
20 that. And that's something that we need to be aware
21 of if we recommend this for the U.S. population
22 because they're a little different. It seems that

1 they have a high propensity for HIV and hepatitis C.
2 DR. RAPPAPORT: I just want to make one
3 clarification. That longer term exposure didn't
4 increase the -- I can't remember what word you used
5 exactly, but you implied exacerbations -- increasing
6 exacerbations or something. It increased the
7 incidence of the events but they weren't necessarily
8 worse all the time.
9 MR. MULLINS: What about liver? I thought
10 liver toxicity -- I read something in the background -
11 - I'll pull it up in a minute, but on page 17 of the
12 background it seemed to imply that those subjects that
13 were in the study for a year longer experienced
14 greater SAEs. And then it was the exacerbations with
15 patients that had hepatitis C.
16 DR. RAPPAPORT: They had greater SAEs
17 because -- they had a greater incidence of bad events
18 but the events weren't worse than the other people.
19 They were just more.
20 MR. MULLINS: More. Okay.
21 DR. WINCHELL: Well, I'll just -- let me try
22 to answer those questions, maybe all at once, which is

1 in addition to the data that we have on the opioid-
2 dependent population from Study 13, the additional
3 data that we have to refer to is the data in the
4 alcohol-dependent population that we reviewed under
5 the original NDA and that we've gone back to look at
6 pooled together. I don't know if you would call that
7 a MedDRA analysis. There are not a lot of other
8 studies of this product. It's only been on the market
9 for a few years and basically the studies that have
10 been done have been conducted by Alkermes and they are
11 part of the safety database.
12 Your concern about events of a hepatic
13 nature in the population with injection drug-related
14 diseases such as viral hepatitis and HIV is a concern
15 to us as well. So that's why we looked as carefully
16 as we did at the data that were submitted to us on the
17 potentially clinically significant hepatic
18 abnormalities that were reported as adverse events and
19 the actual laboratory values themselves.
20 And as Dr. Skeete presented, our conclusion
21 was that we did see mild elevations in hepatic
22 transaminases but we did not see indications of

1 serious drug-induced liver injury. So we actually
2 found that reassuring. Not to say that the drug does
3 not have hepatic effects, but to make the distinction
4 between having hepatic effects and being associated
5 with very severe and concerning hepatic events, we did
6 not see those. And despite having some patients who
7 have been treated as long as three years with the
8 product, we have not seen that. So you can regard
9 that as somewhat reassuring.
10 I would also say that one reason we did the
11 person-time analysis was to correct for the
12 observation that the longer you look at someone, the
13 more opportunity you have to see something adverse
14 happen to that person. So, we don't think that time
15 in treatment is the explanation for seeing more events
16 in all cases. I'm not sure that we have seen an
17 indication that the longer people are on the drug the
18 more likely it is for something bad to happen to them.
19 That's not -- that's not our conclusion from the data
20 that we reviewed.
21 DR. SCHULTZ: I think I have one question
22 that may be an FDA or a sponsor question. And then

1 I'd like to transition to any remaining sponsor
2 questions left over from this morning. We'll try to
3 briefly do those and then have the break.
4 I was intrigued. I think it was Dr.
5 Skeete's presentation by the whole issue of accidental
6 overdose at the conclusion most often or missed dose
7 during therapy. And I am concerned. I think that
8 might be worth attending to. The inference that it
9 was because of trying, you know, high doses trying to
10 overdue the blockade or overcome the blockade or lost
11 tolerance, I'd like to suggest, considering that
12 simple μ-opioid, you know, antagonism withdrawal in
13 and of itself with no change in the patient behavior
14 who may be chronically low threshold using and then as
15 soon as they drop from the study or discontinue from
16 therapy as a patient, without realizing it over the
17 ensuing few weeks, they will have a decline of this
18 blockade and they may run into an overdose situation.
19 I wasn't able to detect if there was any
20 monitoring data that followed patients after
21 discontinuing the study. And it wasn't clear -- the
22 few incidents that you have reported, I wasn't clear

1 how those were detected or if there's a monitoring
2 program that will help us detect those cases.
3 The cases that were reported as adverse
4 events in the clinical trial program, those -- they
5 came in as adverse event reports. Usually this would
6 be reported to the site. Something bad happened to
7 this patient. And when you looked at the time since
8 the last dose it was around the time that the next
9 injection was due. And similarly, this was the case
10 with the reports that have come in to our adverse
11 reporting system, most of which actually came from
12 Alkermes so they know about the same ones that we do.
13 That somebody calls up and says this patient, who was
14 on your drug, had an accidental overdose and the
15 narrative tells the story that either the patient was
16 supposed to get their dose two weeks ago and didn't or
17 they were about due for it.
18 I don't think anyone has been followed up
19 post-treatment because as far as I know almost every
20 study has an open label extension. Patients who are
21 responding to this drug continue to take it. Do you
22 have any post-treatment follow up? Or everybody just

1 stays on it if it's working for them?
2 But I will also comment that accidental
3 overdose after detoxification is a known risk, whether
4 the patient has been treated with an antagonist after
5 being detoxified or they've finished taper of an
6 agonist or they've been simply in a supportive care
7 environment with just symptomatic treatment, that it
8 is true that patients who have been detoxified are in
9 a state of risk.
10 DR. SCHULTZ: Are there other remaining
11 questions? We have some sponsor questions from
12 earlier that we may have remaining. I know Dr. White
13 had one.
14 DR. WHITE: My questions are about slide CC-
15 50. I was wondering -- the secondary endpoint of
16 treatment retention. And the key secondary endpoint
17 when you go out days, both of them are still --
18 there's no plateau. There's no asymptote. They're
19 still going down. And the question -- so one of the
20 questions is six months doesn't seem like it's long
21 enough to know what's really going to happen. And
22 even though there's an open label, it doesn't -- that

1 won't tell me whether -- the difference between what
2 occurs to placebo versus the Vivitrol. I guess unless
3 the Vivitrol reaches a plateau at 168 days. So I
4 wanted to comment on that.
5 And then there's been a lot of discussion on
6 the first four weeks. And there's no -- once you get
7 -- and it's been discussed that after four weeks
8 there's no interaction between the curves. So I guess
9 the question is do you still need the same dose at
10 that point in time?
11 Or -- and I have actually several other
12 questions.
13 DR. EHRICH: Dr. Wei, would you like to
14 address that question?
15 DR. WEI: Lee-Jen Wei, professor of
16 biostatistics at Harvard University.
17 Dr. White, also I'd like to also -- I'm not
18 trying to be nosey. I also want to address the
19 question Dr. Woolson raised about sensitivity analysis
20 later.
21 Could I have EF-62, please? Slide up.
22 Dr. White, if you look at this, this is a

1 very interesting Kaplan-Meier curves. You notice the
2 green one. That is for the Vivitrol group. If notice
3 the horizontal line from 0 to 76 weeks. So that's
4 including the Part B. Okay? But if you look at this
5 lower white Kaplan-Meier curve, that's actually 24
6 weeks. That's for placebo in Part A.
7 Now, Part B is on the top one. That means
8 the placebo patients switched to the Vivitrol group.
9 You notice very interestingly the Vivitrol group, they
10 actually, like you said, they stabilized. Also, the
11 patients from, excuse me, the patients from placebo
12 who switched to Vivitrol also stabilized. So that's a
13 really interesting phenomena of the Kaplan-Meier
14 curves.
15 DR. WHITE: So the 100 percent is the
16 subjects which -- which completed the study which
17 didn't relapse.
18 DR. WEI: We have 47 patients in placebo in
19 Part B.
20 DR. WHITE: Okay.
21 DR. WEI: Sixty-seven from Vivitrol enter
22 Part B.

1 DR. WHITE: Okay.
2 DR. WEI: So let me try to answer the four
3 weeks or five weeks. This will also address Dr.
4 Woolson's question.
5 Any clinical trials we started
6 randomization. Those two groups are comparable, but
7 after four weeks they are not comparable anymore
8 because a placebo arm actually you have those patients
9 -- the good patient. What we call good patient means
10 they actually behave very well. They actually stay in
11 the treatment. But for the Vivitrol group, you see
12 the mixture is different now. So after four weeks
13 they are not comparable anymore. So we cannot utilize
14 randomized clinical trials to compare the two groups
15 anymore.
16 DR. WHITE: Within that first four weeks,
17 what's the rate of usage between the two groups within
18 the first four weeks? Do you have that data?
19 DR. WEI: the first four weeks we had 45
20 people drop out from placebo and 15 drop out from
21 Vivitrol.
22 DR. WHITE: But if they use, they don't

1 necessarily drop out.
2 DR. WEI: I'm sorry sir -- ma'am.
3 DR. WHITE: The use of opioids does not
4 necessarily mean that they dropped out of the study.
5 DR. WEI: No, no. Actually, this is just
6 any kinds of drop out. They have a combination. Lack
7 of efficacy. Also it may be a challenging test is
8 positive. There are all combinations.
9 DR. WHITE: So normal -- I mean, when you
10 look at extinguishing a certain behavior of an
11 addiction, and this was discussed here, people --
12 sometimes the behavior will get worse before it gets
13 better or they will try and override. So I was just
14 wondering, do you have data on attempted overrides
15 within the first four weeks, even if they remained in
16 the study?
17 DR. WEI: I don't know that piece.
18 DR. EHRICH: Could you give us the core
19 slide where we showed all of the urine tests?
20 Slide up, please.
21 So I think this is probably the best way to
22 address your question. And you can see there's

1 relatively little witnessed sampling prior to
2 discontinuation. You can see there are a number of
3 early discontinuations on the placebo groups. So
4 during the first month there were nine positive
5 naloxone challenges and none in the placebo group.
6 And what this -- what we believe the phenomenon that
7 we're seeing is that for many of these patients, you
8 know, in contrast, for example, a smoking study where
9 he might come back in the study and say, hey, I'm
10 smoking more cigarettes.
11 For many patients, it's a terminal event
12 when they go back to addiction -- when they relapse,
13 they leave the study. I think as Dr. Winchell pointed
14 out, for many of these patients with the early
15 termination, we didn't -- there was no evidence of,
16 you know, a positive urine test. It was a terminal
17 event. Much higher in the placebo group and that's --
18 that draws the signal to the study.
19 DR. WEI: So, Dr. Woolson, if I may, to
20 answer your question about sensitivity analysis, if I
21 can have the patient disposition table, please.
22 So, Dr. Woolson -- slide up, please.

1 Dr. Woolson, if you notice we have different
2 reasons for drop out. As Dr. Erich was saying in the
3 beginning, we have a lack of efficacy, adverse effect
4 events, and et cetera. Right? So what we did was
5 instead of impute every drop out as a failure or a
6 positive test, we actually use a different way to
7 impute. For example, for lack of efficacy, we say
8 that's a positive test. But take the rest of the guys
9 as independent sensory. So any way we do the
10 sensitivity analysis, the result is highly
11 significant.
12 If I may have slide EF-53, please.
13 So, Dr. Woolson, if you look at one, two,
14 three, four, five. The fifth one and the sixth one,
15 there's a different way to impute. We get highly
16 significant results. So we only impute, for example,
17 lack of efficacy as a positive test and the rest of
18 the guys we don't impute.
19 One -- if you count one, two, three, four,
20 fifth. The fifth row. Okay, the fifth row and the
21 sixth one. Right? For example, you take the sixth
22 one and impute the missing data as a positive for

1 those who discontinued due to lack of efficacy. Also,
2 a positive challenge test. Also AE. But we leave the
3 rest of the guys like a sensory. So our p-value is
4 .00001.
5 DR. WOOLSON: If I could just follow up. I
6 mean, I guess I was -- the last picture we had up
7 there, I think it was number 47 that showed the
8 longitudinal information, basically the imputation
9 that has been -- the analysis that's been presented in
10 the documents and presentations today rely very
11 heavily on essentially everybody who is incomplete up
12 there. They become orange all the way across. That's
13 what the imputation did. And yet there's nobody
14 observed who was completely orange.
15 And if I'm understanding that correctly and
16 that represents to me an extreme position. I think
17 there's a reasonableness to it in a sense that people
18 who dropped out probably are doing worse, but the
19 other extreme would be that those individuals who
20 dropped out are not doing worse. Now, that's a silly
21 position to take but that represents the other
22 extreme.

1 And so what I'm trying to figure out is
2 what's the break point in there? Is there a point at
3 which I still get a significant result, significant
4 finding by assuming something in between? And I'm
5 trying to figure out what that in between is. I'm
6 just trying -- as if this were my own data. That's
7 what I'm trying to struggle with.
8 DR. EHRICH: I guess the --
9 DR. WOOLSON: So is item 5 that you just
10 showed up there, Dr. Wei, does that speak to that
11 point in some way?
12 DR. WEI: Well, Dr. Woolson, if you -- for
13 example, we can't use so-called observable data for
14 example. Right? Just so you can know about the blank
15 stuff. Right? So that's still -- we call it
16 observable, assuming it's random missing completely,
17 we still get a significant result. That's one
18 sensitivity analysis.
19 Second sensitivity analysis, like I show
20 you, I only impute the positive test results for those
21 guys for lack of efficacy. And that's also
22 significant. So no matter how you manage the

1 imputation, you've got decent p-values.

2 DR. SCHULTZ: I think unfortunately due to

3 time and the interest of being able to get through our

4 voting procedures, we will need to proceed with just a

5 five minute break and then we'll have to return with

6 our closing charge and questions. And I know there

7 were a few more sponsor questions but I think we're

8 going to have to move to the break at this time for

9 just five minutes.

10 (Recess.)

11 DR. SCHULTZ: Hi there. All right. We'll

12 resume our session. I'd like -- and this will begin

13 our panel discussion. I'd like to invite Dr.

14 Rappaport to present the charge to the Committee and

15 the questions that we should focus on

16 **Charge to the Committee**

17 DR. RAPPAPORT: Okay, thank you.

18 So you've heard a lot of information today

19 about the efficacy and safety of this new formulation

20 of the drug and about the integrity and quality of the

21 data. And you've also heard some, I think, very

22 moving and important comments from our speakers at the

1 open public hearing and we don't take those lightly.
2 And I think we've made it clear that we
3 agree with the sponsor that they have demonstrated
4 efficacy and that there are no particularly concerning
5 new safety signals with this formulation. And really,
6 we did not find any concerns related to the data
7 integrity from the one study. But it still raises --
8 the single study, done in Russia, still raises
9 questions that need to be addressed that were brought
10 up by Dr. O'Neill.
11 I think we feel that we've adequately
12 addressed those questions to our level of comfort but
13 we want to hear from you. I mean, we're bringing you
14 in here today because this is one of those situations
15 where we need to have outside experts look at this
16 material and say, you know, maybe you're not thinking
17 exactly clearly about this or you missed this or this
18 is something that you need to take into consideration.
19 So, in addition, the reason we brought you
20 here today is because we do think this has the
21 potential for being very useful to the community of
22 patients who need it. So if it is a drug, an

1 application and a development program that is
2 acceptable, we would like to be able to move in that
3 direction assuming all of the other issues that we
4 deal with -- the manufacturing, chemistry, and all
5 those things -- are taken care of appropriately.
6 So the questions we're putting to you today
7 are pretty simple. Do you agree that this drug is
8 effective? Do you agree that there are no unusual
9 safety concerns? Do you agree that the quality of the
10 data from the single site in Russia supports the use
11 of the product in the U.S. population? And then
12 overall, should we approve the drug?
13 Thank you for your time and consideration.
14 **Panel Discussion and Questions to the Committee**
15 DR. SCHULTZ: I'd like to invite the
16 Committee to discuss those questions. We'll begin
17 with the first question.
18 Dr. Walsh?
19 DR. WALSH: So, this is an interesting
20 situation because we have a drug that was previously
21 approved in the absence of efficacy data many years
22 ago. And that's really because of the peculiarities

1 of the drug. I mean, this is a drug that we, from
2 laboratory studies and under supervised dosing, we
3 know is pharmacologically efficacious. And then you
4 put the patient into the mix and their motivations and
5 the setting.
6 Whether or not you can demonstrate
7 effectiveness is a different question. So we heard
8 from someone in the audience who is a nurse and a
9 mother, who actually was supervising her own child's
10 injections. And it's efficacious and effective.
11 So all of the discussion that we're having
12 about retention and trying to evaluate kind of in a
13 standard double-blind clinical trial is there enough
14 of a signal to determine that it really works?
15 Because we've got high drop out. I think it all needs
16 to be considered in context that we know if people
17 actually take the medication, that it works. And
18 that's certainly the case with the oral version. So
19 it got marketed. It's not widely used.
20 When it is used by people, and in many cases
21 here, you know, it's used with physicians that are
22 under supervision because they've gotten into some

1 trouble and they have a lot of motivation to take it.
2 It's remarkably efficacious and effective. So, I
3 think we're evaluating this in that same context.
4 That we've got high dropout rates. What does that
5 really mean? So, I personally think that it's an
6 efficacious drug.
7 The next, you know, the other question is in
8 the context of how we do our science, are we able to
9 design the study in a way that also shows
10 effectiveness? And I think that the FDA and the
11 sponsor work together to try and figure out how to
12 look creatively at the endpoints to address and
13 anticipate some of those problems by having a little
14 bit of a more flexible outcome.
15 DR. SCHULTZ: Dr. Covington?
16 DR. COVINGTON: And just a quick -- I think
17 it's compelling and it's obvious to everybody that
18 pharmacologically the drug works. What we don't know
19 as much about is what happens to the people. When the
20 people are taking the drug we know that they by and
21 large start using -- stop using opioids. We don't
22 know if they all go out and start smoking crack

1 cocaine and have strokes. You know, there's not much
2 to tell us what happens to the human beings but
3 there's really -- doesn't seem to be much question
4 that the opioid addiction is interrupted successfully.
5 DR. SCHULTZ: Dr. Baxter?
6 DR. BAXTER: Yes. It does appear to be
7 sufficiently efficacious. But I also want to hasten
8 to say that we need to understand that this is an
9 adjunct to the treatment for folks that actually have
10 addiction.
11 And that all of the data to present tell us
12 that there is no one drug that is the magic bullet and
13 that this is not the cure. But actually, that it is
14 part of a full treatment experience that should
15 include psychosocial therapy and a continued
16 monitoring, involvement in 12-step recovery, and so
17 on. So I think that in that context that it does
18 appear to have great efficacy.
19 DR. SCHULTZ: Dr. Tai?
20 DR. TAI: Thank you. My experience working
21 in conducting trials and developing and testing
22 medications for treating addiction has been many, many

1 years.

2 If I tell you, you will figure out how old I

3 am. So I'll just tell you many, many years. And it's

4 rare to see data this robust to show the efficacy.

5 Although it is in one study, but I think I echo Dr.

6 Walsh's sentiment that there are the studies for

7 alcohol and there are the studies, you know,

8 pharmacological studies and experience in being used.

9 And the test in the community was the oral

10 formulation. And even earlier there were pharmacists

11 that just pack it and implant it into a patient's

12 belly.

13 So what I'm seeing here is that I applaud

14 this drug company took the charge in developing

15 something which may not even have a profit margin but

16 it's for the patient need. And if we approve this

17 drug, we provide more tools. And we all understand

18 that one drug is not going to be perfect, efficacious

19 for everyone, but we do need tools. We do need

20 options. And we have so few options for addiction,

21 especially for opioid addiction. Maybe it's even a

22 better one. This is the third drug. And with this

1 new formulation it provides so much potential and so
2 much hope that it may work.
3 I think one study does bother me a little
4 bit but as I said, you know, for this particular
5 submission they did have the opportunity to pool the
6 safety data and efficacy data from some other study.
7 I think the key issue here is studies need to be
8 conducted to see how to best select the patient that
9 has the best success potential, how to best deliver
10 this medication so it can carry its full potential,
11 and all those studies will be facilitated if the drug
12 gets approved, in my opinion.
13 And I know that naltrexone is a very
14 mysterious drug. It has a lot of potential. Many
15 people use this off label right now for many other
16 indications. If we can approve this for addiction
17 indication, it really facilitates so much more study -
18 - how to better study this and how to provide
19 additional information and to let this medication have
20 a chance to be more successful. And if it's
21 continuously not being approved, you see the hurdle is
22 much higher and, you know, by looking at the safety

1 data and with the experts' input, I am fairly
2 convinced this is quite a relatively safe drug.
3 So that's my humble opinion with my many,
4 many, many years experience working at NIDA. And I do
5 think it is something I hope everyone will seriously
6 consider based on the reasons that I just provided to
7 you. Thank you.
8 DR. SCHULTZ: Well, thank you. I think in
9 aggregate this is a good discussion. I think I'm
10 hearing questions about, you know, real world
11 effectiveness may become an issue. There may be
12 issues of people using substitute addictions and the
13 need for concomitant, you know, psychosocial
14 interventions. I think those are all great points.
15 And the need for better strategies to find the most
16 receptive populations.
17 But I think back to the question are we
18 comfortable. Is this effective as a treatment for
19 opioid dependence in the population that was studied
20 here? I think we're ready to vote on that question
21 unless there's other discussion.
22 DR. HWANG: (Off microphone.)

1 DR. SCHULTZ: One comment from Dr. Hwang.
2 DR. HWANG: Okay. Thanks. I do agree with
3 everybody's, you know, what has been presented. But I
4 just want to remind everybody that coming from New
5 York and having seen all kinds of patients, especially
6 substance abusing patients, once approved, this
7 medication will be used in very, very high risk
8 patient populations.
9 And I think that we should keep that in our
10 mind. Potential serious adverse events, such as acute
11 withdrawal symptoms and suicide will be a significant
12 problem. Critical problem. So, but in view of lack
13 of treatment currently -- lack of current treatment in
14 this population, I think that I would also support
15 approval.
16 DR. SCHULTZ: Thank you. And some of those
17 points may come up in further questions about safety
18 as well. So thank you. I think we can proceed with
19 instructions on voting.
20 DR. WAPLES: Yes. For today you will be
21 using the electronic voting system. Each of you have
22 three voting buttons on your microphone -- yes, no,

1 and abstain. Once you begin to vote, please press the
2 button that corresponds to your vote. After everyone
3 has completed their vote, the vote will be locked in.
4 The vote will then be displayed in the screen. The
5 chair will read the vote from the screen into the
6 record. Next, you will go around the room and each
7 individual who voted will state their name and vote
8 into the record as well as the reason why they voted
9 as they did.
10 You can begin your vote with Question No. 1.
11 DR. SCHULTZ: I just voted accidentally.
12 For the record, the voting results are 11 -
13 yes; 2 - no; 0 - abstain for Question No. 1.
14 And Dr. Denisco, if we could start at your
15 end, state your vote and your reason.
16 DR. DENISCO: Richard Denisco. I voted yes
17 because I feel that the study conducted was excellent.
18 The people conducting it have likewise an excellent
19 reputation and I think that sometimes it’s not only
20 the study details that we’re allowed to see but the
21 people behind the study that are as important. And
22 also, that the medication has been used extensively

1 off label without any adverse effects and has been
2 used -- that's all. Thank you.
3 DR. MAXWELL: Jane Maxwell. I voted yes for
4 the same reasons as Mr. Denisco. But in addition,
5 very much we need an additional medication in the tool
6 kit and this one has great potential for relapse
7 prevention.
8 DR. MONTOYA: Ivan Montoya. I voted yes
9 because the pharmacology of the medication is very
10 compelling that it's going to be effective. The study
11 was very well conducted and this medication will play
12 a very important role in the toolbox of medications
13 for the treatment of opioid dependence as a relapse
14 prevention tool.
15 DR. TAI: Same. I think Ivan said that very
16 well. Betty Tai. I vote yes for the same reason that
17 Dr. Montoya has talked and the previous two members,
18 too.
19 DR. BAXTER: Dr. Louis Baxter. And I vote
20 yes. I think that the presentations did answer a lot
21 of questions and I have seen the efficacy firsthand
22 with some of the patients that I've treated and some

1 of the data that I've read.

2 DR. WALSH: Sharon Walsh. And I voted yes

3 for some of the same reasons that have already been

4 described. But in addition to the known pharmacology,

5 we have a lot of experience with this drug. This is a

6 new formulation and we're in a fortunate position to

7 already have a fair amount of experience with this

8 formulation, albeit in a different population. And I

9 also agree that the study appeared to be well done and

10 I also had confidence about the integrity of the study

11 in part because of the FDA's careful evaluation of the

12 data that were presented and their agreement with the

13 sponsor's interpretation of the findings.

14 DR. HWANG: My name is Michael Hwang and I

15 voted yes. I do agree with the comments made earlier.

16 In addition, the medication is not a totally unknown

17 entity. Naltrexone has been used for many years and

18 it's known to be effective in the treatment of alcohol

19 dependency which shares similar neurochemical

20 characteristics as opiate drugs.

21 DR. WHITE: Tonya White. I voted yes for a

22 number of the reasons that have been already stated.

1 The other thing in a medication which targets the
2 actual μ-receptor which is what is the source of the
3 dependence seems like a likely, you know, a good
4 choice.
5 The other question which the FDA -- I guess
6 their mission was -- the study needs to be compelling
7 was the mission to the sponsor. And so I was
8 considering the study on what does compelling mean.
9 And considering substance abuse disorders are so
10 difficult to treat, I think the results are
11 compelling.
12 DR. SCHULTZ: Susan Schultz. I voted yes.
13 I believe that the single clinical trial data were
14 sufficient in view of pre-existing related data from
15 other trials.
16 DR. WOOLSON: Robert Woolson. I voted no.
17 I was concerned about the high dropout rate, the
18 differential dropout rate and equating that to simply
19 non-retention. And since I had that particular
20 concern, that then really then also put into question
21 the idea of one single -- a single clinical trial
22 actually being used to support efficacy. That's the

1 basis for my opinion.
2 MR. MULLINS: My name is Rodney Mullins and
3 I voted no. And primarily because of the lack of
4 comparative data and it was just one single trial. So
5 those factors really concerned me. I had nothing
6 really -- no other data to compare the single clinical
7 trial to so that concerned me. Thank you.
8 DR. MICHNA: Ed Michna. And I voted yes for
9 all the compelling reasons that my colleagues have
10 already stated.
11 DR. COVINGTON: Ed Covington. I voted yes
12 for the same reason.
13 DR. SCHULTZ: Okay. We'll proceed to
14 Question 2. Question 2 is can the results observed in
15 the studied population be applied to the U.S. target
16 population? I'd like to invite discussion on Question
17 2.
18 Dr. Potter?
19 DR. POTTER: Yeah. As Dr. O'Neill
20 articulated, this is a huge question for us to
21 understand as a field when foreign data might or might
22 not be applied and what do we look for. So I just

1 wanted to comment that in areas where we do have vast
2 amounts of data that the Psychopharmacologic Review
3 Committee has seen in areas like depression and
4 schizophrenia, you get some very surprising results
5 sort of counterintuitive, like placebo responses go up
6 in the United States recently and you get better
7 signals with known antipsychotics outside of the
8 United States. So there are no rules to this as Dr.
9 O'Neill articulated.
10 So I guess in thinking through this, I would
11 encourage us -- I wonder, as Committee members look at
12 this and think about it, what would the biases be?
13 And the big question here are dropout rates as Dr.
14 Woolson said. So it seems to be, and I guess the real
15 question is, is there something highly atypical about
16 the behavior of this Russian population versus what
17 you expect? And the data, I think that was shared,
18 and maybe people can comment on this, is that
19 apparently retention and dropout rates in trials of
20 individuals with substance abuse are very high
21 everywhere.
22 And so I guess if one had seen -- I'm just

1 curious how people, I guess if one had seen extremely
2 high retention rates, which I think was Mr. Mullins'
3 point, these people might be motivated. If one had
4 seen very, very high retention rates, you might say,
5 gosh, why are these people retaining? Maybe this is
6 the only thing they can get. That's not what we're
7 seeing. We're seeing in the people who don't get
8 drugs, very high dropout rates.
9 So at least as I look at this, the one area
10 where one might pick up a true, what I call relevant
11 bias in terms of the efficacy measures, it's very hard
12 to see it. I'm just speaking more as a scientist here
13 than anything else because we look for this. Because
14 as drug companies we don't want false positive signals
15 or we can't reproduce other places. But here the bias
16 would seem to be you're getting high dropout rates. I
17 don't know how people feel. That's just a comment on
18 the placebo.
19 DR. SCHULTZ: Mr. Mullins?
20 MR. MULLINS: On this question I have some
21 concerns. And my concerns deal with three areas,
22 going back to a statement Dr. Maxwell said earlier.

1 Is the type of opiate used -- I don't know if we're
2 comparing the same opiate. I mean, we have a narcotic
3 and analgesic versus heroin. So that obviously to me
4 is going to affect performance of the therapy.
5 Secondly, I'm concerned about the
6 underreporting of adverse events. I mean, the
7 testimony, the information from Dr. Sheth concerns me.
8 What Dr. Sheth stated was that there were cultural
9 differences in reporting. I think we have to take
10 that into consideration when we deal with
11 international trials. I mean, the definition of
12 adverse event, that was never defined. So I don't
13 know if it's synonymous between the U.S. population,
14 U.S. subjects and, you know, I don't know -- I
15 question integrity.
16 I'm trying to understand integrity between
17 the two trials because basically what dr. Sheth said
18 because the evidence presented to us showed a
19 disparity between the U.S. reporting of adverse events
20 and the Russia reporting of adverse events, which I
21 was looking for further data on that.
22 Then, also, I am concerned about the one

1 dimensional nature of the patient population. I think
2 the patient population in the U.S. is different. They
3 have co-morbidities. The co-morbidity rate of the
4 U.S. population seems higher as far as HIV and
5 hepatitis C. So, excuse me. Excuse me. Not that.
6 But I think -- I know the patient profile -- the
7 difference in patient profile concerned me between the
8 U.S. population and the Russian population as far as
9 demographics and gender. The mix. So that did
10 concern me. Thank you.
11 DR. SCHULTZ: I'm sorry. Dr. Maxwell.
12 DR. MAXWELL: Let me clarify what I was
13 talking about in talking about the different types of
14 heroin. The heroin used in Russia is the southwest
15 Asian and Afghan heroin. And what I was thinking
16 about as drugs move through, people add different
17 diluents or adulterants, just like right now you're
18 seeing the levamisole being added to cocaine. So we
19 could have adverse events due simply to the heroin and
20 what it's being cut with. West of the Mississippi
21 you're going to pick up adverse events because of the
22 presence of diphenhydramine which is used to cut

1 heroin.

2 So that was my question -- concern that

3 possibly you get different heroins that could provoke

4 different adverse events, higher or lower, just

5 because of what's added to the heroin.

6 And again, the Russians do not have typical

7 treatment programs like we do where you've got a

8 plethora of every kind of treatment known. The only

9 things they've got are long-term residential drug

10 free. So this is the only, to my knowledge, treatment

11 available in Russia that uses medication-assisted

12 therapy. So, this would have been like -- this is a

13 great new program. If I were an addict and I could

14 get into it, I'd get into it. And because it was so

15 much better, just because of the counseling and all,

16 even if I was on the placebo, I'd be very hesitant to

17 complain and drop out because I know my other option

18 is probably pretty unpleasant.

19 MR. MULLINS: But that's my question. We

20 don't have a lot of details on toxicology or

21 information or appearance of other opiates within the

22 subjects. So, in other words, that was a question,

1 too, I had. You know, pre-treatments in the presence
2 of other substances within the subjects.
3 DR. SCHULTZ: Dr. Denisco had a point.
4 DR. DENISCO: Well, just to kind of go over
5 some of the things. First, I think I wanted to jump
6 back and say that the information provided us by the
7 FDA and the sponsor was excellent and thank the FDA
8 for organizing this in such a very well organized way.
9 First comment is 90 percent of all the
10 heroin in the world right now is Afghani. And in
11 terms of different types of cross-reactivity between
12 different opiates, it's generally not more -- there's
13 generally at least 80 to 90 percent cross-reactivity.
14 So what I'm trying to say by that is that an opiate is
15 an opiate is an opiate 80 to 90 to 100 percent of the
16 time. And we know that the μ-receptor is being
17 blocked and that that is the mechanism of action. So
18 that I think that any differences in whether it's
19 prescription opiates or oxycontin or heroin, it
20 doesn't make a significant difference.
21 Number two, I think the Russian people are
22 probably more stoic. Americans complain about

1 everything.

2 UNIDENTIFIED SPEAKER: You?

3 DR. DENISCO: Yeah. Including me.

4 And third, is regarding the gender and

5 ethnic differences. I don't see that -- either of

6 those as making, in my clinical experience with opiate

7 abusers of all types of opiates -- that gender or

8 ethnicity make any difference. It seems to present

9 the same way, whether it's a young, white female, old

10 African male with hair on, it's just the same drug.

11 And so, you know, we're not at the point where we're

12 going to be treating these people with DNA analysis to

13 see if they are specifically in the best group to

14 receive this.

15 So I think that the gender and ethnicity

16 make no difference in this particular case as they

17 might for other situations where it would be

18 important.

19 DR. SCHULTZ: I'd like to make one point

20 that I think we might want to just think briefly

21 about. Addictions may not differ but I definitely

22 think the populations may well differ when you look at

1 the male population in Russia and transporting that to
2 the U.S. You're going to see a couple of things.
3 You're going to see more analgesic users, which is
4 going to translate into probably a higher body mass
5 index. Heroin is typically sort of a wasting
6 condition. The body mass index in the Russian sample
7 was 23, which is sort of low healthy. In the 006
8 study in the U.S., the body mass index was 25.
9 I anticipate if we move this into widespread
10 use, you're going to see female analgesic users and
11 we're going to see a quite different body mass index.
12 And I think that doesn't speak to efficacy, per se.
13 It speaks to the ability to provide the compound in an
14 intramuscular way effectively and avoid the
15 subcutaneous injection reactions which I think is
16 something to attend to and it's really a separate
17 question that probably bears more on safety. But I
18 think we need to recognize it's going to be a
19 different -- it's going to be a different use and we
20 need to think about how to monitor that and what
21 expectations to have from that.
22 Dr. Covington had a point as well.

1 DR. COVINGTON: One of the things that's, I
2 guess, comforting to me, I feel sure that there will
3 be cultural differences in the acceptability of this
4 product.
5 On the other hand, I don't know of any
6 reason to think that anybody would be exposed to it
7 unless they were actually benefitting from it. So I
8 think that's kind of reassuring that, you know, there
9 may be, you know, maybe Americans won't like it as
10 much as Russians or something. And so they're not
11 going to take it. It's not like -- I'm in the pain
12 business and so I'm accustomed to seeing people who
13 are taking 15 drugs, one of which they think might
14 help a little.
15 So, and I don't think that's going to happen
16 here. If people are taking it, it'll be because it's
17 working.
18 DR. SCHULTZ: Thank you. I think Dr.
19 Montoya had a question.
20 DR. MONTOYA: I was going to say that in
21 terms of opioid dependence, the clinical
22 manifestations of opioid dependence and opioid

1 withdrawal are exactly the same in any culture. It's
2 the same goose bumps, abdominal pain, muscle cramps,
3 sweating, and so on and so forth. So that's not going
4 to change.
5 And we also need to keep in mind that this
6 medication is being -- the indication is for relapse
7 prevention. So when people are going to start this
8 medication, they are supposed to be detoxified. They
9 shouldn't have opioid dependence. And according to
10 the study they had a naloxone challenge as a way to
11 confirm that they were not opioid dependent. So they
12 always start from a baseline. From zero opioid
13 dependence.
14 DR. SCHULTZ: Thank you. Dr. Walsh, you had
15 a question?
16 DR. WALSH: Really more of a comment. When
17 we were given the guidelines about differences in
18 bridging studies for different cultures, the one thing
19 that aside from the body mass that I thought about was
20 really what Dr. Maxwell brought up, which is the
21 absence of agonist substitution therapy in Russia and
22 that this is the only game in town so there's more

1 motivation and what would the consequences be to the
2 study that we were evaluating. And I think the
3 consequences would be that the retention rates would
4 be lower.
5 And it's interesting to hear folks on that
6 side of the table talk about how low these retention
7 rates are because I have to say in my experience, if
8 you look at the key secondary endpoint which is
9 treatment retention, they've actually manage to retain
10 more than 40 percent of the patients at six months who
11 have basically just detoxified. I mean, they are
12 getting counseling. They've detoxified. That's all
13 that they've done. I mean, they're on placebo.
14 And if you collapsed the cross studies that
15 have been done here in the U.S. and elsewhere, you
16 know, if you detoxify somebody in an inpatient
17 setting, 90 percent of them have relapsed easily
18 within the first year.
19 So these are really, really high retention
20 rates for placebo shown here. And so I think that,
21 you know, we would see something that's shifted
22 downwards if we redid this study here because, you

1 know, there are alternative treatments, although not
2 really that readily available to most people in
3 reality. So I think, you know, we just need to keep
4 that in context.
5 DR. SCHULTZ: Other comments? I think Dr.
6 Tai did at one point. No? Okay.
7 DR. HWANG: (Off microphone.)
8 DR. SCHULTZ: Yes, Dr. Hwang.
9 DR. HWANG: I think the question is a tough
10 question. The question is can the result be observed
11 in the U.S. population? Based on dealing with the
12 treatment outcome issues here and the treatment
13 outcome is a very complex issue. It's not purely
14 dependent on medications and chemistry, significant
15 psychosocial issues, alternative treatment issues. So
16 I find the question very difficult.
17 DR. SCHULTZ: Thank you. Other comments?
18 I think that was an excellent point. This
19 is an exquisitely difficult question because it
20 requires extrapolation of a not quite not U.S. sample
21 to try to understand how differences might superimpose
22 on the U.S. And so I think with all those caveats

1 that it's a different treatment, opportunity milieu,
2 it's a different stoicism index, there are a number of
3 differences. I think the best we can do is try to
4 make our best estimate as to whether the results
5 observed can be applied to the U.S. in the most
6 general sense unless we have more directions from our
7 FDA -- it is a difficult question.
8 I think we'll go ahead and proceed to vote
9 with -- for No. 2. Can the results observed in the
10 study population be applied to the U.S. population?
11 Please vote.
12 The voting results for Question No. 2 are
13 yes - 10; no - 1; abstain - 2.
14 We'll start with Dr. Denisco. Mention your
15 vote and why.
16 DR. DENISCO: Richard Denisco. I voted yes.
17 And I voted yes primarily for the reasons that I
18 previously stated. Should I state them again?
19 DR. MAXWELL: Jane Maxwell. I voted yes for
20 the same reasons. And actually, I'm going to be
21 fascinated to see the data when they start using it
22 and to see are there really differences. How the

1 treatments get adjusted. This will be a fun study.
2 DR. MONTOYA: I voted yes because the
3 pharmacology of the medication assures me that it's
4 going to work in any population in the world. And I
5 also -- it assured me to listen to the testimony of
6 the 10 people who came here who are Americans. Nobody
7 had my accent at least. So. And they -- and see that
8 they were able to come and stop using heroin or
9 opiates.
10 DR. TAI: I voted yes despite the fact that
11 I totally agree with Dr. Hwang. This is a very tough
12 question. So I did a little parceling of the words.
13 The wording was saying this population be applied to
14 the U.S. target population. I think from Dr. Earley's
15 presentation he said in his practice experience he's
16 seen this is good medication for young, short
17 addiction history, highly motivated, such as addicted
18 professionals, and also with a strong social and
19 family support. Based on those, I think that's
20 comparable to the Russian population in study based on
21 the report I have reviewed. So that's why I voted
22 yes. Thank you.

1 DR. SCHULTZ: And that was Dr. Tai.
2 DR. BAXTER: Dr. Louis Baxter. I voted yes
3 primarily because I'm of the belief that no one piece
4 of treatment decides totally what an outcome is. So
5 using this medicine in conjunction with the other
6 elements of addiction treatment, I believe that we
7 will actually be able to observe those same results
8 and perhaps even better.
9 DR. WALSH: Sharon Walsh, and I voted yes.
10 In part because I believe that the pharmacological
11 efficacy will be comparable. We didn't see any
12 evidence on differences in metabolism or toxicity that
13 would suggest otherwise from just a very basic
14 pharmacology standpoint. And then we acknowledge that
15 there are cultural differences and stoicism, things
16 like that. We're going to see the same differences
17 within our own population. And so the actual outcome
18 for effectiveness I think is going to be highly
19 contingent on the conditions under which the treatment
20 is delivered.
21 DR. HWANG: I'm Michael Hwang. I voted to
22 abstain from this question basically because I've seen

1 substance abusing patients in varying environments and
2 I find the question very difficult to answer. So I
3 voted to abstain.
4 DR. WHITE: Tonya White. I voted to abstain
5 also. I found it also a difficult question and could
6 answer yes to some aspects and no to some aspects.
7 From the standpoint of the neurobiology, I think
8 there's really no question that it blocks the μ-
9 receptor and that it's going to be, from that aspect,
10 effective. There's many unknowns that I had and I'm
11 currently living in the Netherlands.
12 I was asking myself, you know, would this
13 be, you know, the differences in systems, of which
14 there are differences in systems between the health
15 care in the Netherlands and health care here in terms
16 of support and other aspects. And then extrapolating
17 that to the Netherlands, I realize that there's many
18 things that I don't know about the system in Russia.
19 DR. SCHULTZ: Susan Schultz. I voted yes,
20 largely because the neurobiologic factor that μ-opioid
21 receptors are universal.
22 DR. WOOLSON: Robert Woolson. I voted yes,

1 largely following Dr. Schultz's directive right before
2 we voted that we had to sort of weigh things and I
3 thought there were more similarities than
4 dissimilarities.
5 MR. MULLINS: Rodney Mullins. And the
6 reason I voted no is because I think other than the
7 biochemical and biokinetics -- biokinetic behavior of
8 a compound, there are other issues that play into the
9 whole process of cessation from usage of a drug and
10 abuse of a drug. I think there are social issues. I
11 think there are psychological issues that play into
12 this entire treatment process. I don't think we know
13 enough about that. I don't think we know the factors
14 that inhibit or the factors that aid that whole
15 process. So I think that we have to take that under
16 consideration before we make these gross assessments
17 and these blanket statements about efficacy.
18 And more importantly, safety. I think
19 obviously with efficacy we can make some statements
20 because of the biochemical behavior of the treatment.
21 But I think when it comes to safety we have to be a
22 little bit more concerned about our assumptions.

1 Thank you.

2 DR. MICHNA: Ed Michna. I voted yes for

3 similar reasons that Dr. Walsh had stated.

4 DR. COVINGTON: I voted yes. And certainly

5 taking into consideration Dr. Hwang's statements which

6 I think are critically important, but for me the

7 question is, you know, would a person in America be as

8 likely as a person in Russia to find that their

9 efforts to maintain sobriety were facilitated if they

10 could be sure that they were sober and thinking

11 straight for the next 30 days. And I think the answer

12 to that is not going to be dependent on cultural

13 context.

14 DR. SCHULTZ: Okay. Question No. 3. If the

15 answer to Question 2 is no, what additional data are

16 needed? So I'd like to invite Drs. Hwang, White, and

17 Mullins that felt that the answer was no or abstain,

18 if you'd like to discuss what additional data may be

19 needed or what may be helpful or direction for the FDA

20 on addressing that point.

21 DR. HWANG: Michael Hwang. I do agree. I

22 think that it's enough evidence, historical evidence,

1 and also, you know, pharmacological evidence that this
2 medication is effective in treatment of opioid
3 dependency.
4 What I would want to see is more data on
5 controlled studies where the treatment milieu between
6 Russian patient population and the U.S. patient
7 population, or even any other country's study subjects
8 be exposed to similar environment and want to see
9 outcome data from those studies.
10 DR. SCHULTZ: Thank you. Other comments?
11 DR. WHITE: The -- I guess when naltrexone
12 was first approved, it was approved and then had
13 questionable efficacy because of issues of non-
14 adherence or proposed non-adherence. It would be nice
15 to see studies performed in the U.S. where there are a
16 number of other treatment options that are available.
17 I think as I voted yes for the efficacy, I think it's
18 potentially a very powerful tool in a difficult to
19 treat population. But I would like to see -- to make
20 sure that it's efficacious here in the population in
21 the U.S.
22 DR. SCHULTZ: Any other comments on needed

1 data? Any other discussion or we'll move to Question
2 4.
3 DR. MONTOYA: (Off microphone.)
4 DR. SCHULTZ: I'm sorry. Dr. Montoya.
5 DR. MONTOYA: Ivan Montoya. I voted yes and
6 I think that in terms of the approach and even in the
7 target population is perfectly fine. One thing that
8 is very important to keep in mind is that the
9 population in Russia was already detoxified because
10 people -- they don't have methadone over there so one
11 important study for the U.S. is to the transition from
12 opioid agonist treatment, methadone or buprenorphine
13 to the depo naltrexone to make sure that people have a
14 good tolerance to the medication.
15 DR. SCHULTZ: Dr. Walsh?
16 DR. WALSH: Am I allowed to ask a question
17 about labeling to the FDA staff? Though it kind of
18 follows on from Dr. Montoya's question, and that is
19 with respect to the specific product.
20 One of the things that we've seen with
21 saboxone, even with the requirement of having a
22 special license, is that there are a lot of physicians

1 who get a special license who actually don't have a
2 lot of experience with addiction. They come from
3 other specialty areas and they do an eight-hour
4 training and then they're treating patients. And the
5 specifics of naloxone challenge to ensure the absence
6 of physical dependence is, you know, it's not rocket
7 science but if you haven't done it before and you
8 don't know what kind of tool to use in order to assess
9 the appearance of precipitated withdrawal, it may not
10 be so obvious to someone who doesn't work in
11 addictions.
12 I'm wondering what kind of information will
13 be in the labeling so that when -- if and when the
14 drug is marketed and then allowed for widespread use
15 for the average physician who decides that they just
16 want to enter into treatment of opiate dependence,
17 what instruction set will they get so that we can
18 ensure that we're not putting people into precipitated
19 withdrawal that then last for many, many, many hours
20 or days?
21 DR. WINCHELL: Alkermes will correct me if
22 I'm wrong, but I think there's just a brief

1 description at present. It's not a set of directions
2 on how to conduct it, although it looks like Dr.
3 Silverman has something to say.
4 DR. SILVERMAN: We agree it's very important
5 for physicians to ensure that people are opiate free
6 at the time of initiation of Vivitrol. One of the
7 things our field force does is distribute instructions
8 on how to conduct an oral naloxone challenge.
9 DR. WALSH: Thank you.
10 DR. SCHULTZ: Yes. Dr. Baxter?
11 DR. BAXTER: Yes. There is another piece to
12 that also -- is that that's short acting so it won't
13 be hours of agony. And that there are other support
14 systems being developed, sort of a physician's
15 clinical support network. So those individuals that
16 will be interested in using this medication will have
17 the support that they need in order to ask questions
18 and get some clinical direction.
19 DR. SCHULTZ: We'll move on to discussion of
20 Question No. 4. Taking into account the indication
21 are the safety data adequate?
22 Any additional discussion on Question 4?

1 Safety data.
2 Dr. Potter?
3 DR. POTTER: Again, in terms of the
4 experience with those central nervous system-related
5 studies where we have large datasets, we do observe
6 huge differences by geographic region in terms of the
7 report of side effects. But those differences occur
8 both in placebo group and the drug group. So the
9 question that we usually try to look at to know
10 whether a region is informative is do we have any
11 evidence that the drug versus placebo differences are
12 within the same competence limits, if you will, the
13 population estimate where we have clear drug placebo
14 data?
15 So I guess the only thing we really have
16 here to address that, and it's not a complete thing,
17 would be the patients treated in the placebo United
18 States with naloxone for alcohol abuse versus placebo.
19 Does that have a placebo arm, if I remember correctly?
20 I mean, maybe someone can comment on that.
21 And so the real question is, is there any
22 evidence that the significant side effect incidence

1 corrected with placebo would appear to be any
2 different in the United States data and the Russian
3 data? So I haven't heard that explicitly discussed
4 but that would seem to me the one most compelling
5 piece of information, whether or not the safety data
6 were really represented. I mean, just from a
7 practical point of view.
8 DR. WINCHELL: The overall adverse event
9 rates in the placebo arm in the American study in
10 alcoholics, Study 3, was a whole lot higher.
11 DR. POTTER: Exactly.
12 DR. WINCHELL: Than the reporting in the
13 placebo arm in Study 013.
14 DR. POTTER: So --
15 DR. WINCHELL: So it was an across the board
16 lower propensity to report.
17 DR. POTTER: So the specific question then
18 was in your estimates of the side effects, the ones
19 that we'd be concerned about, medically concerned
20 about, was there any evidence that the difference
21 between drug and placebo where you had compelling
22 evidence that it was a drug-related side effect, were

1 the estimates of that effect any different in the
2 Russian data for the opiate abuse versus the alcohol
3 abuse? Which isn't a perfect comparison, I
4 understand, but it's what you've got.
5 DR. WINCHELL: If you're asking whether we
6 did placebo subtracted rate for each individual
7 reported event and compared them, we didn't do that.
8 DR. SCHULTZ: Dr. Walsh?
9 DR. WALSH: I just have one quick question
10 for Dr. Winchell, and that's related to the reports of
11 overdose. One of the things I didn't see was whether
12 or not there was urinalysis done for those overdose
13 cases that provided evidence that there were other
14 drugs, illicit or licit onboard for those patients who
15 overdosed.
16 DR. WINCHELL: Dr. Silverman, do you know
17 the answer?
18 DR. SILVERMAN: I think it's important to
19 keep in mind that overdose is an inherent risk in this
20 population, with or without naltrexone. Naltrexone's
21 competitive blockade reduces the consequences or the
22 likelihood of having a severe overdose for any given

1 dose of opioids. I know that for some of the -- I
2 can't -- at least one of the post-marketing cases --
3 again, we're doing very small numbers despite a post-
4 marketing database of 45,000 people. I think there
5 were a total of four or five overdose cases -- one or
6 two of them did have other drugs in their system at
7 the time that the overdose was reported.
8 DR. WALSH: But all of them -- just -- all
9 of them were confirmed that opiates were involved. Is
10 that right? I mean, I'm just wondering whether or
11 not, even in this small number of cases of overdose
12 that are reported, do we even know that they were
13 related to opiates?
14 DR. SILVERMAN: Yeah. The FDA had four
15 cases in their reporting. In those four cases there
16 were opiates detected. We had listed five cases. The
17 fifth case was just someone who said that they had an
18 overdose. We didn't know when, where, or who reported
19 it. Just in the spirit of full disclosure. But in
20 the four cases, we agree with the FDA. Those were
21 confirmed.
22 DR. SCHULTZ: While I agree with the point -

1 - this is Susan Schultz -- while I agree with the
2 point that overdose is a risk in this population, I
3 think the labeling should be clear. The label right
4 now is very good about cautioning don't try to
5 override the blockade. There's good attention to that
6 and I think it calls the patient's awareness to if you
7 override the blockade that could have bad
8 consequences.
9 But I think it's also very important to
10 recognize that withdrawal of the compound will enable
11 the opioid receptors, you know, to respond to
12 continued use that may not be trying to override or
13 may not be a change in the patient's behavior and that
14 patient awareness of that is extremely important
15 because they may not think they're trying -- they
16 might not have changed their behavior but they stopped
17 the injections and they suffer from evidence of
18 toxicity.
19 So I just think it's an issue that just
20 requires, I think, clear disclosure so that we don't
21 infer that it's a patient behavior when, in fact, it's
22 withdrawal of the compound.

1 DR. WINCHELL: I'll just remind you there is
2 a Med Guide for this product, which his required to be
3 dispensed every time the product is dispensed. And
4 since the product is actually dispensed by the health
5 care provider, it's packaged with the individual dose.
6 And the Med Guide was developed primarily to alert the
7 patients to what to look for with regard to injection
8 site reactions, but at the same time it provides those
9 other pieces of information and is a very good vehicle
10 for alerting patients to the need to be cautious.
11 And we are modifying the language to
12 emphasize the end of the dosing interval as a period
13 of risk as opposed to the idea of high doses only and
14 overriding the blockade. It might be a typical dose
15 at the end of the dosing interval. So we'll be fixing
16 that language.
17 DR. MAXWELL: Can I add in one thing very
18 quickly? I'm sorry.
19 DR. SCHULTZ: -- Maxwell?
20 DR. MAXWELL: I'm sorry, Mr. Mullins. I
21 just want that in. Let's make sure there's also some
22 emphasis on informing the family. I've spent a lot of

1 time recently looking at methadone overdoses where the
2 family had no idea. And I think particularly this in
3 understanding that he's going to get the shot and at
4 the end of the month, if he doesn't get another shot,
5 you know, this is what's going to happen. Because
6 programs tend to say, well, the programs don't listen,
7 but I think they do.
8 MR. MULLINS: I just had a question on
9 suicidality and was there a particular subpopulation
10 that was predisposed to this particular adverse event.
11 I know this was in the post-marketing information so I
12 was just curious about that. It would be helpful to
13 know was there a certain predisposition for this
14 particular event?
15 DR. SILVERMAN: I'm sorry, which event?
16 MR. MULLINS: Suicidality.
17 DR. SILVERMAN: Suicidality. You know, we
18 had no evidence of suicidality in the 013 study. In
19 post-marketing it's very --
20 MR. MULLINS: Yeah, it was in post-
21 marketing. Right?
22 DR. SILVERMAN: It's very difficult to

1 determine underlying characteristics there because
2 people report as much -- and it may be the person
3 themselves reporting. It may be their physician or
4 another health care provider. So to my looking at the
5 cases there was no common thread there.
6 MR. MULLINS: Yeah. I just wanted to
7 understand that better and see if there was any causal
8 relationship.
9 DR. SILVERMAN: Again, this is a population
10 with very high risk of not just suicide attempts but
11 from literature I've read, 18 to 25 percent of people
12 with both sorts of dependence. We hope this drug will
13 be labeled alcohol and opioid. Eight (sic) to 25
14 percent die -- have a lifetime risk of death by
15 suicide.
16 DR. SCHULTZ: Dr. Hwang?
17 DR. HWANG: I would suggest that the company
18 collect and compile post-marketing data on suicide
19 after approval -- it gets approved.
20 DR. SCHULTZ: Other discussion on safety?
21 Are the safety data adequate and safety data
22 monitoring?

1 I guess I would just have one brief comment.
2 I don't mean to be stuck on the injection site
3 reactions and body mass index, but I think that is
4 something we may need to pay attention to as this
5 moves into a U.S. population.
6 Potentially looking at data on -- as we move
7 into more females, higher body mass index, the number
8 of subcutaneous as opposed to intramuscular, you know,
9 injections. I'm not even sure how that could be
10 monitored. It clearly came up when there was an
11 injection site reaction. Whether it also translates
12 into differences in, you know, serum levels of the
13 compound is another question I think we might need to
14 start thinking about that.
15 It may be that it could lead to guidelines.
16 For example, a certain body mass index, you might want
17 to start with a two-inch needle to avoid the risk of a
18 one and a half-inch needle or if there is an injection
19 site reaction, that patient should automatically use
20 the two-inch needle. I mean, guidelines like that
21 might help us avoid adversity. If we think more about
22 it upfront and think about perhaps a certain hip

1 circumference could guide the clinician onto how to
2 approach the patient, whether they're eligible or not
3 and how to approach the treatment.
4 At this point I think we can move to voting
5 on Question 3. So taking into account the indication,
6 are the safety data adequate? I'm sorry. Question 4.
7 Taking into account the indication, are the safety
8 data adequate based on the collective discussion that
9 crossed many topics?
10 The results from Question 4 are yes – 12; no
11 – 0; abstain – 1. We'll go around the room starting
12 with Dr. Denisco. Please state your name and reason
13 for your vote.
14 DR. DENISCO: I should have seen that
15 coming. This is Dr. Richard Denisco. I voted yes. I
16 think there was extensive information presented today
17 on the safety that raised no concern, in addition to
18 the extensive safety data we have in use in other
19 populations, including those with, one would assume,
20 some alcoholic liver disease with no signals of severe
21 hepatic failure or hepatic failure. So I felt that
22 based on those two findings that adequate safety was

1 shown.

2 DR. MAXWELL: Jane Maxwell. Yes, for the

3 same reasons.

4 DR. MONTOYA: Ivan Montoya. Yes. One,

5 because the data with oral naltrexone shows that it's

6 very safe. Two, the data from alcohol also shows that

7 it's safe. And three, the data from the Russian

8 study, AE and SAE profile, shows that it's very safe.

9 So I don't have a concern about the safety of this

10 medication.

11 DR. TAI: Betty Tai. I abstained only

12 because I don't have the expertise -- I yield to my

13 other colleagues. I don't have the experience of

14 seeing patients. Thank you.

15 DR. BAXTER: Dr. Louis Baxter. I agree with

16 my colleagues' reasons.

17 DR. WALSH: Sharon Walsh. I agree with the

18 reasons that were outlined by Dr. Montoya.

19 DR. HWANG: I'm Michael Hwang. All

20 medications inherently carry some risks and I think

21 that considering this global problem that we have

22 here, I think the medication is safe.

1 DR. WHITE: Tonya White. I voted yes. I
2 agree for some of the same reasons stated. Suicide is
3 a problem in this population and the thought is that
4 if this could be adequately treated, the long-term
5 rates of suicide would actually be less if you look
6 over the course of the illness.
7 The one thing that I would like to say,
8 which also relates to the abstain on the other
9 question, is that the study was mainly in males and
10 it's the females that have the injection site
11 reaction. But on the other hand, this is something
12 that would also be seen in the 45,000 people who have
13 already been on the medication for alcohol and other
14 problems.
15 DR. SCHULTZ: Susan Schultz. I voted yes.
16 While I do think the safety data are adequate, I do
17 think that it will be crucial to have provider
18 education, patient education, and sufficient
19 monitoring to make sure it does translate in a safe
20 way to the U.S.
21 DR. WOOLSON: Robert Woolson. I voted yes.
22 I thought the data were adequate and the summary

1 provided by the sponsor and the FDA were convincing.
2 MR. MULLINS: Rodney Mullins. I voted yes
3 because I think that it was -- information was fairly
4 comprehensive. The only question I had was behavior
5 of the substance in subjects that had hepatitis C or
6 some type of liver damage. That still concerns me.
7 So I had that concern. Thank you.
8 DR. MICHNA: Ed Michna. I voted yes because
9 I thought the data was compelling.
10 DR. COVINGTON: Ed Covington. I voted yes
11 for the same reasons that have been articulated.
12 DR. SCHULTZ: I don't believe we need to
13 have further discussion on additional safety data that
14 may be needed given that the relative consensus.
15 If we can move on to discussion of Question
16 6. Should the supplement -- should this supplement
17 for treatment for opioid dependence be approved?
18 I'd like to invite discussion on Question 6.
19 If there's no discussion, we'll go ahead and
20 vote on Question 6.
21 Okay. The voting result for Question 6 is
22 yes – 12; no – 1; 0 abstain. And to shake it up we'll

1 start with Dr. Covington. If you could state your
2 name and your vote.
3 DR. COVINGTON: Well, I think it's been
4 pretty compellingly shown to be effective and I think
5 it's adequately been shown to be safe. And so, why
6 not?
7 DR. MICHNA: Ed Michna. I voted yes and,
8 you know, based on everything that's been said I think
9 it's pretty obvious that it's a pretty compelling
10 reason to approve this drug.
11 MR. MULLINS: I voted yes with some
12 reservations and because I think there's obviously
13 qualitative data and obviously there is quantitative
14 data but I think there's still some questions about
15 long-term usage and other issues like that. And we
16 only have one clinical trial and I think there's no
17 comparison of the long-term effects of usage of this
18 particular treatment. Thank you.
19 DR. WOOLSON: Robert Woolson. I voted no in
20 large part because I voted no for the first question.
21 I had questions there.
22 DR. SCHULTZ: Susan Schultz. I voted yes.

1 I think the compelling reasons for this product are
2 the clinical need, which is substantial. There are
3 limitations to a single clinical trial but I think
4 with adequate monitoring I think this is an
5 appropriate drug for use.
6 DR. WHITE: I'm Tonya White. I voted yes.
7 I think it's, from what I said before, it's an
8 efficacious medication. I think there needs to be a
9 look at specific targeted groups where it might be
10 more effective but I think from the standpoint of
11 neurobiology and pharmacology it looks to be very
12 effective.
13 DR. HWANG: I'm Michael Hwang. I voted yes.
14 I think that there's a clear need for the medication.
15 However, I think that there is also an indication the
16 serious adverse events need to be monitored after the
17 approval.
18 DR. WALSH: I'm Sharon Walsh and I voted yes
19 because we have extensive history with this same drug
20 given as an oral treatment. The lack of effectiveness
21 has been usually attributed to a lack of compliance or
22 adherence and this formulation is one that potentially

1 circumvents that barrier by requiring less frequent
2 treatment. That makes it easier for patients and
3 easier under monitoring circumstances, as well. We
4 have experience with that formulation in the alcoholic
5 population and I didn't see anything in the new data
6 that take this formulation into this new population
7 that caused me alarm to think that it wouldn't be
8 safely tolerated. So I think there's a great need and
9 to the extent that we can reach however many people
10 with this medication, I think it'll be valuable.
11 DR. BAXTER: Dr. Louis Baxter. And I voted
12 yes, basically for the reasons articulated by Dr.
13 Schultz and Dr. Walsh. But to a significant extent,
14 I'm very happy to have another drug in my
15 armamentarium that I can treat patients that suffer
16 from addictive disorders.
17 DR. TAI: Betty Tai. I voted yes because I
18 reviewed the submission as well as FDA review summary
19 and the data was robust and convincing. I hope when
20 the drug is approved, that it would offer more
21 opportunity for addiction scientists to further
22 research on this particular medication and fine tuning

1 its utility for both providers and for patients.
2 DR. MONTOYA: Ivan Montoya. I voted yes
3 because this medication can be safe. The data shows
4 that it's safe and effective for the treatment of one
5 of the aspects of opioid dependence, which is relapse
6 prevention.
7 DR. MAXWELL: Jane Maxwell. I voted yes for
8 reasons that have already been stated. But again, my
9 concern is in the need for this medication in the
10 field for relapse prevention.
11 DR. DENISCO: Richard Denisco. I voted yes
12 for the reasons already stated. I think this is a
13 life-saving medication.
14 DR. SCHULTZ: Dr. Rappaport, do you have any
15 concluding comments?
16 DR. RAPPAPORT: I'd just like to thank the
17 Committee, Dr. Schultz. You've given us some very
18 useful input. We will certainly take it into
19 consideration as we move forward with making a
20 decision on the application. This has been a long day
21 and I appreciate your sticking around through the
22 technical glitches. And thank you.

1 DR. SCHULTZ: Thank you. Thank you, we'll
2 adjourn. Please remember to drop off your name badge
3 at the registration table on the way out so they can
4 be recycled. Thank you.
5 (Whereupon, at 4:45 p.m., the meeting
6 was adjourned.)
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