FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS

ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Wednesday, January 23, 2008

PARTICIPANTS:
Committee Members:
ALAN LEWIS BUCHMAN, M.D., Chair
Division of Gastroenterology
Northwestern University
LIN CHANG, M.D.
Center for Neurovisceral Sciences and Women's Health
University of California, Los Angeles

MICHAEL S. EPSTEIN, M.D.
Anne Arundel Medical Center
KENNETH LOUIS KOCH, M.D.
Department of Internal Medicine
The Wake Forest University School of Medicine
GARY ROTH LICHTENSTEIN, M.D.
Gastroenterology Division
University of Pennsylvania
PANKAJ JAY PASRICHA, M.D.
Stanford University School of Medicine

SUZANNE ROSENTHAL Crohn's & Colitis Foundation of America
Temporary Voting Members:
JoELLEN CORKERY-DeLUCA
Patient Representative

JOSEPH J. CULLEN, M.D.
Division of Gastrointestinal, Minimally Invasive & Bariatric Surgery
Veterans Affairs Medical Center
SEAN P. HENNESSY
University of Pennsylvania School of Medicine

PARTICIPANTS (CONT'D):
Temporary Voting Members (Cont'd):
JUDITH M. KRAMER, M.D.
Duke University Medical Center

ALEXANDER H. KRIST, M.D.
Virginia Commonwealth University
ROBERT A. LEVINE, M.D.
State University of New York
Upstate Medical University, Syracuse
ABRAHAM MICHAEL LINCOFF, M.D.
Department of Cardiovascular Medicine
The Cleveland Clinic Foundation
MICHAEL A. PROSCHAN
Office of Biostatistics Research
National Institute of Allergy and Infectious Diseases

RONALD RICHARDSON, M.D.
Department of Medical Oncology
Mayo Clinic

DOUGLAS R. ROSING, M.D.
Cardiology Consultation Service
National Institutes of Health

MARK A. TALAMINI, M.D.
Department of Surgery
UCSD Medical Center

Food and Drug Administration (Non-Voting):

JULIE G. BEITZ, M.D.
Office of Drug Evaluation
Center for Drug Evaluation and Research

TAMAL CHAKRABORTI
Division of Gastroenterology Products
Center for Drug Evaluation and Research

PARTICIPANTS (CONT'D):
Food and Drug Administration (Non-Voting)
MARJORIE DANNIS, M.D.
Division of Gastroenterology Products
Center for Drug Evaluation and Research
RUYI HE, M.D.
Division of Gastroenterology Products
Center for Drug Evaluation and Research
CLAUDIA KARWOSKI
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
JOYCE A. KORVICK, M.D.
Division of Gastroenterology Products
Center for Drug Evaluation and Research
JOYCE WEAVER
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Designated Federal Official:
MIMI T. PHAN
Center for Drug Evaluation and Research

Other Attendees:

JOHN ALEXANDER, M.D.
Duke University
JOHN CAMM, M.D.
St. George's Hospital Medical School

SONIA CASTILLO CONOR DELANEY, M.D.
University Hospitals of Cleveland

PARTICIPANTS (CONT'D):
Other Attendees (Cont'd):
CHARLIE FUCHS, M.D.
Dana-Farber Cancer Institute

DEANNE GARVER, M.D.
Consultant to Adolor Corporation
DAVID JACKSON, M.D.
Adolor Corporation

GARY KOCH
University of North Carolina
KENNETH LYLES, M.D.
Duke University

ERIC MORTENSEN, M.D.
GlaxoSmithKline
GINNY SCHMITH
ANTHONY SENAGORE, M.D.
Spectrum Health

LEE TECHNER, D.P.M.
Adolor Corporation
LINDA YOUNG
Adolor Corporation

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P R O C E E D I N G S

(8:00 a.m.)

DR. BUCHMAN: Good morning, everyone. I'm going to call the meeting to order here. I'm Dr. Alan Buchman, professor of medicine and surgery at Northwestern University's Feinberg School of Medicine. And I'm going to introduce Mimi Phan, who's got some business statements to read.

MS. PHAN: Good morning. Before we start the meeting, I just want to read some procedure for the public and the members who are here.

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

record only if recognized by the chair.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic today take place in the open forum of the meeting and not during lunch or breaks.

We are also aware that members of the media are anxious to speak with the FDA about these proceedings. However, like the advisory committee members, FDA will refrain from discussing the details of this meeting with the media until its conclusion. For the convenience of media representatives I would like to identify the FDA press contact, Ms. Rita Chappelle. Are you in the audience? Please stand. To your left.

And finally, I would like to remind everyone present to please silence your cell phone or pager if you have not already done so. We look forward to an interesting and

productive meeting. Thank you for your participation and cooperation.

DR. BUCHMAN: I'm going to open the meeting of the Gastrointestinal Drugs Committee to evaluate Entereg, alvimopan, for the acceleration of recovery time for upper and lower gastrointestinal recovery following partial large or small bowel resection surgery and primary anastomosis.

Let's begin with a roll call. If the voting members of the committee could introduce themselves by name and institution or where you're from, and we'll start with Dr. Rosing and work our way around the table. Please press the red button on your microphone to speak.

DR. ROSING: Douglas Rosing, the National Institutes of Health.

DR. CULLEN: Joe Cullen, University of Iowa.

DR. KRIST: Alex Krist, Virginia Commonwealth University.

MR. PROSCHAN: Mike Proschan, National Institute of Allergy and Infectious Diseases.

DR. PASRICHA: Jay Pasricha, Stanford University.

DR. LEVINE: Bob Levine, State University of New York, Upstate Medical University, Syracuse.

MS. CORKERY-DeLUCA: JoEllen DeLuca, Spartanburg, South Carolina, your patient consultant.

DR. RICHARDSON: Ron Richardson, Mayo Clinic, Rochester, Minnesota.

DR. CHANG: Lin Chang, UCLA.

DR. KRAMER: Judith Kramer, Duke University Medical Center.

MS. PHAN: Mimi Phan, federal rep, designed federal official.

MR. HENNESSY: Good morning. I'm Sean Hennessy. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. LINCOFF: Michael Lincoff from the Cleveland Clinic Foundation.

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DR. TALAMINI: Mark Talamini, University of California, San Diego.
MS. KARWOSKI: Claudia Karwoski, team leader for risk management, Office of Surveillance and Epidemiology at FDA.
MS. WEAVER: Joyce Weaver, Office of Surveillance and Epidemiology, FDA.
DR. HE: Ruyi He, medical team leader, Division of GI, FDA.
DR. KORVICK: Joyce Korvick, deputy director, Division of Gastroenterology, FDA.
DR. BEITZ: Julie Beitz, office director, CDER, FDA.
DR. BUCHMAN: Thank you. I'd like to introduce Dr. Korvick, who's going to introduce the speakers for our sponsors. But prior to that, Ms. Phan is going to read a Conflict of Interest Statement.
MS. PHAN: Good morning. This is the Conflict of Interest Statement for the Gastrointestinal Drugs Advisory Committee. Today is January 23, 2008.

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The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.
The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this committee are in compliance with federal ethics and conflict of interest laws.
Under 18 U.S.C. 208, Congress has

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authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.
Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees, or regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.
Related to the discussions of today's meeting, members and consultants of this committee who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. 208, their employers.
These interests may include

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investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.
Today's agenda involves discussion of safety and efficacy of Entereg (alvimopan) new drug application 21-775 by Adolor Corporation for the proposed indication of acceleration of time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.
Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, conflict of interest waivers have been issued in accordance with U.S.C. 208(b)(3) and 712 of the FD&C Act for Drs. Epstein and Hennessy.
Dr. Epstein has been granted this waiver for his speaker bureau activity for a competing firm on an unrelated issue.

Dr. Epstein received less than $10,001 per year.

Dr. Hennessy has been granted this waiver for his unrelated consulting to the competing firm.

Dr. Hennessy received less than $10,001 per year. In accordance with 18 U.S.C. 208(b)(1), a conflict of interest waiver has been issued to Dr. Joseph Cullen. Dr. Cullen has been granted this waiver for his activities as a co-investigator on a competing product. The study is funded for less than $100,000 per year.

The waiver allows these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waivers document, which are posted on FDA's web site at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 6-30 of

the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

FDA regrets that there is no industry representative participating in today's meeting. Four different industry representatives were invited. However, none could attend.

In addition, FDA wants it noted for the record that our consumer representative cancelled her attendance yesterday due to a critical illness in her family.

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

other participants to advise the committee of any financial relationships that they may have with any firms at issue.

DR. BUCHMAN: Dr. Korvick is going to introduce our first presenter from the sponsor. Please note that all questions for the sponsor are to be held until the end of the sponsor's full presentations.

Joyce?

DR. KORVICK: Thank you, Dr. Buchman. Welcome, members of the advisory committee. Today, before we get started with the sponsor's presentation, I'm going to give you a brief introduction.

As you said, we're here to talk about the efficacy and safety of alvimopan, or Entereg, for the proposed indication, which is to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

Currently, there are no drugs

approved for this indication.

As the sponsor proposes, this product is not intended to be used as an outpatient therapy for this indication. Today, you will discuss the efficacy and safety.

First of all, there are five studies submitted for the postoperative ileus indication. And it's been described in your background package that Adolor is the sponsor that is developing that indication. It will be of interest to FDA for you to have a discussion regarding the primary evaluation endpoint for this indication.

As has been noted in your background packages, this development program evolved over time. In the course of development in the five different studies, there were different patient populations, so these included total abdominal hysterectomy patients as well as small and large bowel surgery resections. And as well, the primary

outcome variable was originally in some of these designed GI-3. Currently, we focus on GI-2, which we've agreed with the sponsor is probably a very relevant endpoint.

There is also a secondary endpoint called discharge order written and ready as defined as the time from the end of surgery to the time ready for hospital discharge, based solely on the recovery of GI function as determined by a surgeon. So for that part of the advice that we're seeking from you, we're interested in, you know, the usefulness of these various indications, but we also have to look at the specific primary outcome variable and get your impression on the efficacy with regard to how that worked out in these studies.

And you will see, we have a list of questions. And one that is very interesting to us is what is the minimum time? That would be clinically meaningful for a statistically significant outcome.

Then we move on to safety. For the postoperative ileus indication and studies, as you'll hear from the sponsor and Dr. He, I think the safety was relatively straightforward. However, during the development of this product by GSK for the longer-term opioid-induced constipation, there were some adverse events that showed up in those studies.

They're here today to present some of that preliminary data. And you should realize that those projects are still in development, and that we are not here to discuss the indication for opioid-induced bowel dysfunction. But that information was brought to you today to further illuminate the safety profile of this drug. So regarding safety, we're interested in the committee's opinion regarding the short-term use of alvimopan, and how any of these safety information data that you hear will affect your evaluation of the short-term use of the drug.

And finally, it will be important then to put that in a sort of risk-benefit equation. And we will take a vote on whether you recommend approval or not. But prior to that, we also want your input on the proposed risk management plan and have some discussion there as proposed by the sponsor.

So we look forward to a lively day's discussion. And I will turn the meeting back over the Dr. Buchman and the Adolor company for them to resume their presentation.

DR. BUCHMAN: Okay. Our first presenter from the Adolor Corporation is Linda Young, a registered pharmacist, who's vice president of regulatory affairs, who's going to give an introduction on Entereg capsules.

MS. YOUNG: Good morning. I am Linda Young, vice president of regulatory affairs. And welcome, Dr. Buchman, members of the FDA, the committee, and guests. Thank you for being here today.

We are here today to discuss the safety and efficacy of Entereg, a novel compound in a new class for the management of postoperative ileus and bowel resection. Postoperative ileus, or POI, is a serious condition, with an adverse impact on both the patient and the health care system.

There is a recognized morbidity associated with POI, one of the most common causes of delayed hospital discharge. Currently, there is an unmet need in POI, as there is no FDA-approved agent for this condition. But as the data will show, Entereg provides for the effective management of POI following bowel resection.

Entereg is the trademarked name for alvimopan, a selective, peripherally acting, mu-opioid receptor antagonist. Entereg mitigates the adverse effects of opioids on the GI motility without blocking their beneficial analgesic effects.

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In patients undergoing bowel resection, this results in earlier resolution of GI recovery and earlier hospital discharge.

Adolor has been developing Entereg since 1999, and we've collaborated with the FDA throughout the development process. Over the years, several indications have been studied with Entereg, but since 2000, Adolor has focused on postoperative ileus and acute care indication in an inpatient setting.

GlaxoSmithKline is working toward an indication for chronic care opioid bowel dysfunction, or OBD, in outpatient setting. Because we are only seeking the postoperative ileus indication today, we will focus our discussion mainly on the safety and efficacy of Entereg for POI.

We filed the NDA for Entereg in 2004. It included Phase III study data from mixed populations of largely bowel resections, but also total abdominal

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hysterectomy patients, with the doses of both 6 and 12 milligrams. We saw variability in responses in the combined population, but there was a consistent response in the bowel resection subgroup and especially at the 12-milligram dose. We agreed with the agency to focus future studies on bowel resection, the subgroup that did well, and we also proposed the 12-milligram dose because it gave the most consistent response, and the safety profile was similar to 6 milligrams.

During the NDA review, GSK was conducting a POI study in Europe: Study 001. In this study Entereg did not show clinical superiority to placebo. But we learned that in Europe, clinical practice and socioeconomic systems are different. This point will be further explained by my colleague, Dr. Techner.

Given these data, the agency issued an approvable letter and asked for further efficacy data. We then submitted Study 314,

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a robust data set from a study of bowel resection patients using the 12-milligram dose. During the review of Study 314, we received interim data from Study GSK014, a 12-month safety trial, not in POI, but in the OBD patients on chronic opioid therapy. These data led the FDA to issue another approvable letter, asking for final data from GSK014 and a risk management plan. Therefore, as requested by the agency, we will also briefly address these safety findings from the study. And all of this brings us to today's meeting.

Adolor believes that robust safety and efficacy data that will be presented today provides compelling evidence to support approval of Entereg for POI following bowel resection. When used in this acute care setting, there is a favorable benefit-risk ratio, permitting this product to enter the market to fulfill the unmet need and to provide a clinically meaningful benefit to

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patients.

Adolor has also shown its commitment to the safe use of this product through the development of a risk management plan, which Dr. Jackson will review later in our presentation.

We are fortunate to have with us today several experts who will help us demonstrate the medical need and the clinical benefits of Entereg and POI. Dr. Senagore will share a surgical perspective of POI. Dr. Lee Techner will outline the POI development program and present the efficacy data. Dr. Jackson will present the safety data from our clinical trials.

And Dr. Eric Mortensen from GlaxoSmithKline will discuss the safety findings from the OBD study, GSK014.

Dr. Jackson will then conclude with a summary of our findings and an overview of our proposed risk management plan.

In addition, we are joined today by

the following experts who will be available to answer your questions: John Alexander, cardiologist, Duke University; John Camm, cardiologist, St. George's Hospital Medical School; Conor Delaney, surgeon, University Hospitals of Cleveland; Charles Fuchs, oncologist, Dana-Farber Cancer Institute; Gary Koch, statistician, University of North Carolina; and Kenneth Lyles, endocrinologist, Duke University.

I now would like to invite Dr. Senagore to the podium.

DR. SENAGORE: Thank you, Linda, Dr. Buchman, members, and guests. My name is Anthony Senagore, and I'm a professor of surgery at Michigan State University College of Human Medicine, and vice president of research and education at Spectrum Health in Grand Rapids, Michigan. I've been asked to give a surgical perspective on the condition of postoperative ileus.

Postoperative ileus and bowel

resection is a significant problem. There are about 400,000 bowel resections performed annually in the U.S. It is estimated that 90 percent of these cases are still performed by open surgical technique. Postoperative ileus occurs in all of these patients.

Postop ileus is the most common cause of prolonged hospital stay after bowel resection, frequently leading to additional interventions. And surgeons cannot predict which of these patients will go on to develop a more severe form of POI.

POI is defined as the transient cessation of coordinated bowel motility after surgery, preventing effective transit of intestinal contents and/or tolerance of oral intake. When I trained as a surgeon, we were taught that POI was a protective response to surgery, that it rested the anastomosis, and improved healing. Today, we know better. POI offers no physiologic benefit or advantage for an anastomotic healing, and

only impairs the patient's recovery.

Postoperative ileus is traditionally associated with several clinical signs, including the presence of nausea and vomiting, the absence of passage of flatus or stool, abdominal bloating, distension of the abdomen, and in turn, abdominal pain and discomfort.

Over the last decade, we have gained considerable knowledge regarding the etiology of ileus. One of the components of developing ileus is the surgical stress response. This happens after major surgical intervention, and is a complex interplay of biological factors, including neurogenic factors related to the autonomic nervous system, and a variety of hormones and neuropeptides which are released in direct response to the stress.

There is also increasing knowledge showing that a variety of inflammatory mediators contribute to the development of

postoperative ileus. Surgical anesthetics may also be involved. Both inhalational gases and intravenous agents may impair GI motility, and they tend to have a primary effect on the colon.

The most significant identified factor, however, is the role of opioid analgesics, particularly with parenteral administration. Opioids are known to bind to the mu-opioid receptors with the enteric nervous system. They block the excitatory neurons, which innervate intestinal smooth muscle, and thereby inhibit both gastrointestinal motility and secretion.

But from the patient's perspective, opioid-based patient-controlled analgesia has become the standard of care for the management of postoperative pain, particularly after bowel resection. Opioid-based PCA pumps have been shown to provide more effective analgesia, shorten hospital stay, and improve overall patient

satisfaction. Despite these benefits, PCAs are associated with a higher incidence of documented postoperative ileus on hospital coding.

So in an ideal world, when should a patient recover after abdominal surgery? A recent consensus conference data suggests that an optimum time to recovery would be within five days of surgery, after which we would diagnose prolonged or serious POI. Unresolved ileus is associated with an extended hospital stay as well as with a variety of associated morbidities, including nosocomial infections and pulmonary complications.

Furthermore, management of prolonged POI and associated complications frequently results in additional medical and surgical interventions. For this reason, the primary clinical objective following bowel resection is the avoidance of POI. Thus, in studies relating to enhanced recovery

pathways after major abdominal surgery, the time to recovery of bowel function has been the primary clinical endpoint.

Patients with POI suffer discomfort from nausea, vomiting, abdominal distension, and NG tube insertion, which can cause complications such as pneumonia and atelectasis.

As I mentioned previously, POI is the most common cause for prolonged hospital stay after bowel resection. The POI patient consumes significantly greater hospital and nursing resources. There's a need to manage the NG tube, monitor fluid balance, and assess vital signs more frequently. This support often will progress to the administration of TPN for nutritional support and further monitoring and data collection.

Prolonged hospitalization adversely affects patient census and hospital throughput. And it is directly correlated with the risk of the so-called preventable

complications, such as intravenous catheter infection, urinary tract infection, and pulmonary compromise.

The costs associated with severe POI are substantial. When we examine large administrative data sets, we see two distinct patient populations: Those where surgeons have documented the development of POI and hospital coders have captured that data for bill submission; and those that are uncoded, and therefore, were not felt by the caregivers to have POI. Looking at length of stay, patients with coded POI have nearly a week's longer length of stay. And that prolonged hospitalization translates into a nearly doubling of hospital costs.

Further examination of these data reveal that these patients also have a significantly higher in-hospital mortality rate.

Current treatment options for POI focus on the use of multimodal accelerated

postoperative care pathways, which frequently require intense nursing and physician input and coordination. These pathways involve early removal of the nasogastric tube, early acceleration of dietary advancement, and an emphasis on early ambulation of the patient. Opioid-sparing analgesia is sometimes used to minimize the deleterious effects of opioids.

Prokinetics have also been studied. However, none are approved or routinely available in preventing or treatment postoperative ileus. In fact, none of these approaches have consistently shortened hospital stay in large population studies.

From a clinical perspective, a commonly used metric for evaluating the treatment strategy is NNT, or number needed to treat. How can we compare the NNT of alvimopan for POI prophylaxis with two commonly recommended and currently CMS-mandated prophylactic measures for other surgical patients?

A large meta-analysis of prophylactic measures for DBT and surgical site infection in colorectal cancer patients revealed an NNT that ranged from 4 to 17. In comparison, as you will hear shortly by Dr. Techner, the NNT for alvimopan for POI prophylaxis, using discharge order within seven days as the outcome measure, is five to nine, clearly within this same range.

Thus, we are left with no approved drugs for the prevention or management of postoperative ileus, and the current management options are limited and not consistently effective. We have no reliable criteria to predict who will develop either a prolonged or severe postoperative ileus, and the burden on the patient and the health care system is severe. So as clinicians, we feel that postoperative ileus should be managed proactively in bowel resection patients with an agent that should decrease the manifestations of this condition.

I'd like to ask Dr. Techner now to discuss Adolor's clinical development and POI efficacy results.

DR. TECHNER: Good morning. I'm Lee Techner, senior medical director for Adolor. Today, it is my privilege to share with you the efficacy results from the Phase III clinical trials supporting the use of alvimopan, 12 milligrams, for the management of postoperative ileus following segmental bowel resection. I'll start by providing a brief overview of alvimopan's mechanism of action, then review study design endpoints and the efficacy results. I'll conclude the presentation with a brief summary.

An extensive clinical pharmacology program has been completed, characterizing the mechanism of action, pharmacologic efficacy, pharmacokinetic profile, and exposure response of alvimopan. An overview of the findings has been provided in your briefing document. This morning, I will

focus on alvimopan's mechanism of action and rationale for its use in the management of postoperative ileus.

Alvimopan is a highly selective, competitive antagonist at the mu-opioid receptor. It is metabolized to an active metabolite by gut microflora. The metabolite is equipotent to alvimopan, but is not required for efficacy in POI.

Alvimopan and its metabolite are peripherally acting, and much less potent at both delta and kappa receptors. Furthermore, alvimopan demonstrated no activity at any of over 70 non-opioid receptors, enzymes, and ion channels, thus reducing the potential for off-target effects.

Alvimopan competes with opioid analgesics such as morphine or fentanyl for binding it in the opioid receptors located within the enteric nervous system. In fact, alvimopan's affinity for the mu receptor is over 40-fold greater than that of morphine.

Once bound, alvimopan blocks the negative effects of opioids on bowel motility without compromising central analgesia.

As you've heard this morning, opioid analgesics are a key factor in the development and duration of postoperative ileus. Therefore, the use of a peripherally acting mu-opioid receptor antagonist directly targets a primary component of this serious surgical condition.

Now let's turn our attention to the alvimopan Phase III POI clinical development program. Overall study design was similar across all Phase III trials. Initially, we evaluated both 6- and 12-milligram doses. Patients received their first dose of alvimopan or placebo preoperatively in order to mitigate the GI effects of highly potent opioids commonly administered during induction of anesthesia.

Dosing continued postoperatively until discharge, or for a maximum of seven

days, if the patient remained in the hospital.

Adverse events were assessed up to Day 14. Active monitoring of sites for serious adverse events continued for 30 days following the last dose of study drug, or until resolution. Patients typically returned to their surgeon for the initial postoperative evaluation within two to four weeks of discharge, corresponding to the adverse event monitoring period.

Four alvimopan doses were evaluated in Phase II dose-ranging studies, of which two were chosen for the initial Phase III trials: 6 and 12 milligrams. Of these, the 12-milligram dose appears to be optimal for the bowel resection population when examined from several perspectives.

Population PK analysis demonstrate that with BID dosing plasma concentrations remained above the KI for the mu-opioid receptor for 12 hours in 95 percent of

patients receiving the 12-milligram dose, two times longer than that achieved with 6 milligrams.

Clinical trial results demonstrated a consistent and robust treatment effect with alvimopan 12 milligrams, particularly in the North American trials enrolling the largest number of bowel resection patients, which I will discuss shortly. And the safety profiles of both the 6- and 12-milligram doses are comparable. Therefore, consistent with the proposed label, efficacy results will be presented for the 12-milligram dose only.

A standardized accelerated multimodal postoperative care pathway was implemented in all trials in order to be consistent with current best practices. This consisted of early removal of the nasogastric tube -- that is, no later than Postoperative Day 1, early ambulation initiated on Postoperative Day 1, and early diet

advancement, with liquids offered on Postoperative Day 1 and solids on Day 2.

Key inclusion criteria required that patients over 18 years had an ASA score of I to III and were scheduled for partial large or small bowel resection with primary anastomosis or total abdominal hysterectomy, all performed by laparotomy. In addition, patients were required to receive opioid-based IV patient-controlled analgesia for postoperative pain management. The opioid used was at the discretion of the investigator.

Patients were excluded from the trials if they were scheduled for total colectomy, colostomy, ileostomy, or had a complete bowel obstruction, used opioids chronically, or received more than three doses of opioid analgesics within seven days prior to surgery.

In the POI development program, three measures were evaluated to support

clinically meaningful benefit. GI recovery, the primary measure of clinical progress following major abdominal surgery, and the main driver for discharge.

Hospital length of stay. As we've heard from Dr. Senagore, reduction in length of stay is associated with substantial benefits to both the patient and the health care system.

Insertion of a nasogastric tube for symptoms of POI increases patient risk for associated complications, some of which may lead to serious morbidity or mortality. Therefore, the incidence of postoperative NG tube insertion was assessed in order to determine whether alvimopan, through accelerating GI recovery, could reduce the need for this intervention.

Upper and lower GI recovery are required for complete resolution of POI. For the initial alvimopan clinical trials, the primary endpoint was a three-component

composite: GI-3, the last to occur of upper GI recovery, represented by the time to tolerating solid food, and lower GI recovery, the first to occur of either flatus or bowel movement.

Resumption of colonic motility is generally considered the rate-limiting factor for complete resolution of POI. Clinically, passage of stool is more closely associated with this event when compared with flatus. Therefore, for assessment of alvimopan's treatment effect on GI recovery in bowel resection patients, a two-component composite endpoint is more clinically relevant. This is represented by GI-2, the last to occur of the time to tolerating solid food and the time to first bowel movement.

In agreement with FDA, GI-2 was the primary endpoint in the most recent trial, Study 314. GI-2 was a pre-specified secondary endpoint in two of the North American studies, 313 and 308; the non-U.S.

Study 001; and a post hoc analysis in Study 302.

The length of hospital stay was characterized using several measures: ready for discharge based solely on the time of GI recovery as defined by the surgeon; time to discharge order written, DOW, preferred over actual time to hospital departure, as it avoids the potential influence of confounding factors such as social or transportation issues; and finally, an approach more consistent with how this measure is typically reported, discharge order written by postoperative day, referred to as "length of stay." This measure uses the calendar day the order was written as opposed to its occurrence relative to the end of surgery time.

Because there is no precedent defining a responder in POI, several analyses were explored in the earlier trials, all based on a single component: time to GI

recovery. Today, we'll present our results using an expanded responder definition developed in collaboration with FDA and surgeons for the most recent trial, Study 314, and retrospectively applied to the other North American studies. A responder is defined as a patient that achieves the endpoint of interest on any of Postsurgical Days 3 through 8 and has no subsequent adverse event reports of POI, which, according to the investigator, either delayed discharge or resulted in hospital readmission within seven days of discharge.

GI recovery by Day 5 and early discharge are primary clinical objectives following bowel resection. Therefore, using our responder definition, we evaluated whether treatment with alvimopan would allow more patients to achieve these important clinical milestones, thus potentially reducing patient risk.

In keeping with the proposed label

indication, the efficacy results will focus only on patients who underwent partial small or large bowel resection with primary anastomosis. Study 314, which enrolled only bowel resection patients, Study 313 in which 93 percent of the patients enrolled underwent bowel resection, will provide the primary confirmation of clinical benefit.

Studies 302 and 308, although not designed to evaluate the bowel resection population independently, provide additional support for alvimopan's benefit in these surgical patients.

Study 306 was a safety study enrolling only hysterectomy patients, and unlike the other trials, had an outpatient component. Therefore, this study will not be included in discussion of the POI efficacy results. The POI safety presentation, however, will include data from all patients who had surgery.

Study 001 was the only non-U.S.

study, and differed from the North American trials with respect to opioid use and length of stay. Therefore, I will discuss results from this trial first and then focus the remainder of the presentation on the North American studies.

The prospectively defined analysis population used to evaluate efficacy outcomes was the modified intent-to-treat population, defined as all patients who had at least one dose of study drug, surgery as per protocol, and at least one post-surgery efficacy assessment. Ninety-four percent of bowel resection patients in the North American trials were included in the MITT bowel resection population.

The pre-specified primary approach to evaluating alvimopan's treatment effect was the Cox proportional hazards model, using the P value associated with the resulting hazard ratio. To describe the magnitude of treatment effect, estimates of the mean time

as well as the median and 75th percentile time will be presented, and are derived from the Kaplan-Meier curves as pre-specified in the analysis plan. The FDA briefing document provides median and 75th percentile estimates derived from the Cox proportional hazards model. In most cases, the results based on either method are comparable.

The difference in the mean times was obtained from the area between the two treatment group curves. As such, this area may be viewed as the sum of differences between the curves over the entire 10-day observation period, or alternatively, across the various percentiles. Differences in the median and the 75th percentile supplement information provided by the mean. Additional measures further characterizing clinical benefit include a responder analysis, which I described earlier, and numbers needed to treat, or NNT.

Now that we've reviewed the key

elements of the Phase III POI clinical development program, let's turn our attention to the efficacy results, starting with the non-U.S. Study 001.

Study 001 was conducted outside North America. Results for the bowel resection population were not statistically significant for the primary endpoint, GI-3. Post hoc analyses provided additional perspective, allowing a better understanding of this outcome. Results of these analyses highlighted significant differences between Study 001 and the North American trials, primarily with respect to opioid use and length of stay.

In the North American trials, use of opioid-based IV PCA and restricted use of non-opioid analgesics was mandated. This was not the case in Study 001, which led to greater than 60 percent higher use of non-opioid analgesics, and 55 percent lower utilization of opioid-based IV PCA. Overall

postoperative opioid exposure was two times higher in the North American trials.

With respect to length of stay, we learned that GI recovery was not a primary determinant of discharge in Study 001. In fact, the average time from GI recovery to discharge order written, along with the average hospital stay, were approximately three days longer in the 001 placebo group as compared with placebo patients in the North American studies. This may be related to regional variation and practice patterns, along with other cultural differences that impact decisions on discharge.

Due to these differences, meaningful interpretation of discharge-related endpoints within the context of the North American trials is confounded and will not be presented. However, the results are in your briefing document.

The mean age for the bowel

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resection population in Study 001 was approximately 64 years, which is consistent with the primary reason for surgery: Colorectal cancer. Approximately 80 percent of the patients completed treatment, and there was a low discontinuation rate for adverse events.

For the bowel resection population in Study 001, statistical significance was not achieved for the primary endpoint GI-3. For GI-2, the hazard ratio was 1.3, and statistically significant when compared with placebo. Mean and median differences between treatment groups for GI recovery ranged from 3 to 11 hours, and 4 to 20 hours at the 75th percentile, all favoring alvimopan.

We will now focus on the results from the North American studies. Over 2,200 patients were included in the North American trials. Eighty-two percent underwent bowel resection. As mentioned previously, the highest proportion of bowel resection

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patients were enrolled in Studies 314 and 313, 100 percent and 93 percent, respectively.

The proportion of patients completing was slightly higher in the alvimopan 12-milligram group compared with placebo across all trials, with the exception of Study 302. Adverse events were the most common reason for discontinuations and higher in placebo, primarily due to a numerically higher incidence of nausea, vomiting, and postoperative ileus as compared with alvimopan-treated patients, again, with the exception of Study 302.

Patient demographics were well-matched across treatment groups. Forty percent of bowel resection patients were 65 years or older, and 17 percent greater than or equal to 75 years or age, populations at higher risk for perioperative complications. Over 90 percent of resections were large bowel, and consistent with clinical practice,

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a higher proportion performed on the left versus the right colon. Surgery duration was similar across treatment groups and within the expected range for these procedures. The most common reasons for surgery was colon or rectal cancer, followed by diverticular disease, consistent with the frequency of GI conditions requiring elective bowel resection in the general population.

These Kaplan-Meier curves represent the pattern of GI recovery in bowel resection patients based on integrated data from the four North American trials. No events, bowel movement or toleration of solids, are occurring within the initial 48 hours following surgery. At that point, the curves separate, and they remain separated throughout the entire postoperative observation period of 10 days.

The orange line, alvimopan 12 milligrams, remains to the left of the gray placebo line at all time points. This

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shifting of the curve indicates that patients treated with alvimopan had a higher probability of earlier GI recovery from Postoperative Day 2 through Day 10 as compared with placebo. Between Postoperative Days 5 and 6, representing patients with more prolonged ileus and potentially at higher risk for complications, the curves are at their widest divergence.

The mean difference in GI-2 recovery between alvimopan and placebo over the 10-day observation period is 18.8 hours, the difference at the median 10 hours, and a 22.4-hour difference at the 75th percentile. These findings are supported by results from the individual studies.

In studies with the highest proportion of bowel resection patients, 314 and 313, hazard ratios in the alvimopan treatment group for both GI-2 and GI-3 were greater than 1.4, and statistically significant when compared with placebo.

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Further support is provided by Studies 308 and 302, where hazard ratios for GI-2 were also statistically significant. A positive trend was observed for the GI-3 endpoint in these studies. However, statistical significance was not achieved.

In Studies 314 and 313, statistically significant results as measured by the hazard ratios were associated with a mean difference of 20 to 26 hours between the treatment groups for GI-2 recovery. The difference at the median, 17 hours. And at the 75th percentile, GI recovery occurred up to approximately 1-1/2 days earlier with alvimopan as compared to placebo. These data are supported by the other studies as well. Although somewhat less robust, similar trends were observed for GI-3.

The treatment effect of alvimopan 12 milligrams was consistent regardless of sex, age, or race, with hazard ratios and associated confidence intervals all above 1.

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Across all studies, a higher proportion of patients receiving alvimopan achieved GI recovery by Postsurgical Day 5, ranging from 10 to 18 percent greater than placebo-treated patients.

When converted to NNTs, 5 to 10 patients would require treatment with alvimopan to move one patient into this earlier GI recovery period.

Resolution of POI is the driver for discharge following bowel resection. Therefore, achieving this clinical milestone early may reduce overall hospital length of stay. In patients receiving alvimopan, hazard ratios for ready were 1.4 and 1.5 in Studies 314 and 313, both statistically significant when compared with placebo. Similar results were demonstrated in Studies 302 and 308.

The magnitude of treatment effect by all measures was comparable to that observed for GI recovery in both Studies 314

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and 313, with mean differences from placebo ranging from 13 to 21 hours, and with similar results seen in supportive studies. Across all studies, differences from placebo at the 75th percentile were robust, ranging from approximately 1 to 2 days.

The pattern of discharge order written in the four North American studies is represented by these Kaplan-Meier curves. The repeating steps occur approximately every 12 hours, corresponding to clinical practice patterns, with these orders typically written during the first two nursing shifts.

In the North American trials, approximately 90 percent of the discharge orders were written between 7:00 a.m. and 7:00 p.m. The mean difference in DOW is 18 hours, the difference at the median 15.6 hours, and a 27-hour difference at the 75th percentile.

In Studies 314 and 313, hazard ratios for DOW were greater than or equal to

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1.4, and statistically significant when compared with placebo. Similar findings were demonstrated in Study 308. A positive trend favoring alvimopan was observed in Study 302. However, this was not statistically significant.

Mean differences from placebo range from to 19 hours in Studies 314 and 313, and were comparable in Study 308. Differences at the median range from 6 to 22 hours and 21 to approximately 45 hours at the 75th percentile across all studies.

A higher proportion of patients in the alvimopan treatment group had discharge orders written prior to Postsurgical Day 7 as compared to placebo-treated patients, 12 to approximately 15 percent in Studies 314 and 313, and similar findings in Studies 302 and 308. These differences correspond to NNTs ranging from 5 to 9. When calculated using the calendar day the discharge order was written, mean postoperative length of stay

was shortened by 1 day in Studies 314 and 313, with a comparable reduction in Study 308.

Integrated results from the four North American studies demonstrate hazard ratios and associated confidence intervals above 1 for primary and secondary endpoints.

Intervention to relieve symptoms associated with unresolving postoperative ileus often involves insertion of a nasogastric tube. This can be associated with serious complications, and does not shorten the duration of POI. Treatment with alvimopan 12 milligrams was associated with a significant reduction in the incidence of postoperative NG tube insertion as compared with placebo. The difference of approximately 5 percent corresponds to an NNT of 20.

Effective pain management following bowel resection is frequently achieved with opioid-based IV PCA. Therefore, the

potential for alvimopan to compromise analgesia was assessed. In the North American clinical trials, treatment with alvimopan had no impact on either opioid consumption or VAS pain scores. This finding has been consistent across all studies.

In summary, treatment with alvimopan 12 milligrams in the studies where greater than 90 percent of patients enrolled underwent bowel resection resulted in statistically significant acceleration of GI recovery and an associated reduction in hospital length of stay; mean differences from placebo in these key clinical milestones of about a day, and up to 2 days at the 75th percentile, corresponding to patients with prolonged POI and likely a higher risk for delayed discharge; a higher proportion of responders achieving GI-2 recovery by Day 5; and hospital discharge prior to Day 7, with corresponding NNTs below 10.

These outcomes were supported by

the other North American trials, and achieved even with implementation of a standardized accelerated care pathway.

In the four North American trials combined, treatment with alvimopan reduced the incidence of postoperative NG tube insertion by 43 percent. Across all studies, treatment with alvimopan 12 milligrams had no impact on pain management. We believe that these results demonstrate clinically meaningful benefit to patients undergoing bowel resection.

I would now like to ask my colleague, Dr. David Jackson, to lead the presentation on the safety profile of alvimopan.

DR. JACKSON: Thank you and good morning. I'm David Jackson, the chief medical officer for Adolor. And this morning, I would like to present to you the POI safety data. Before we do, I'm going to go and sit down again and invite Dr. Mortensen from GSK to address the

agency's request to provide more information about the GSK-sponsored OBD trials and in particular, Study GSK014. Eric.

DR. MORTENSEN: Thank you, Dr. Jackson. Eric Mortensen, group director, GlaxoSmithKline, clinical development. And good morning, and thank you to the committee for the chance to present some of our data today.

I'll be talking to you today about studies of alvimopan in the setting of OBD, the opioid-induced bowel dysfunction that's frequently observed in patients with chronic opioid use. I'll be focusing most of today's discussion upon the results of a single clinical trial, a long-term safety study, Protocol 014, and I'll conclude with a few remarks from our study in patients with cancer-related pain.

Now, opioid bowel dysfunction, or OBD, is a chronic condition characterized by severe constipation and associated symptoms. The patients we studied with OBD were quite

distinct from those in the POI population, in that they generally had chronic pain of several years' duration for which they had required much higher doses of opioids than those commonly used in POI for acute analgesia.

Now, because long-term exposure to opioids sensitizes patients to the effect of opiate antagonists, patients with OBD were intolerant of the much higher alvimopan doses used in the POI condition, experiencing abdominal cramping and diarrhea. Doses of 1 milligram alvimopan increased those symptoms on the first day of treatment of OBD.

And for that reason, patients in the OBD program were treated with only 1/2 a milligram alvimopan twice daily as opposed to the proposed dose of 12 milligrams twice daily in the POI indication.

Patients in the OBD population suffered a debilitating pain condition for an

average of greater than 10-1/2 years. They'd required opioid analgesia for these conditions for greater than 7-1/2 years, with a mean total daily dose of opioid that was equivalent to about 232 milligrams of morphine.

Now, this was in significant contrast to the experience in the POI condition, where there were generally no underlying pain conditions, and patients received approximately a tenth of this dose of opioid for fewer than two weeks. Per protocol, those patients did not have any significant prior opioid exposure. And the data I'll be presenting today comes from our studies in patients with OBD.

Study 014 was a 12-month randomized, double-blind, placebo-controlled trial assessing the effect of alvimopan in patients with chronic non-cancer pain and symptoms of OBD. Patients were randomized to either alvimopan, 1/2 milligram twice daily,

or placebo at a ratio of 2-to-1. And it should be noted that relative to today's concern about safety, that this study's inclusion criteria did not require baseline chest radiography or electrocardiography.

Now, the adverse events will be discussed and consist of three categories: Myocardial infarctions and other significant cardiovascular events, and events that were encoded as either neoplasia or as bone fracture. No imbalance in these events was seen in prior studies, and hence, no pre-specified definitions were established to permit uniform case ascertainment or comparison between treatment groups. We note these events were uncommon, and therefore, risk estimates have very wide confidence intervals.

Our review of the various events included careful evaluation of the index cases along with examination of the biological, clinical, and epidemiologic

plausibility of each event. Exposure response relationships were assessed. And finally, integrated reports were subjected to both internal and external expert review.

A global review of the cardiovascular events in Study 014 using categories agreed with the FDA showed low incidence of events on alvimopan, but a numerical increase compared with the absence of events on placebo. This was largely driven by an increase in myocardial infarctions in the alvimopan group.

The low frequency of individual events results in the wide confidence intervals seen here around the relative risk estimates. Subsequent assessment showed that all the events of myocardial infarction in the alvimopan patients occurred in those with prior cardiovascular disease, with a clustering of events noted so that 5 of the 7 events occurred at 2 of the 232 study sites in the trial.

A time-to-event analysis of CV events observed in Study 014 is shown here, and shows the separation versus placebo for the 538 patients on alvimopan. Few cardiovascular events were observed beyond six months, suggesting no accumulation of risk, and no events were observed in the period relevant to postoperative ileus. Importantly, none of the myocardial infarctions, the initial event of concern, occurred at less than 30 days or at more than four months after initiation of study drug.

Prior to the observation of the imbalance of Study 014, no evidence of an increase in cardiovascular events was identified from clinical studies at less a duration in essentially the same patient population. This included two studies with three months' duration of drug exposure.

Now, focusing upon the adverse event of myocardial infarction, the principal observation of imbalance in the 014 study,

these studies showed no association with alvimopan compared with placebo. Again, the number of adverse events are small, reflecting the low incidence rate, and resulting in the wide confidence intervals that we see here around the relative risk estimates.

A time-to-event analysis of the cardiovascular events in these other OBD studies of patients with non-cancer pain is shown here. The maximum duration of exposure is here three months, but largely overlaps the period of accumulation of cardiovascular events in Study 014. Here, with a larger population of 1,190 patients exposed to alvimopan, the curve showed no separation from placebo with respect to incidence.

A combination of these CV events from the OBD program in non-cancer pain is shown here. After integrating all data, we saw a persistent but lesser imbalance of cardiovascular events, primarily driven by

the results of Study 014. In particular, the imbalance of myocardial infarctions was less pronounced. And once again, the confidence intervals around the relative risk estimates for individual events are wide, owing to the overall low incidence of events in both groups with all intervals embraced with a value of 1.

Now, as I've stated, the lack of pre-specified disease definitions confounded our ability to analyze cardiovascular events. As a result, an independent data monitoring committee was established to provide standard definitions to improve the uniformity of case ascertainment, to review individual cases, and to provide a blinded comparison of the incidences of cardiovascular events across the OBD database.

The resulting IDMC's analysis showed no significant difference in the frequency of CV events between alvimopan and placebo, and similarly, no significant

difference was observed in either ischemic or non-ischemic cardiovascular events.

Recognizing the limitation of making conclusions from adverse event reports, the IDMC concluded that the risk of ischemic heart disease with alvimopan exposure was largely discharged.

Furthermore, they found no significant evidence of an elevation in the incidence of other or non-ischemic cardiovascular events with alvimopan versus placebo. Nonetheless, they suggested that a further study be conducted in the OBD population to confirm these observations, and that any studies should include an enhanced monitoring of cardiovascular events and IDMC oversight to confirm this interpretation.

Following the completion of Study 014, a second imbalance was observed with respect to the number of adverse events encoded as neoplasm. The incidence rates following the inclusion of an additional case

reported post-study are also shown here. And I think the change in the relative risks seen with this addition shows how this value is being driven by very small numbers of events.

A review of individual case reports shows this group encoded as neoplasm was quite heterogeneous, including some instances as post-traumatic neuroma, lipoma, benign hair follicle tumor that are not pre-malignant and do not show clinical development or progression. The range of lesions was also considered to be atypical for an agent with primary or secondary carcinogenic potential.

Now, given questions about the clinical meaningfulness of the range of events in this broad grouping, we'll examine those events of malignant neoplasm to assess potential treatment and balance. Adverse events associated with significant risk of malignancy were identified without respect to drug treatment. The separations were then

assessed by an advisory committee of external oncologists for consistency. Apart from minor differences between the FDA and GSK with respect to classification, there was general agreement for all events classified as malignant.

Here, we see that malignancies constitute a small number of the cases, that the relative risk estimates are modest, while confidence levels all embrace the NULL value. With the inclusion of Study 014 of the additional unsolicited neoplastic adverse event reported post-study, we see the perceived imbalances further diminished.

These imbalances of the militant neoplasm were significantly affected by the small number of events in the safety database, and the likelihood that several patients may apparently have had pre-existing lesions prior to randomization. We see in the third line the inclusion of all cases from all non-cancer OBD studies produces a

relative risk, but also approximates the NULL value, and with little difference in the distribution of cases.

To further explore the potential observed imbalance of neoplastic events in the non-cancer OBD studies, an examination was conducted of results from a study in patients with cancer-related pain requiring an opioid analgesia. Study 008 and its extension 101684 were intended to assess the effect of alvimopan in patients with cancer-related pain requiring opioid analgesia and with symptoms of OBD.

Eligible patients were randomized unequally to placebo or 1 of 3 doses of alvimopan at a ratio of approximately 2.5-to-1 alvimopan to placebo by study's end. Patients completing the three-week efficacy trial were allowed to continue with their assigned treatment for as long as they desired.

Like most palliative care studies,

Study 001 predominantly selected patients with advanced disease and a high likelihood of mortality. Enrollment of eligible patients was challenging, given the limitations that many patients with severe illness had in providing detailed study reports of their symptoms. Of note, this study was not designed to measure the progression of patients' underlying cancer diagnosis, nor to ensure that prognostic factors for disease progression were balanced between the treatment groups.

As a conservative clinical assessment then, we therefore compared the number of deaths by treatment group. In this population, we saw a numeric imbalance for deaths, with 20 patients in the alvimopan group compared with 3 on placebo. We have, however, provided a detailed analysis in the briefing document that examines potential reasons for these findings.

These demonstrate the total

exposure to study agent was much greater in the alvimopan group. Furthermore, subjects in the alvimopan arm had markers of more advanced disease than subjects on placebo. Overall, our analysis indicated that alvimopan exposure was not the significant predictor for death, and suggested the patients' experience of potential drug efficacy may have led to the greater retention of patients in the alvimopan group for the extension study.

Finally, the observation of an imbalance in bone fractures are summarized here. There was an excess of fractures reported among alvimopan users in the 014 study. Based upon the evaluation of all data across all OBD studies in cancer and non-cancer subjects, this finding appears to be limited to Study 014.

The assessment of events in the OBD studies was hampered by the lack of perspectively defined fracture criteria and a

lack of collection of radiography. No negative action was identified to explain these findings, and studies of other opioid-receptor antagonists have not identified any effects on bone metabolism.

In summary, we believe that no confirmed association between drug exposure and any of the adverse events has been established. The OBD population is in general at high risk for each of these problems. The presence of hypertension, hyperlipidemia, and tobacco use increases the risk of cardiovascular events. Tobacco use is further associated with aero-digestive cancers. Opioid users have an increased risk of falls and often use concomitant medications associated with osteopenia.

In each case, the frequency of events was low, and the relative risk estimates uniformly included the NULL value. Finally, we see that these events were principally confined to Study 014, a

long-term trial, and were not replicated in other OBD or POI studies.

Now, based upon these findings, the preclinical data were reviewed for any potential association. With respect to cardiovascular events, the preclinical program failed to identify any evidence of cardiotoxicity. Similarly, monitoring of cardiac function during clinical pharmacology studies demonstrated no negative cardiac effects. In addition, preclinical assessments of alvimopan, including clastogenicity, mutagenicity, and carcinogenicity assays, were all negative.

Definitive QT studies in humans showed no effect at doses up to 24 milligrams given twice daily. An evaluation of exposure response relationships showed no relationship between levels of alvimopan and either cardiovascular events, neoplasia, or fractures. Overall, preclinical and clinical data do not suggest a clear pattern of either

beneficial or deleterious effects on cardiovascular function, neoplasia, or bone metabolism as associated with long-term treatment with opioid agonists or antagonists.

In summary, the findings of interest were primarily related to a single study in the OBD patient population. These findings did not reflect the experience of other OBD studies, nor did the time to these events generally overlap the period for treatment of the proposed indication of POI.

With respect to the risk of ischemic heart disease, the independent monitoring committee concluded that the available data indicated that the risk for treatment effect had been largely discharged.

While the clinical significance of these findings remains unclear, we recognize these observations require further investigation in the OBD population to fully establish the safety of long-term

administration of alvimopan. These findings have not ever been replicated in shorter term studies of alvimopan in either the OBD or the POI populations.

With that then, I'll turn things back over to Dr. Jackson to complete the discussion of the POI safety program.

DR. JACKSON: Thank you, Dr. Mortensen. So now, if we may turn our attention back to the POI safety database. I'm going to address the following four points, including the safety follow-up in the POI studies.

The POI safety database includes nearly 4,000 patients worldwide. It consists of, as you've seen, three Phase II studies and six Phase III studies. This database includes all patients who underwent bowel resection or total abdominal hysterectomy and who received at least one dose of 1, 3, 6, or 12 milligrams of alvimopan or placebo. Disposition of these patients, as you've seen

already, shows that approximately 80 percent completed treatment, and about 8 to 11 percent discontinued as a result of an adverse event. It's worth noting, I think, that fewer patients treated with 6 or 12 milligrams discontinued due to adverse events. Now, because very few patients received doses of 1 or 3 milligrams of alvimopan in these studies, this is the last time I will discuss this group.

As you would expect, following major abdominal surgery, the most commonly reported treatment-emergent adverse events were nausea and vomiting. And as you can see here, the frequency of nausea, vomiting, abdominal distension, pyrexia, and hypertension were essentially comparable across the treatment groups. Less common events occurring with a frequency of less than 10 percent in any group also showed comparable frequency across the treatment groups.

Focusing on serious adverse events, overall rates were low. The most common serious adverse events were POI and small intestinal obstruction, which are, as you may know, often difficult to differentiate in this setting, both of which were less frequent in the alvimopan group. SAEs resulting in death were rare and comparable between groups.

Now, because of the numerical imbalance of myocardial infarctions in GSK014, the agency asked us to provide additional documentation, such as ECG tracings and cardiac biomarkers for POI patients who had a cardiovascular event of interest. Both the agency and Adolor used these additional data to adjudicate and categorize these cardiovascular events as noted here, to determine if any imbalances existed.

The rates for these CV events of interest were low, and there was no evidence

of an increase in cardiovascular events among the alvimopan group. Because event rates were low, the 95 percent confidence intervals surrounding the relative risks are generally wide. And when we combine all cardiovascular events of interest in the second line here into a single category, we see that the incidence is somewhat lower in the alvimopan group.

To provide further assessment, we also sought an independent analysis from the Duke Clinical Research Institute Clinical Events Committee, the team of practicing physicians specializing in cardiology or neurology. Now, they provided a blinded adjudication of all POI cardiovascular adverse events using patient-level source documents. The DCRI used the American Heart Association, American College of Cardiology, guidelines, as well as clinical judgment to define specific events. Hence, their numbers differ slightly from the Adolor analysis, but

the results confirm no imbalance in CV events exists between the two treatment groups.

In addition to the Adolor and Duke analyses, we also looked for references in the literature regarding the incidence of myocardial infarction following a bowel resection. The data shown here are from a paper by Khuri et al. using the NSQIP database, the VA database. And we see that the observed incidence of myocardial infarcs in our POI trials was generally consistent with that shown in this very large database of bowel resection patients.

Turning to the secondary category of imbalance seen in the GSK014 study of OBD patients' bone fractures, we saw only one in the POI database.

And finally, looking here at treatment-emergent malignant neoplasia in the POI studies, the incident of neoplasia was low and balanced between the groups.

Now, a question has been raised

regarding the adequacy of follow-up in the POI studies to detect later adverse events. We're confident in the quality of our data, given that 88 percent of the patients in the worldwide POI safety database were followed up after their last dose of medication. Three-quarters were contacted by telephone, most at one to two weeks, to ask about adverse events. Another 13 percent had a follow-up visit with the surgeon. And in Study 001, there was also a six-week follow-up visit where 76 percent of patients were seen and questions were asked about adverse events.

In the North American studies, site visits by monitors assessed all follow-up data for 30 days after the last dose by review of records. Bowel resection patients, as you heard from Dr. Techner, are routinely seen by the surgeon and evaluated, usually within two to four weeks for an initial postop visit. And it has been suggested,

again, that metabolite concentrations may be significant beyond this observation time. But, in fact, by six-plus days following the last dose, metabolite levels are negligible. Therefore, we believe that the follow-up safety monitoring in the POI population was appropriate and was comprehensive.

In summary, alvimopan 12 milligrams was well-tolerated. There's no evidence of increased cardiovascular, fracture, or cancer risk seen in this large clinical safety database. As Dr. Techner noted earlier, there was no evidence of a reversal of opioid analgesia with alvimopan. Collectively, the efficacy, morbidity, and safety results you've seen today we believe support a positive benefit-risk profile for the use of alvimopan 12 milligrams in patients undergoing bowel resection.

I would now like to turn to and provide an outline of our proposed risk management plan. In November 2006, we

received an approvable action letter requesting that we provide a risk management plan to address possible cardiovascular risk of longer term exposure, and to minimize off-label use.

With this risk management plan, our primary goal is to ensure appropriate use of Entereg, and to prevent any use of Entereg outside of the hospital.

We recognize the importance of providing Entereg within the proposed indication, because POI is an unmet medical need. There is no approved pharmacological option available for patients or for those who care for them. In addition, I think it's clear from the data presented today that Entereg provides clinically meaningful benefit to patients undergoing bowel resection without an increased risk of adverse effects.

Now, in our evaluation of the various different options, other

considerations were also important. The dose of Entereg which will be available for the management of POI is 12 milligrams. The potential for inappropriate use of Entereg outside of the hospital would be in patients already receiving opioids.

From our data, we know that opioid-tolerant patients who receive 3 milligrams or greater experience gastrointestinal side effects that would make it highly unlikely that they would want to use a 12-milligram dose again. We also know that the physical-chemical properties of the 12-milligram formulation make it very difficult to divide it into smaller doses. These facts make it unlikely that the 12-milligram capsule would be used outside of the hospital.

In addition, we know from past experience that limiting distribution from the wholesaler can significantly reduce inappropriate distribution. However, the

process employed for this type of distribution should not be overly burdensome for the health care system, and we want to make sure that Entereg is readily available for those patients who will benefit from its use.

Therefore, our risk management plan comprises four components. Each of these serves a specific function, and they need then to be considered in totality.

The first and most important component will be the distribution process. We will not distribute samples. We will put contracts in place that require wholesalers only to distribute to acute care hospitals identified in their databases. Wholesalers will place an NDC block on Entereg, which will remove Entereg as an ordering option for retail pharmacies.

In the unlikely event that Entereg should reach a retail pharmacy, the major pharmacy information systems would alert the

pharmacists that Entereg is for hospital use only and should not be used outside of that setting.

We plan to institute systems to monitor compliance with these requirements, and these will include daily reports from wholesalers detailing where Entereg was shipped. In the event of a shipment to an non-approved pharmacy, we will take immediate corrective action. The use of this approach has already been applied by others in the industry, and has resulted in a high rate of compliance, ensuring that the product reached the appropriate end user in over 99 percent of shipments.

The second component of our risk management proposal is our professional labeling. We're proposing that the numerical imbalance in myocardial infarcs from GSK014 be described in the Warnings and Precautions section of the label. In addition, the proposed label is very specific about where

the drug should or should not be used. Specifically, we state that Entereg is contraindicated in patients who have received prior opioids for more than seven consecutive days. The Warnings and Precautions section also describes the most common gastrointestinal adverse events that would occur in opioid-tolerant patients.

Entereg is limited to seven days or 15 doses in the hospital only. And we have highlighted our professional labeling and modified our packaging, both the blister and the carton, so that it clearly states, "hospital use only."

Our educational effort will be directed at health care providers involved in the management of bowel resection patients, who will be in strict compliance with the approved label, reinforcing that Entereg should be used in the hospital only. In addition, promotional efforts will also be directed only to the appropriate professional

audience involved in the care of bowel resection patients. We will have our hospital sales force visit hospital outpatient pharmacies to ensure that that they are aware that Entereg should not be dispensed. And we feel that through this risk management plan, we can safely provide access to Entereg in the hospital, thus meeting an unmet clinical need without placing an unnecessary burden on the health care system.

In summary, the data from the extensive development program of Entereg clearly demonstrate a clinically meaningful acceleration of GI recovery, resulting in fewer patients with prolonged hospital stays.

Dr. Senagore has illustrated the benefits associated with early resolution of POI. These include fewer postoperative nasogastric tube insertions, fewer patients with prolonged hospital stays, and a marked reduction in all-cause readmissions within 10

days of hospital discharge. This meaningful improvement was observed in addition to an accelerated care pathway without any significant safety issues in the POI population.

The numerical imbalances observed in the OBD study, GSK014, were unprecedented and not seen in the other OBD studies. Given that these events occurred in a time period not relevant to POI, and that no plausible explanation for their occurrence has been identified, we feel that Entereg is safe for use in the management of postoperative ileus.

However, to ensure that Entereg is appropriately used, we are proposing a risk management plan that will limit the use of Entereg to the hospital and keep it out of the retail space.

As a result, we believe that Entereg represents a favorable and compelling benefit-risk profile, which makes it appropriate to market alvimopan for the

indication we proposed at the beginning.

This concludes the sponsor presentation. Mr. Chairman, ladies and gentlemen, I thank you for your attention.

DR. BUCHMAN: We're going to now open the discussion to questions for the sponsor. Members of the committee who have questions for the sponsor, please raise your hand and make sure when you speak that you press the red button on your microphone.

Dr. Talamini?

DR. TALAMINI: Mark Talamini, University of California at San Diego. I'm a temporary voting member. I'd like to commend the company for an excellent presentation and a set of data beforehand as well, as well as the FDA preparation package was terrific. A couple of questions, and I'll ask them all at once.

In your protocols, were there any aspects of the surgical procedure itself that were part of the protocol, such as how the anastomosis is done or how the operations

were conducted, or was that simply at the surgeon's discretion? So that's one question.

The second question, in all of your postoperative ileus study patients, I believe they were all screened with EKGs and chest X-rays. But in your risk management or risk -- this most recent aspect that you discussed, are you proposing that that also be a screen for all patients who receive this drug if it's approved? I guess it's just those two questions right now.

DR. JACKSON: Thank you, Dr. Talamini. If I could take the second question first, and then I'm going to ask Dr. Techner to come up and address the surgical issues.

We are not proposing that the label currently contain recommendations in regard to clinical management, but certainly, as you well know, all of these patients undergoing elective surgery do have pretty extensive work-up as part of their preoperative

evaluation. And we did not see anything in the clinical studies suggesting changes in EKG between the alvimopan and placebo groups.

Dr. Techner?

DR. TECHNER: Lee Techner, Adolor. To address the first part of your question, the answer is no. There was no standardized surgical procedure or standardized methodology for the anastomosis across the clinical trials. That was basically left to the discretion of the surgeon, and of course, I would assume, based on the clinical condition.

DR. BUCHMAN: Dr. Kramer, did you have some questions or comments?

DR. KRAMER: Dr. Judith Kramer, Duke University. Dr. Techner I think probably might want to answer this. As a competitive antagonist of the mu-opioid receptor, I would have thought that a strong predictor of alvimopan's GI effects would be the dose of concomitant opioids administered. Yet I didn't see an attempt to quantify the dose in any way

and look at that in a multivariable analysis for the effect -- on peripheral effects on the GI system or the GI endpoints.

Could you comment on that?

DR. TECHNER: Sure I could. We have looked extensively to see whether or not there's any relationship between dose of opioid used and pharmacologic effect. We have evaluated the current POI database to see whether or not we could determine if there's any threshold that one needs to achieve with respect to opioid dose, and thus produce either a more or less robust response.

What we have found is we have not been able to determine that type of relationship or demonstrate one. And I think the reason for that is, certainly in the U.S., the vast majority of patients are receiving a fairly consistent amount of opioid-based IV PCA, at least within the first 48 to 72 hours following surgery. So you don't get that broad range of patients

getting virtually very low doses to patients getting very, very high doses. So we have not been able to see that across any of our clinical trials.

But what we have been able to see, I'll show you this right now, is that for the vast majority of patients who received opioid IV PCA, the choice of opioid was morphine. That was in approximately 90 percent of patients. And what you see here is the GI-2 Kaplan-Meier recovery curve in those patients who did receive IV morphine. And I think you can see here that the curves look very similar to what I showed you before. So we see the alvimopan treatment group always to the left of the placebo treatment group, and the magnitude of effect, as we represent by the Kaplan-Meier curve across the observation period, is about the same.

DR. KRAMER: You said that you looked very carefully at those, but is there any reason that you didn't quantify the quintiles of dose

and look at that as a covariate endpoint?

DR. TECHNER: We have done that. And again, in doing so, we did not see any relationship, even looking at quartiles or even looking at opioid consumption in other ways, a relationship between opioid dose and response.

DR. KRAMER: And yet in the European trial where you had an opioid-sparing approach, you were not able to demonstrate a benefit?

DR. TECHNER: In the European Study 001, we had certainly more patients using opioid-sparing technique. And I think what we saw there, as I showed you in the core slide, is that when we look at GI-2, the endpoint that I believe we and FDA feel is a more reasonable endpoint with respect to assessing the treatment effect in patients undergoing bowel resection, although it was somewhat less robust, it was still a statistically significant effect.

DR. KRAMER: But about four hours.

DR. TECHNER: Excuse me?

DR. KRAMER: But more on the order of

4 hours difference rather than 24 hours.
DR. TECHNER: Well, it depends on what measure you're looking at, yes.
DR. KRAMER: One last question. Given that your successful efficacy studies all required planned PCA, and the one study that didn't require it, the European study, was negative, will your label specify that this should only be used in patients getting opioid postop PCA?
DR. TECHNER: Well, I'll address your question in two parts. One, I don't believe that -- certainly we don't believe that Study 001 was a negative study. I think when you look at the GI recovery endpoint by GI-2, as we've just said, it is statistically significant, and the mean and median differences are all favoring alvimopan. So that's number one.
Number two is with respect to the label, we have not really negotiated with FDA the label at this point. They have our

proposed label, and certainly we are willing to discuss things like this that would be appropriate.
DR. BUCHMAN: Dr. Pasricha?
DR. PASRICHA: Thank you. Jay Pasricha, Stanford. I have several questions, and I'll ask them one at a time. First is a follow-up on the issue of the mechanism of action. I think the emphasis so far has been that this is primarily due to antagonism of exogenous opioids, but it's true that it also has some intrinsic motility effect.
And some of the discrepancies that you're seeing between the doses of morphine and the effect, and particularly the lack of efficacy in the transabdominal hysterectomy group, may be because what's at play here. The underlying pathophysiology is not so much due to exogenous opioids, but activation of endogenous opioid systems.
So I wonder if you have any comments on that, and I'll go on to my other

questions.
DR. TECHNER: Sure. I think let's address the second part of your question with respect to the hysterectomy population. And I think it's important to note that part of the reason for us moving to the bowel resection population is because in the hysterectomy patients, there was an important finding. And that is, in general, they were only in the hospital for three days. And so in essence, the window of opportunity to demonstrate an effect on either GI recovery or length of stay in a patient who's only in the hospital for two or three days becomes very challenging.
I will say that in that study, and that's Study 306, we allowed the patients to take the dose for a total of seven days and they left the hospital with drug. We did show, when you look at the entire treatment period -- so that seven-day treatment period both in and out of the hospital, we did show an acceleration of about one day in time to

first bowel movement.
So it's not that alvimopan was ineffective in the hysterectomy population. It's just the fact that they're in the hospital for such a short period of time does not really allow us to assess the impact in a hospital setting as compared with bowel resection patients, who, as you saw from our data, with an accelerated care pathway, the mean length of stay is somewhere around six days.
As far as -- does that help to clarify that point? Okay.
DR. PASRICHA: So the other question I had was related to -- I think one of the questions that the FDA has asked us to look at is the clinical significance of improvement of recovery by one day.
And so you had an opportunity perhaps to look at all this data. And have you seen any correlation between GI-2 and other nosocomial infections or other

complications related to that? And have you shown a benefit of your drug with respect to those non-POI hospital complications? Which is really implied, but I'm not sure has been actually demonstrated.

DR. TECHNER: Yeah. I think that gets at a very important question, and certainly one that we are very interested in. And I think you have to take a couple things into consideration.

One, the studies really weren't designed to evaluate differences in those types of events between the active groups and placebo. So that's number one.

Number two is we don't have predefined or prespecified definitions for those events. However, we did look at that, and we did try to see what potential effect we may have on those more common nosocomial complications. And let's show you that now.

So what we did was we looked at several categories. One, thromboembolic events, DVT-PE, and also under a broad

category of postoperative infection, we looked at wound infection, respiratory tract infections, sepsis, and UTI.

Now, one thing you'll notice here immediately is that the event rate for these are quite low. I think part of that is related to the fact that, at least these days, in the preoperative arena, surgeons will aggressively try and prophylax for all of these events. But what you do see here is that the incidence of these events is low and it's comparable. However, there is a trend -- when you look here, particularly in the broad category of postoperative infection, that the incidence is lower in the active treatment groups. And that pretty much pertains across the board.

So that is the extent to which we have tried to get at the point that you're getting to. But what I'd like to do to try and elaborate even further is I'd like to bring up Dr. Senagore so that he can address

from his clinical perspective. Yes?

DR. PASRICHA: So related to that, your all-cause readmission rate was higher in the placebo group?

DR. TECHNER: That's correct.

DR. PASRICHA: Did you analyze by category of --

DR. TECHNER: Yes.

DR. PASRICHA: And what did you find?

DR. TECHNER: Yes, let's show you that as well. All-cause readmissions broken down by category. Now, again, understanding the caveats that I mentioned before, we look at the events that were classified by the physician, by the investigator, as the primary cause for readmission.

And what you can see here is we've broken these out into three categories: GI events, surgical complications, and the category of other. And I think when you look down this list you can see that postoperative ileus, certainly the readmission for POI as

per the investigator, was lower in the 12-milligram group as compared to the placebo group.

Same thing for readmission for vomiting. Now, it's difficult to ascertain what the underlying diagnosis was there. I mean, this could represent unresolved ileus as well. Interestingly, when you look at anastomotic leak, you see a lower readmission rate for an anastomotic leak in the 12-milligram group, and same thing with postoperative abscess. I think everything else is fairly comparable.

So yes, we have tried to break this down and see where the trends may be. And what we conclude from this, realizing that the event rate is low and realizing the trials really weren't prespecified and designed to look at this, that it looks as though that there's a tendency for a lower readmission rate when the readmission is caused by a GI complication, if you will, in

the Entereg group versus placebo. And again, I'll caveat that by we certainly understand these rates are low and we can't draw any definitive conclusions, but we are certainly interested in looking at this.

DR. BUCHMAN: I'm going to ask a follow-up question on that particular issue. You showed the data on readmissions, but the premise is that if a patient is discharged from the hospital earlier, there would be a lower risk of nosocomial infections. The previous slide showed postoperative complications related in some way to the operation.

We know that there's an epidemic of Clostridium difficile within the hospitals. You had virtually no one who was readmitted for that. But what about during the admission in which they had their surgery? Did you see a difference in either aspiration pneumonias or in Clostridium difficile toxin-positive patients between treatment and placebo groups?

DR. TECHNER: Yeah, it's an interesting question, and we have looked at that. And the answer to your question is no, we did not see any differences in either of those events in the data that we have. Now, again, the event rates are low, so it's hard to draw any conclusions. But the bottom line is we did not see any differences there.

DR. BUCHMAN: Dr. Rosing, did you have a question?

Ms. Corkery-DeLuca?

MS. CORKERY-DeLUCA: Dr. Techner, I was reading a recent journal, JAMA, and they had an article, and the article's on rise of opioid use in surgery. Not being a doctor, doesn't that mean that the morphine would keep you in the hospital longer?

So are you saying that the alvimopan would get -- by even the one day, would be a better alternative than to the increased opioid use and morphine?

DR. TECHNER: That's an interesting

question, and I think that I'd like to bring Dr. Senagore up here to answer that question based on his clinical experience directly with these patients.

Tony?

DR. SENAGORE: I think your question's focused on -- there is a strategy now to examine postoperative pain management more aggressively than we may have in the past. And there is a much broader application of narcotic analgesia, at least in the States, for that. And so the data you saw here was for a very focused application in a very structured enhanced recovery program. If you look at hospitals across the States, you'll probably see much higher doses of narcotics administered to the postoperative patients in a variety of forms. So the hope would be that these data would actually be replicated and enhanced by showing even a greater advantage for the patients that receive alvimopan.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: Hi. Lin Chang, UCLA. I was just trying to get a better feel for what's the applicability of the side effect profile in the longer term opioid bowel dysfunction studies, and how it's applicable actually to the POI population. So I was wondering if you looked carefully at the patients who did get cardiovascular events in the POI population, if they at all have any similarities to the opioid bowel dysfunction patients who had cardiovascular?

For example, did they have any cardiovascular risk factors? Had they been previously on opioids, not in the seven days before the study, but in the past? I mean, is there any -- because the risk management plan isn't going to exclude anybody with a pre-existing condition. So I just wanted to know, are there some people at risk, or do you really believe that you get the side effects because you're on opioids longer, that there's something different in the

opioid bowel dysfunction patients having long-term opioid use with either metabolism or something like that?

DR. JACKSON: Thank you. Firstly, in regard to the imbalance in cardiovascular effects that we did see in the OBD patients, largely confined to Study 014 and -- as you saw from Dr. Mortensen's data, not replicated in the other studies that essentially covered 90 percent of that same period for the myocardial infarctions, we did not, I believe, see anything different about the patients in Study 014 that might have accounted for this.

In terms of the POI database, we did indeed look for established cardiovascular disease and cardiovascular risk factors, both in the placebo and the alvimopan population. If we focus over here primarily on the bowel resection subjects, it was interesting that there is no imbalance in terms of cardiovascular adverse events, but established cardiovascular disease just

turned out to be a little higher in the alvimopan patients.

The sorts of things we saw are those you would expect. Smoking was perhaps a little less frequent than the U.S. common numbers, and it's certainly much less than we saw in OBD Study 014, where Dr. Mortensen said about 40 percent of those patients were smokers.

Apart from that, we really don't see anything in here that is predictive other than age.

DR. TECHNER: If I just might add one thing here. I think it's important to keep in mind that these patients, as you know, are going to undergo, as I believe Dr. Jackson said, a fairly aggressive preoperative screening program. They're undergoing major abdominal surgery. And as such, we would expect that patients at high cardiovascular risk would not be cleared, particularly from a cardiology perspective, to undergo such a surgery. So that

in and of itself is almost somewhat of a protective mechanism, we believe.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: I just wanted to go ask you a little bit about dose response actions as far as the primary goals that you had on solids-in and solids-out, which you didn't show so much here. But in the studies that previously you showed from your publications on 314, and in 313 and on 308, the 6-milligram dose for solids-in/solids-out it was .01, the P value, .05 for the 12-milligram. It was .001 for the 12 in 313 and .05. And in the -- there was a difference of about seven hours in the 313, which was the published paper. Putting it all together, you showed the pharmacokinetic data, that certainly it sounded like the 12-milligram had overall better efficacy.

Do you feel confident that there is a dose-response curve in any of these primary or secondary endpoints, including hospital discharge, between 6 milligrams and

12 milligrams?

DR. JACKSON: Dr. Techner, I'm going to ask to provide a more detailed response, but essentially from my clinical perspective, there is a subtle dose-response curve. You've got to look in specific places for it to establish the 12 milligrams as superior to the 6. And maybe, Lee, you would --

DR. TECHNER: Sure. Interesting point, and we have looked at this carefully. I think to take the last part of your question first, to establish that up front, we do feel confident that the 12-milligram dose is the appropriate dose in this population. There are several perspectives we look at, as I was discussing with you before.

One is the PK perspective. So we do see a higher plasma concentration achieved and maintained for a longer period of time with the 12-milligram versus the 6-milligram dose.

In addition, when you look at the

clinical efficacy results, the consistency of the 12-milligram dose seems to beat out the 6-milligram dose pretty much at all time points. And let's just show you an example of this.

We're going to look here at the studies, the initial trials, 313, 308, 302. And the reason I'm focusing on that is because those are the studies where in fact there were two doses. As you've correctly pointed out, there was only one dose in 314, and there was a reason for that. We felt that that was the appropriate dose. Here, what you see is the hazard ratios for the key endpoints:

GI-2 ready for discharge and discharge order written for the 6-milligram dose. Now, let's bring on the 12-milligram dose. And what you can see is that in each instance, there is a somewhat more robust response with the 12-milligram group as compared to the 6-milligram group.

So when you combine the PK profile of 12 versus 6, the efficacy profile, the safety profile which Dr. Jackson has shown you is comparable. And you take into consideration that for this condition, we don't have the ability to titrate. There's no time to titrate. We want to be sure that that dose that we choose is the right dose for the largest number of patients possible.

When you combine all of that collectively, that provides what we believe is support for the 12-milligram dose. And I think certainly we feel that that was borne out in the results from the 314 study in bowel resection only.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I have two types of questions, one just associated with some pharmacokinetics and pharmacodynamics, which I'll ask first, and then some regarding the cardiovascular events.

First, from the pharmacodynamic

standpoint, what is the property that determines the relative central versus peripheral action of this opioid -- this selectivity? Because, is there any potential agonist effect that may relate to the issue of fractures or falls, et cetera, or other potential complications? So is there any central effect, and what determines the difference in central versus peripheral?

DR. JACKSON: I'll give you the answer as best I understand it from my limited clinician's perspective. If we need more, we'll ask one of our chemistry colleagues to come up. But it is based on the physical-chemical behavior of the molecule. It does not cross membranes well. It is low in variable absorption from the GI tract. And the parent compound, therefore, doesn't get into the blood -- into the CNS.

DR. LINCOFF: Doesn't get into the blood or doesn't get into the CNS?

DR. JACKSON: Doesn't get into the

CNS. It gets into the blood. We have adequate plasma levels to exceed the KI for the vast majority of the time in most patients at a 12-milligram dose.

DR. LINCOFF: And then focusing on the cardiovascular adjudications that were done for both the OBD studies and the postoperative ileus studies, I understand that the Duke Clinical Research Institute did the cardiovascular adjudication for the postoperative ileus. And when we compare the slides, I guess your Slide CP-9 and CP-11, with adjudicated and non-adjudicated, it's fairly straightforward to look at the two, because the same endpoints are used, and we also know a bit about the details of how the DCR did they analysis.

The concern that came up with the cardiovascular, of course, came up with the OBD. And I didn't see too much detail in terms of what the constituency of this IDMC was, or what constituted the IDMC. Who were they? What was the process by which their

events were adjudicated?

Because if you compare the slides of unadjudicated versus adjudicated there, the endpoints are classified differently. So among the questions who was on the committee, How were the -- which cases were chosen for adjudication and by what criteria, what source documentation they had? Can you provide some more details about that adjudication? Because that's really what brought the concern was that the OBD study.

DR. JACKSON: You bet. I'm going to ask Dr. Camm. We're very fortunate to have the chairman of the IDMC here, and let him provide you that information.

DR. CAMM: Good morning, Dr. Buchman. Good morning, ladies and gentlemen. My name is John Camm, and I'm from St. George's and the University of London in the U.K. I was the chair of the IDMC to which you refer. The other members of the IDMC were Tom Koch, a statistician; Jim Eisenach, a pain specialist;

and two other cardiologists, Chris Cannon and Marc Pfeffer, both from Boston. We were constituted, as you probably know, about halfway through the ongoing 014 study, when it became apparent from the ongoing pharmacovigilance that there was an accumulating numerical excess of myocardial infarction appearing in association with treatment with alvimopan.

Our mandate was to look at the opiate-induced bowel dysfunction development program for GSK and review the cardiovascular events in detail.

So we chose prospectively to consider all deaths and all adverse events which were serious enough to require hospitalization. All of the latter were trawled by a third-party extractor to see if any of them had any cardiovascular element.

We then as an adjudication group, which consisted just of the three cardiologists, looked at all of those cardiovascular serious adverse events which

were identified, and looked at all deaths. We used a standard criteria for definition of myocardial infarction and ischemic events, plus, of course, clinical judgment, because many of the cases did not have full documentation, although we had available to us all the source documentation that could be got back from the field.

You'll recall that the GSK014 study did not start out seeking particularly to identify and evaluate cardiovascular safety as such. And therefore, there was no baseline electrocardiography lipid profiling, detailed cardiovascular history, and so on and so forth, nor was there for the first part, and as it turned out the most important part with regard to cardiovascular events -- the first part of GSK014 did not have any prospective data collection, so it all had to be trawled back from the field.

So I hope that that answers your question of what constituted the committee

and how the committee worked.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: I have three questions. My first question is why is it that the studies using the GI-2 criteria seem to have a more favorable outcome for the drug than those using GI-3, when the only difference is dropping flatus as an endpoint? I mean, one would think that it should be no worse using GI-3 versus GI-2. So I'm wondering whether there are data, in fact, that combine both of these that we can see.

Secondly, the second speaker indicated that there was a reduction in the incidence of nasogastric tube insertion by 43 percent. And what were the actual percentages of those events in the placebo and drug treatment group?

And I guess I'd like to get back to that question again on cardiovascular events. It seemed to me that from one of the slides, there was an excess number of patients I

think in the OBD group that had arrhythmias. And could you comment on that?

DR. JACKSON: All right. Thank you. In terms of the first two parts of your question on GI-2 versus GI-3 and the actual percentage of nasogastric tube insertions, I'm going to ask Dr. Techner to respond.

DR. TECHNER: There's one key difference between GI-2 and GI-3, and that is flatus. And I think certainly as clinicians, we all know that the accurate reporting and recording of that endpoint is very challenging. And so certainly what we found in the data is a lot of variability in that endpoint. Certainly when patients are sleeping, whether or not they feel comfortable reporting it to their physician, I think it's a combination of factors that contribute to that variability as opposed to a bowel movement.

So number one, we feel, and I believe FDA agrees, that GI-2 is the more relevant endpoint and the more objective

endpoint in measuring the treatment effect on GI recovery.

DR. RICHARDSON: But GI-3 also included bowel movement.

DR. TECHNER: Yes, it did.

DR. RICHARDSON: Right. So GI-3 can't be worse than GI-2.

DR. TECHNER: Well, it's --

DR. RICHARDSON: You don't have to satisfy all three requirements.

DR. TECHNER: For GI-3, it's whichever occurred first.

DR. RICHARDSON: Correct.

DR. TECHNER: Right. And the variability in reporting is how many times it occurred first, how many times it occurred last, et cetera. Whereas bowel movement seems to be very consistent across the board. However, let's look at the data.

And what I'm showing here is Study 314, where the primary endpoint was GI-2, and then the initial trials, 313, 308,

and 302, where GI-3 was the primary endpoint. I think you can see here that certainly in 314, both GI-3 and GI-2 were statistically significant; same in 313; close in 308, and this may be due to the rule for adjusting for multiple comparisons here, but the hazard ratio, if you look at it itself -- and competence interval could be considered statistically significant if we didn't have that little adjustment for multiple comparisons; and 302, again, trending in the right direction.

So I think you're correct in saying it can't be that much worse. We agree, it wasn't that much worse. However, in evaluating the impact of alvimopan in this population, we feel that GI-2 is the more consistent and more appropriate because it eliminates that variability of flatus.

Your second question -- I'm sorry, I cannot -- ah, yes. May I have my core slide, please? So here's the actual

percentage, about 11-1/2 percent of the placebo patients had an NG tube inserted postoperatively, versus approximately 7 percent of the Entereg 12-milligram patients.

DR. RICHARDSON: Now, this is postop insertion or reinsertion, the tube has come out and having to have it put back in?

DR. TECHNER: It's postoperative insertion. In other words, the patients were required to have their NG tube removed by the morning of Postoperative Day 1. In the vast majority of cases, that did occur. If the NG tube had to be inserted after that, reinserted, that's what's counted here. Okay? So if they had an NG tube or an OG tube during the case and it was pulled, that was fine within the time frame. If it was then inserted once again, that's what makes up these percentages.

Does that clarify it for you?

DR. RICHARDSON: Right.

DR. BUCHMAN: It was announced,

though, that you had a 43 percent decrease in the number of reinsertions of the NG tube. I don't see where that 43 percent comes from.

DR. TECHNER: It's the relative difference between 11-1/2 percent and 6.6 percent.

DR. BUCHMAN: I'm going to ask actually a follow-up question on the NG tubes. We've known for over 15 years, based on studies with feeding jejunostomies, that patients could be fed as early as even in the recovery room following small bowel resections. So my question is, what was the rush to remove the NG tube? And why wasn't it actually placed in the duodenum, for example, and perhaps the second dose of medication, or the first postoperatively, administered via the nasogastric tube, and if the medication actually has any effect on the stomach, which is actually the major problem in terms of trying to feed patients postoperatively and not the small intestine?

DR. TECHNER: I'm going to ask Dr. Delaney to help answer that question with respect to placement of the NG tube. While he's making his way up here, certainly we, during the trials, as you know, did not allow the use of -- insertion of Entereg or placebo through the NG tube if it was in place. There are multiple reasons for that. As you know, that can be fraught with potential complications, and it's difficult to tell whether or not the patient actually received the dose. So that was not permitted within the trials.

As far as the second part of your question, Dr. Delaney, could you respond, please?

DR. DELANEY: Thank you, Lee. Dr. Buchman, ladies and gentlemen, I'm Conor Delaney from Case Western Reserve University.

You're quite correct that nowadays, we do know that we can feed people early. What we also know nowadays is that you actually don't even require a nasogastric

tube. So rather than leaving it or placing it in the duodenum until the morning after surgery, we can simply avoid it altogether. So the rationale for getting it out as soon as possible, if it's placed, is the correct one, and perhaps not even use it at all. And then patients can get diet or liquids immediately after surgery. And that's why when you give this medication orally and know now that it works well orally, it's obviously beneficial to be able to do it in that manner.

DR. BUCHMAN: Does the drug have any effects on the stomach or gastric endthing (?) I should say?

DR. TECHNER: We have, as you I believe saw in your briefing document, done a number of studies in order to try and understand the pharmacokinetic-pharmacodynamic relationship and the effect of this drug on GI transit time. What we have found in all of those studies is although alvimopan has an impact on both large

bowel and small bowel transit, we have not seen a clear response with respect to its effect on GI transit time. So we have clear responses in alvimopan being able to reverse the inhibition of small bowel and large bowel motility, but we don't have, at this point, clear data on how it impacts gastric motility.

DR. BUCHMAN: So do you think that the postoperative effect could be mediated solely by the one preoperative dose, because postoperatively, you've got doses -- a multiple dose of medication sitting in the stomach and not getting actually out of the stomach to have a topical effect on the small bowel?

And would you, therefore, potentially recommend perhaps only a preoperative dose rather than postoperative dosing, and has that been evaluated?

DR. TECHNER: The second part of your question, the answer is no, we have not evaluated that.

The first part of the question is,

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I believe what we have to take into consideration here is that these patients are being exposed over a relatively short period of time to a consistent level of opioid. And as long as they're exposed, that opioid is going to have an impact on bowel motility. We certainly believe that it is important to mitigate those effects by maintaining coverage on the receptors as long as exogenous opioid, particularly parenterally, is being administered. So that is the reason for the dosing regimen.

DR. BUCHMAN: Our last question is going to be Dr. Krist. I know there's a lot of burning questions from the rest of the committee. We'll have additional time this afternoon that we're going to allot for additional questions for the sponsor.

Dr. Krist?

DR. KRIST: I just have two questions and they're unrelated, and I apologize for that. One is further clarification about

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cardiovascular events.

I heard a statement made that in the POI studies, that patients were followed for 90 percent of the time period of when the cardiovascular events occurred in the OBD studies. And what I just wanted was a clarification. Because when I look at Slide CS-7 on the time to cardiovascular events, it looks to me in the 014 study like cardiovascular events are occurring between 40 and 120 days. And what I heard was in the POI studies, that patients were followed up to two to four weeks after a procedure, so that seemed inconsistent.

The second question I had is just I wanted to hear a little bit about the hospital settings where these studies were conducted. My guess would be that these are more academic settings. And I'm just thinking about the external validity or generalizability of the time to discharge in other settings, and whether we could expect

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that the findings here in these studies might apply if released into other community and other settings.

DR. JACKSON: Thank you. I appear to have engendered some misunderstanding in terms of those data. The observation in the POI studies was primarily in the first 14 days pretty extensive and out through 30 days if and when it could be done. And you're absolutely correct that the myocardial infarctions in Study 014 occurred between 40 and about 115 days or whatever it was, so there was no overlap. The point we were trying to get at with those curves was that the period during which POI and its observations took place did not result in any excess cardiovascular morbidity in the OBD studies either.

Then in regard to the hospital settings, Dr. Delaney, would you have anything to add about that? Because it's very interesting when we look at how long patients are in hospital, you're absolutely

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right, most of these were academic centers.

DR. DELANEY: Conor Delaney, Case Western Reserve University. Actually, one of the strengths of this data set is that it was accrued over a large number of centers, including private practice and smaller centers as well as larger academic institutions. So I think the data set particularly shows that it probably is very generalizable throughout multiple types of clinical practice.

So I hope that answers your question.

DR. BUCHMAN: We're going to take a break for 15 minutes. Please be back here sharply.

For committee members, feel free to talk about your kids or the weather, but refrain from talking about any of the data that's been presented so that we can get it transcribed in the record. Thanks.

(Recess)

DR. BUCHMAN: We're going to get

started now. The FDA's presentation is going to start with Dr. Ruyi He, who is the medical team leader of the Division of Gastrointestinal Products, and he's going to speak on the FDA's analysis of the efficacy data.

DR. HE: Good morning. My name is Ruyi He. I'm medical team leader in the Division of GI.

Today, I will present clinical efficacy and a general safety evaluation for alvimopan. My presentation will focus on alvimopan and a proposed indication.

I'll wait for a minute. Okay.

My presentation will focus on alvimopan and a proposed indication, regulatory history, POI clinical program, POI efficacy results, POI general safety results, and OBD clinical program. Then I will turn to Dr. Dannis for a special safety evaluation. She will be followed by the presentation of non-clinical evaluation and risk management.

Alvimopan is a new molecular entity. It's a peripherally-acting opioid-receptor antagonist. Alvimopan has a low systemic oral bioavailability, only about 6 percent. Tmax is about 2 hours and a half-life ranged from 4 to 17 hours. There is one active metabolite.

The sponsor's proposed indication is acceleration of time to upper and lower GI recovery following partial large and small bowel resection surgery with primary anastomosis. In other words, the indication is management of POI, postoperative ileus.

POI is a transient impairment of GI function after surgery. It is characterized by inability to tolerate liquids and solid food, nausea and vomiting, and/or abdominal pain. Complications include prolonged hospitalization and delayed nutrition. No product is currently approved for POI indication in the U.S. Off-label therapies include metoclopramide and erythromycin.

Main regulatory history. The sponsor submitted the initial IND in August 1998, and a fast-track designation was granted for POI indication in February 2004, because we did believe that POI is a serious condition with no available therapy for POI indication. The sponsor submitted the original NDA in June 2004, and approval action was taken in July 2005, because of insufficient evident for efficacy.

In May 2006, the sponsor submitted a complete response, a second review cycle start. During this period, a serious cardiovascular event was identified in an ongoing OBD study. That is Study 014, as mentioned in the sponsor's presentation. In November 2006, the sponsor submitted -- in November 2006, FDA issued a second approvable action letter and requested the final 12-month safety funding and a risk management plan for the potential cardiovascular adverse event.

In April 2007, FDA put the alvimopan program on clinical hold because of an additional two cardiovascular events, neoplasms, and a bone fracture were identified in OBD studies. In August 2007, the sponsor submitted a second complete response. Now we are in the third NDA review cycle. Due date is February 10, 2008.

For the POI clinical program, the sponsor conducted six Phase III clinical studies. All are randomized, double-blind, placebo-controlled studies in patients undergoing partial large or small bowel resection, or total abdominal hysterectomy surgery. Study 001 was conducted in Europe and Australia. All other studies were conducted in the U.S. and Canada. Patients on chronic opioids were excluded from the studies.

Since efficacy was not demonstrated in the total abdominal hysterectomy surgery subgroup in the original NDA submission, the

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sponsor decided to narrow proposed indication to the bowel resection surgery population only. Study 306 is not included in the efficacy evaluation because no bowel resection patient was enrolled in that study.

Treatment. The initial dose was given a half-hour to two hours prior to surgery. Subsequent doses were giving 12-milligram PO, BID from Post-Surgery Day 1 until hospital discharged, or until Post-Surgery Day 7. The maximum number of doses is 15, and a study drug only given in hospital.

Key endpoints. GI-3 is time from end of surgery to time of recovery of both upper and lower GI tract function. Recovery of upper GI tract function is indicated by toleration of solid food, and a recovery of lower GI tract function is indicated by first bowel movement or first flatus. GI-3 was the primary endpoint for Studies 302, 308, 313, and Study 001.

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GI-2 basically is the same as GI-3 except without the evaluation of flatus. And GI-2 was the primary endpoint for Study 314. I do agree with the sponsor that GI-2 may be a more objective endpoint than GI-3 because it is very difficult to objectively assess flatus.

Both DOW and Ready are the secondary endpoints for all the studies. Ready is time from end of surgery to time ready for hospital discharge, based solely on recovery of GI function as defined by the surgeon. DOW is time from end of surgery to time discharged order is written.

Now let's move to the efficacy results. This table summarizes efficacy results of time to recovery of GI tract function measured by GI-3. As I mentioned before, GI-3 was the pre-specified primary endpoint for the first full study on this slide and a secondary endpoint for Study 314. Three time points were selected for this

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evaluation: The 25th percentile, median, and the 75th percentile.

From this table you can see that the patient trial medical alvimopan group had a median time to achieve GI-3, 4.4 to 13.4. All were earlier than the patient did in the placebo group: 4.4 for Study 001, 13.4 for Study 308. At the 75th percentile, the differences were larger, from 7.5 hours to 21 hours. Hazard ratios are between 1.3 and 1.49. Because two different doses, 6 milligrams and 12 milligrams, were tested, a significant level for P value per protocol was less than 0.025. In this way, you can see that for the first full study, only Study 313, which is highlighted in here in yellow, reached protocol-specified statistically significant levels.

Based on those results at the end of the first review cycle, the agency issued an approval letter and required additional efficacy data prior to approval. Study 314

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was then submitted in the second review cycle.

Now let's see GI-2. GI-2 was the primary endpoint for Study 314 only, which is highlighted in here in yellow. From this table, you can see that a patient in the 12-milligram alvimopan group had a median time to achieve GI-2 -- 4.4 hours to 21.7 hours earlier than the patient did in the placebo group. At the 75th percentile, the differences were larger, from 18.7 hours to 28.9 hours. Hazard ratios are between 1.3 and 1.63. For Study 314, P value was less than 0.001 and it is statistically significant.

This table summarizes the results for Ready, time from end of surgery to time ready for hospital discharge. Ready was one of the secondary endpoints for all studies. From this table, you can see that the patient in the alvimopan group had a median time to achieve Ready 8 hours to 17.3 hours earlier

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than the patient did in the placebo group. Hazard ratios listed here are between 1.1 and 1.54.

This table summarizes the (inaudible) time to discharge order written, DOW, in days. DOW was one of the secondary endpoints for all studies. From this table, you can see that Study 001, which was conducted in Europe and highlighted here in yellow, shows no difference between the two groups.

However, for other (inaudible) American studies, a patient in the alvimopan group had a median time to achieve DOW .3 to .8 days earlier than the patient did in the placebo group.

At the 75th percentile, the differences were larger, about one day early shown here. From this column, you can see that in all four North American studies, DOW was consistently between six and seven. However, in the Study 001, DOW was 11 days.

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When compared to the U.S. study, Study 001 has a similar time to recovery of GI tract function measured by GI-3 and GI-2, but a different time to discharge order written, DOW, suggesting different clinical practices in Europe with regard to hospital discharge. In Europe, discharge may be delayed beyond GI recovery.

This table summarizes results of mean length of hospital stay by study. Three of four North American studies indicate that the hospital stay was one day shorter for patients in the 12-milligram group than patients in the placebo group, shown in here. Again, Study 001 has a longer hospital stay than the U.S. studies. Nine days versus five to six days.

Efficacy summary in POI population. Efficacy data demonstrated that there was acceleration of recovery of upper and lower GI tract function by roughly about 20 hours measured by GI-2, and a reduced length of

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hospital stay by roughly 1 day in the U.S. The questions are: What is the minimum acceptable efficacy difference for recovery of GI function measured by GI-2 or GI-3 for alvimopan relative to placebo? Do you consider the efficacy results from the POI studies which I present here today to be clinically meaningful? Discussion will help us to do benefit-risk assessment not only for this drug, but also for other drugs with similar indications.

Now let's move to general safety evaluation in the POI population. A total of 4,000 patients are included in the POI safety database. That includes 2,000 patients received alvimopan.

This table summarizes demographic data for overall POI population. Mean age was 57 to 58 years old, and 35 percent of them were patients 65 years old or older. The majority, 85 percent, were Caucasian in all groups. More female patients were

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enrolled in the POI program, because initially, the target population included patients with hysterectomy surgery. For the patients with bowel resection surgery only, male and female were similarly represented in each group, and equally distributed between the treatment groups.

In the POI population, mortality was the same in the placebo and in the alvimopan group. So here, 0.5 percent, and at 0.7 percent in the placebo.

Non-fatal serious adverse events were numerically lower in the alvimopan group compared to the placebo group -- 12 percent, 12 percent versus 18 percent. This was mainly due to fewer postoperative ileus and small bowel obstruction in the alvimopan groups. So in here, 2 percent, 2 percent versus 6 percent.

This slide summarizes the results for discontinuations due to adverse events. The data indicates that a proportion of

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patients with discontinuations due to adverse events was numerically lower in the alvimopan groups compared to the placebo group, 8 percent versus 12 percent. This was also mainly due to fewer GI adverse events in the alvimopan groups. Fewer GI adverse events in the alvimopan groups may indeed support efficacy claim of acceleration of GI tract recovery.

For treatment-emergent events in the bowel resection population, there was either a smaller or similar proportion of patients with treatment-emergent events in the alvimopan groups compared to that in the placebo group, as shown in this slide:

43 percent, 49 percent, 12 percent, 21 percent, 12, 14, 8, 9.

General safety summary in the POI population. Similar or lower incidences of death, nonfatal SAEs, discontinuations due to AEs, and treatment-emergent events were identified in the alvimopan group in

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comparison with the placebo group in the POI population.

Now let's move to chronic opioid-induced bowel dysfunction, OBD, program. OBD is a chronic condition characterized by decreased frequency of bowel movement and associated symptoms. Patients in the OBD studies were treated for chronic pain with opioids for months or years instead of days in the POI program. Although current submission is only for POI indication, imbalances in cardiovascular events, neoplasms, and bone fractures were identified in the OBD clinical studies.

This slide shows the difference in dosing regimen in the POI and OBD studies. In the OBD program, the dose was much smaller: 0.5 milligram QD or BID, in comparison with 12 milligrams BID in the POI program. However, duration was longer, up to a year in the OBD program, instead of up to eight days in the POI program. Another

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difference is that it's used in the hospital only for POI indication, but in the OBD program, it's mainly used for outpatient therapy.

Before I turn to Dr. Dannis for a special safety evaluation, I want to say thanks to everyone in the review team, especially my thanks to Eric Brodsky. Eric was the primary medical reviewer for this submission, and did excellent clinical evaluation. Thanks.

Now is Dr. Dannis.

DR. DANNIS: Good morning. I'm going to be discussing three special safety issues: Serious cardiovascular events, neoplasms, and fractures. Each of these issues was identified as a possible safety problem in a year-long safety study for opioid-induced bowel dysfunction, or OBD, while alvimopan was under review for the POI indication. Because of these potential safety concerns, the studies for the POI indication and the OBD indication were

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reanalyzed, concentrating on each problem. Thus, I'll be discussing each issue as it relates to both indications, POI and OBD.

First, cardiovascular safety in the POI program. The cardiovascular risk factors in the worldwide POI population were well-balanced between treatment groups. The average age was about 57 for both groups, and each had an equal percentage of patients with diabetes, hypertension, and obesity. Smokers made up about 9 percent of both groups.

Here, we have the total number of patients who had serious cardiovascular events in the whole POI population. As you can see, patients in the alvimopan treatment group had a similar number of cardiovascular events as compared to patients in the placebo group. Cardiovascular death as well as all-cause death were essentially balanced between treatment groups.

The total cardiovascular events which occurred were separated into ischemic

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events and other serious cardiovascular events. Ischemic events were defined as myocardial infarction, cerebral vascular accident, and unstable angina. Other serious cardiovascular events included congestive heart failure, serious arrhythmia, cardiac arrest, and non-ischemic cardiovascular death.

Once again, there does not seem to be any difference between treatment groups in the percentage of these events. Multiple independent analyses of the specific cardiovascular events were carried out. And although the interpretation of certain events was different, the overall assessment was the same: There were no apparent differences in the occurrence of serious cardiovascular events in the alvimopan group as compared to the placebo group. The time-to-event analysis shows that the occurrence of CV events are distributed fairly uniformly over time for both groups.

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This table describes what happened to the patients after they left the hospital. In most all of the POI studies, the protocol-defined hospital follow-up was by telephone call. As you can see here, the majority of patients had their last contact by telephone at between 6 and 14 days. Some had phone follow-up one to five days after discharge. Few patients had any follow-up beyond two weeks.

For the patients who did have an investigator follow-up visit, most were also seen 6 to 14 days later. This visit occurred in 7 percent of the placebo patients and 14 percent of alvimopan patients. Less than 1 percent of patients had a protocol-specified investigator visit more than two weeks after discharge.

In addition, there were 580 patients who discontinued treatment for any reason. It's unclear how many of these patients were lost to follow-up. Also, 257

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patients who completed the study per the sponsor's protocol had no follow-up after discharge.

In the POI program, a patient was considered to have completed the study if all protocol-specified in-hospital assessments were completed. Therefore, there were some limitations of the POI study designs.

As I mentioned, follow-up was by phone call only. Important safety endpoints such as 30-day and 60-day morbidity and mortality were not collected. Cardiovascular events were not prospectively defined nor consistently assessed post-exposure, and the fact that the data wasn't there doesn't really imply that there were no serious cardiovascular events that occurred. In conclusion, the POI studies were not adequately designed to properly assess cardiovascular risks.

Next, we'll move on to cardiovascular safety in the OBD population.

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The major OBD trials were divided into two categories: Studies with patients taking opiates for non-cancer pain and studies with patients taking opiates for cancer pain.

Here's a table of all of the relevant Phase II and Phase III studies. In white are all the non-cancer studies except Study 14, which is in red. As I mentioned, this was the large, year-long, non-cancer study which had some potential safety issues.

In green are the cancer pain studies. Here, we have the total number of patients who had serious cardiovascular events in the non-cancer OBD population. More than twice as many patients who took alvimopan had a serious cardiovascular event as compared to patients who took placebo.

Here, once again, the events were divided into ischemic and non-ischemic events. Both of these show an imbalance between treatment groups.

Now we look at Study 14 alone.

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2.6 percent of all the alvimopan patients had a serious cardiovascular event, yet the placebo patients had no events. Of note here is the lower confidence bound of about a twofold risk increase for CV events.

Here, the events are broken down into ischemic and non-ischemic events. Still, large differences between treatment groups exist. Of note is that 7 of the 11 ischemic events in Study 14 were MIs.

Now we look at the entire OBD population, non-cancer plus cancer studies. There are continued differences between treatment groups in the total cardiovascular events, cardiovascular deaths, and now also in all-cause death. Broken down into ischemic and non-ischemic events, the differences persist, with more events occurring in the alvimopan group.

This table presents the time to all CV events by varying intervals. As can be seen, most of the events in the alvimopan

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group occur between 31 and 180 days. This table presents the time to all ischemic CV events by varying intervals. Again, most of the events in the alvimopan group occur between 31 and 180 days.

Here is the time to CV event analysis. The risk appears constant over the entire time period even though the majority of CV events in the alvimopan group occur between 31 and 180 days. The plot also suggests increased risks with increased exposure to alvimopan. Note that the number of patients in the risk set drops off around Day 42 and again at Day 84 due to the completion of 6-week and 12-week studies. What remain are those patients in the long-term Study 14.

In looking for reasons to explain the imbalance, there were no differences in patient demographics or underlying CV risk factors between Study 14 and the other OBD trials, and there were no differences in

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patient demographics or underlying CV risk factors within Study 14. But the duration of most of the other OBD studies was from 3 to 12 weeks, and for Study 14, it was 12 months.

In summary, there is a numeric imbalance of the serious cardiovascular events seen in the pooled analyses of OBD studies, and most strikingly in Study 14 alone. These findings are not predicted by the preclinical findings, as my colleague will discuss in the next presentation. This may suggest that chronic alvimopan use can increase risk of serious CV events in the OBD population. However, the implications for the short-term POI use are unclear.

Now we move on to the next topic, neoplasms. And first, neoplasms in the POI population. There were several different types of neoplasms identified. No particular kind of malignancy seemed to predominate. As mentioned, these studies were of short duration with mostly phone follow-up, which

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usually didn't exceed two weeks. Both treatment groups appeared balanced for neoplasia events.

There isn't much to say about neoplasms in the POI studies, but to summarize, the percent of neoplasms reported in each treatment group appears to be similar. The POI study design doesn't allow for any real conclusions to be drawn.

For OBD, I'm going to discuss neoplasms in the non-cancer studies, and then the neoplasm deaths in the cancer studies. In general, the incidence of neoplasia was low across all non-cancer OBD studies.

But numerical imbalances were observed between treatment groups in the number of total neoplasms. Alvimopan-treated patients had a higher percentage of neoplasms than those patients who received placebo. Similarly, when the total number was divided into malignant and benign neoplasms, in both categories, the same imbalance persisted.

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The alvimopan treatment group had a higher percent of neoplasms as compared to the placebo group.

Given that the original neoplasm imbalance was reported from Study 14, this study was again analyzed separately. Even with an additional placebo case discovered 50 days after study completion, the relative risk of all neoplasms was 2.5 in alvimopan-treated subjects compared to placebo-treated subjects.

The time to malignant neoplasm for alvimopan patients varied from less than 1 week to greater than 10 months. Six cases occurred in two months or less. Many of the others occurred after six months, all of these in Study 14. All except one of the benign neoplasms occurred in Study 14. The majority occurred after six months of treatment.

There were three neoplasms reported in the placebo patients. These cases

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occurred from about 6 weeks to greater than 52 weeks. The time-to-event analysis is difficult to interpret with such a small number of events, but it suggests that increased exposure to alvimopan may increase neoplasm events.

The most common neoplasms reported in the non-cancer studies were squamous cell carcinoma, breast cancer, and lung cancer.

Now we move on to the OBD studies in patients with cancer. Study 008 and the Extension Study 684 were the two main OBD studies in cancer-related pain.

While reviewing the neoplasms in these studies, an imbalance between treatment groups and the death rates was noticed. There were 10 deaths in Study 008; 9 occurred in the alvimopan group. In Study 684 there were 13 deaths; 11 occurred in the alvimopan group. Combining these studies, 13 percent of the alvimopan group died as opposed to 4 percent of the placebo group. The

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time-to-event analysis is once again difficult to interpret. As time increases there are so few patients left in the study, especially in the placebo group.

There were imbalances noticed between treatment groups in the percent of certain malignancies. For example, in Study 008, more subjects with head and neck cancers received alvimopan than placebo. However, the deaths were almost entirely in GYN, GY, and breast cancers. In contrast, in Study 684, more subjects with non-small cell lung cancer received alvimopan than placebo and here more deaths did occur in patients with non-small cell lung cancer.

There were also imbalances noticed in the baseline performance status between treatment groups. In Study 008, Karnofsky Performance scores appeared balanced between treatment groups. However, in Study 684, there was a higher percentage of patients with lower Karnofsky Performance scores in

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the alvimopan group as compared to the placebo group: 42 percent versus 13 percent, respectively.

The demographic characteristics and extent of metastatic disease were similar between the Study 008 and Study 684 populations, and were balanced between treatment groups within each study.

In summary, for the non-cancer OBD population, alvimopan-treated patients had a higher incidence of neoplasia events as compared to placebo. These results were possibly driven by the imbalance in neoplasia events seen in the only long-term safety study for non-cancer patients. There's no apparent reason for the observed imbalance between treatment groups in this placebo-controlled study.

In summary, for the cancer OBD population, there was a large discrepancy seen in the death rates between treatment groups in Study 008 and Study 684. However,

some differences in cancer etiology and patient performance status did exist.

The final topic is fractures, beginning with the POI population. Only one patient with a fracture was identified. This patient sustained multiple rib fractures secondary to a syncopal event and fall after a bowel resection surgery. No real conclusions can be drawn from this one case.

Now, fractures in the OBD population. When you look at the fracture incidence in the entire OBD population, non-cancer plus cancer studies, there wasn't any difference between treatment groups. However, again, when you look at Study 14 alone, the difference between treatment groups is apparent. There was a 3.7 percent fracture rate in alvimopan patients, versus a 1.1 percent rate in placebo patients.

This table describes the location of all of the fractures. Interestingly, the more typical osteoporotic-type fractures,

such as hip and vertebral, were rarely seen. The bones most frequently broken were the ribs and extremities. The same fracture locations were seen in Study 14, where the majority of events occurred. More of the fractures in the alvimopan group were in women, but once again, these were not osteoporotic fractures.

When we looked at time to fracture, fracture rates were reasonably balanced between treatment groups until about six months. After this, most of the events occurred in the alvimopan treatment group. Although the causality for many of the fracture cases was not determined, the overwhelming majority of cases were secondary to falls.

Here is the time-to-fracture analysis only for Study 14. The majority of fractures were reported after 12 weeks of treatment. In the alvimopan group, there appears to be a relationship between duration

of treatment and risk of bone fracture. But given the small number of fractures, this analysis is somewhat limited.

When adverse events were reviewed, there did not seem to be an imbalance between treatment groups for factors that might increase fall risk, fractures such as dizziness, syncope, gait instability, et cetera. Of the subjects who reported fractures, certain demographic characteristics were imbalanced between treatment groups.

The alvimopan group had a higher percentage of women, more individuals aged 65 or older, and a higher average BMI. Baseline demographics, except advanced age, were well-balanced between treatment groups in Study 14 as well as in the total OBD population. Additionally, the mean opioid daily dose was similar between treatment groups.

In summary, for the OBD population

fractures were not the typical osteoporotic fractures, such as hip and vertebral. The patients with fractures in the alvimopan group were more commonly women than in the placebo group. More fractures were secondary to falls, and confirmatory information was often not available. The etiology for the imbalance seen in fracture rates between treatment groups, mainly in Study 14, is unclear.

So, to summarize overall, what we have is the largest long-term safety study of alvimopan for the OBD indication showed potential safety signals in three specific areas: Serious cardiovascular events, neoplasms, and fractures. The POI studies did not show any evidence of these safety signals. However, the follow-up of patients was extremely limited.

Next we'll hear about the preclinical findings.

MR. CHAKRABORTI: Good morning. I'll

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present the nonclinical studies and the results of the nonclinical studies for alvimopan.

Alvimopan has been adequately tested in a wide variety of nonclinical studies at sufficiently high doses. These studies include several in vitro and in vivo pharmacology studies -- safety pharmacology studies that examined the effects of alvimopan on the central nervous system, gastrointestinal system, cardiovascular system, and renal system.

In addition to that, the absorption, distribution, metabolism, and excretion studies are also conducted in several species, in rats and rabbits. The acute, subacute, subchronic, and chronic toxicology studies were also conducted in mice, rats, and rabbits.

The genotoxic potential for alvimopan and its active metabolite, ADL 08-0011, was also tested in a complete battery of genotoxicology studies. The

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carcinogenicity studies were conducted by using two-year (inaudible) in mice and rats. And lastly, the reproductive and developmental toxicity of alvimopan was tested in rats and rabbits.

Let me walk you through some of the major findings from these nonclinical studies. I'll first discuss the cardiovascular safety pharmacology studies.

In hERG assay, alvimopan did not show any significant inhibition of hERG current up to 50 micromolar concentration. In isolated canine or dog Purkinje fiber experiment, there was no significant effect on action potential duration or any other parameters that were tested up to 100 micromolar concentration.

In rats, the cardiovascular effects of alvimopan was tested up to 200 milligrams per kilograms by oral route, and there was no significant effect on any of the cardiovascular parameters. In anesthetized

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and conscious dogs, alvimopan did not produce any significant effect, including prolongation of QT or any other effects on ECG up to a dose of 2.5 milligrams per kilogram, IV.

The toxicology studies, there is no significant target organ in any of the toxicology studies in any of the species tested. There was no significant effect on either bone, including the bone marrow, and alvimopan did not produce any significant toxicity in the heart in any of the toxicology studies. The no observed adverse effect level, or NOAEL, was identified in a six-month chronic toxicity study in rats at 200 milligrams per kilograms per day. And the value for dog was 100 milligrams per kilograms per day in a six-month oral toxicity study.

As I mentioned before, the genotoxicity for alvimopan and its active metabolite was tested in a complete battery

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of genotoxicity studies that includes Ames test, mouse lymphoma assay, chromosomal aberration test, and mouse micronucleus test. In all these studies, alvimopan was negative.

The active metabolite was tested in Ames assay, chromosomal aberration assay in Chinese hamster ovary cells, and mouse micronucleus test. And in all these tests, this active metabolite was also negative.

Two-year oral carcinogenicity studies were conducted in rats and in mice. In rats, the doses were 100, 200, and 500 milligrams per kilograms per day. And in mice, these doses were 100, 1,000, and 4,000 milligrams per kilograms per day.

These are the neoplastic findings for the carcinogenicity study. I'll first discuss the results on the mouse. There was a statistically significant positive trend and pairwise difference versus vehicle control at the highest dose, which is 4,000 milligrams per kilogram in the combined

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incidences of fibroma, fibrosarcoma, and sarcoma in the skin and subcutis only in the female mice. In addition, there was a statistically significant positive trend and pairwise difference compared to the vehicle control at the highest tested dose of 4,000 milligrams per kilograms per day in the combined incidences of osteoma and osteosarcoma in the bones in female mice. Alvimopan was negative in the rat and did not produce any significant tumor.

This table summarizes the incidences of tumor in the female mice in the two-year bioassay. The first column shows the type of the organ and the second column shows the tumor type, and then the dose groups and the P value for the trend test.

As you can see for the bone, there is combined incidences when osteoma and osteosarcoma were combined. There were no incidences in the vehicle control or the low-dose, one incidence in the mid-dose, and

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there were four incidences at the high dose. And it was statistically significant, at the level of P 0.025. If we look at the skin and subcutis, when these tumors were combined, fibroma, fibrosarcoma, and sarcoma, you see there are five incidences of these tumors at the high dose and none in control, low-, or mid-dose, and it was also statistically significant.

Now, these findings in the female mice was observed about eight times the human exposure at the recommended dose. These tumor incidences were statistically significant only in one sex. And there was no statistically significant findings either in the male mice or in the female rates, or in other words, alvimopan was not a transspecies or a transgender animal carcinogen.

And the relevance of these findings to human is unknown. And such type of tumor findings in the female mice generally do not

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preclude approval of alvimopan.

To summarize, the nonclinical findings for alvimopan in cardiovascular safety pharmacology studies or in other safety pharmacology studies, there are no notable effects. In toxicology studies, there is no significant target organ of toxicity. And in genetic toxicology studies, alvimopan and its active metabolite was negative. In carcinogenicity studies, it was only positive in female mice. However, it was negative in rat. And in reproductive toxicology studies, alvimopan didn't show any adverse effect on fertility and reproductive performance in rats. And it is not teratogenic in rats and rabbits.

I thank you everybody in the agency for contributing to this project, and also thank you all for your attention.

MS. WEAVER: I'm going to talk about Risk Minimization Action Plans, or RiskMAPs. I'll present some background about the content

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and use of RiskMAPs, and then I'll address what the sponsor has proposed for alvimopan.

So what is a RiskMAP, a Risk Minimization Action Plan? A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing product risks. A RiskMAP employs one or more RiskMAP tools to achieve the goals and objectives of the RiskMAP. And RiskMAPs go beyond the FDA-approved labeling.

So how do RiskMAPs work? There are several strategies that are used within RiskMAPs. Depending on the nature of the product and the nature of the risk, one or more of these strategies might be used.

The use of a product could be limited to settings or patients with a good risk-benefit profile, or to look at the reverse of that, the use of the product could be prevented in high-risk settings or patients. The RiskMAP can encourage or mandate safety-related monitoring. Therapy

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could be started in a closely monitored setting if that's a period of high risk. A RiskMAP can empower patients to participate in medication-related decisions and safety monitoring, with education or informed consent. And RiskMAPs can educate health care providers on safety-related issues and monitoring.

So what are the components of a RiskMAP? A RiskMAP has goals and objectives. And that's the desired end result or goal, with intermediate steps, often stated in terms of the health outcome we're trying to avoid. For example, the goal in a clozapine RiskMAP is to have no episodes of agranulocytosis. An objective or intermediate step to this goal is to perform periodic white blood count monitoring in patients receiving the product.

A RiskMAP uses tools. These are processes or systems beyond labeling to achieve the goals and objectives. We

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characterize the tools into three different categories: Education and outreach, reminder or prompting systems, and finally, restricted distribution, also called performance-linked access systems.

RiskMAPs also include an evaluation component. We look at the health outcomes or the surrogate of health outcomes to evaluate the success of the RiskMAP, often numbers or rates of an outcome or event. RiskMAPs can also be evaluated for compliance with important RiskMAP processes and procedures or process outcomes. And RiskMAPs can be evaluated by assessment of comprehension, knowledge, or desired behavior, often through surveys. And we often use that to assess the educational component of a RiskMAP.

Now, to turn to the RiskMAP tools, targeted education and outreach is used to communicate risks and appropriate safety behaviors to health care practitioners and to patients. Education and outreach can be

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delivered many different ways, including "Dear Health Care Practitioner" letters; training programs for health care practitioners and patients; continuing education; patient labeling, such as medication guides and patient package inserts; RiskMAP program guides; videos; DVDs; and also limits in marketing or promotion, such as no direct-to-consumer advertising, or detailing only to certain specialties.

The next level of tool are reminder or prompting systems. And the purpose of reminder and prompting systems is to assist health care providers in following appropriate prescribing practices. Examples of these systems include: limiting the supply of product per prescription, such as dispensing only a 30-day supply; limits on the number of refills, or not allowing refills at all; prescription expiration, such as requiring a prescription to be filled

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within a certain period of time; specialized packaging; packaging may require certain warnings on the packaging; the packaging may include a medication guide or patient package insert; the specialized packaging may have a pharmacist checklist; and there may be limitations to the amount of product packaged together.

Another example of a reminder or prompting system is prescriber or other health care practitioner attestation of conditions of safe use, and physician-patient agreements as an informed consent.

The highest level or most restricted of the tool categories are restricted distribution or performance-linked access systems. The purpose of these systems is to target the population and conditions of use to those most likely to confer benefits, and to minimize particular risks. This can include restrictions on prescribing, distribution, dispensing, and administering

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the product. Examples of these kinds of systems are: Prescriptions only by specially certified health care practitioners; product dispensing that's limited to pharmacies or health care practitioners that elect to be specially certified; mandatory pharmacy enrollment to dispense; mandatory enrollment of infusion centers or hospitals to administer; the drug could be dispensed or administered only in certain health care settings -- for example, the drug could be administered in an acute care hospital; product dispensing only to patients with evidence or other documentation of safe use, for example, required pregnancy testing or required liver lab testing; and wholesaler agreement to distribute product only to registered entities.

So when should a RiskMAP be considered? Products with important benefits should be considered for a RiskMAP if the risks are serious, but preventable; if safe

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and effective use requires specialized health care skills or settings; when intervention is needed to increase the benefits relative to risks; and when the product is in a class of products with similar risks that require a RiskMAP.

So now with that background, let's turn to the RiskMAP proposed for alvimopan. The proposed RiskMAP addresses cardiovascular risk. So far, the sponsor has not made a complete RiskMAP submission.

An outline of a proposal has been submitted, but the outline did not include any goals, objectives, supporting documents, detailed implementation plans, an evaluation plan, metrics for evaluation, or the frequency and content of RiskMAP reports to the agency. The RiskMAP outline addresses cardiovascular risk, and the logic of the RiskMAP framework relies on the assumption that cardiovascular risks will be minimized by limiting use to inpatient settings.

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So the first question that we have is whether the logic model holds. Do we understand the risks? From Dr. Dannis' presentation, you saw that the follow-up in short-term trials might not have been sufficient to ascertain cardiovascular and other events that might have occurred outside the period of observation. Additionally, we note that the proposed daily dosage is 24 times higher than the dose that produced the cardiovascular safety signal in longer term testing.

The RiskMAP outline submitted proposes a RiskMAP comprised of these elements: agreements with pharmaceutical wholesalers to sell only to hospitals; targeted education, sales, and promotion to acute care hospitals; packaging that specifies hospital use; and an alert system for outpatient pharmacies to alert pharmacists not to dispense on an outpatient basis.

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We are concerned that the current proposal may not prevent longer term use or outpatient use. We understand that pharmaceutical wholesalers do not have a definition of "acute care hospital," and they may not be able to distinguish acute care hospitals from surgery centers, rehabilitation hospitals, or nursing homes, for example.

Many hospitals dispense for outpatients. Physicians may want patients to finish a course of therapy at home that they've started in the hospital. Extended inpatient stays are possible, and the product could be used in that situation. And the alert system for outpatient pharmacies is available in 50 percent of pharmacies, and the pharmacists can override the alert.

We also note that the proposal does not provide for the collection of medical outcomes to determine if cardiovascular events are indeed minimized. So we would not

have that information to use to evaluate the success of the RiskMAP.

To address some of the concerns I showed you on the last slide, we have some thoughts on tool selection that may address some of them. We think that hospitals may require more support for the safe use of the product, and it might be useful to have hospitals register and attest that they have a safe-use protocol in place. And we have experience with a RiskMAP for dofetilide that uses attestation of a safe-use protocol.

Also, because of the problems we see with wholesalers making the decision on who can buy the product, we would suggest that the sponsor retain control of who purchases it. And we do have an example of that as well in which the product is ordered through the wholesaler, but then okayed and shipped through the sponsor.

So our conclusions about the proposed alvimopan RiskMAP: we need much more

detail about the goals, objectives, implementation plans, evaluation plan, metrics, and RiskMAP reporting to the agency. We think that operational changes are needed in the proposal that was submitted, and we propose that the sponsor retain control over the supply chain. And we think there may be a need for a systematic program for hospitals to prevent diversion to outpatient use and to prevent longer term inpatient use.

Finally, even with these changes, the RiskMAP framework is acceptable only if short-term use is safe and if process evaluation of the RiskMAP is sufficient, because medical outcomes would not be measured.

DR. BUCHMAN: Okay. We're going to open the meeting up to questions for the committee, to the FDA and FDA presenters.

Dr. He, in your analysis, did you evaluate the efficacy difference between the earlier studies where the 6-milligram dose

was used? There is publicly submitted data that would suggest an improvement in efficacy over the 3-milligram dose, but I'm still curious as to why the 12-milligram dose was chosen. And can you shed some light on the agency's evaluation of the efficacy difference?

DR. HE: So I answer again here or I should go there? I can stay here? Okay.

You are right, we do have a concern which dose is the best dose for this product -- for this program POI indication. As you indicated, in the early study, they do study several different doses, 3-milligram, 6-milligram, and 12-milligram. In my presentation, I did not show the data for 6 milligrams, but I did include those data in my background package.

In the initial submission, we have a lot of discussion about which dose is the best dose. Some studies do show 6 milligrams is better than 12 milligrams. And we are

concerned -- focused on the primary endpoint and a second endpoint, like GI-2 and GI-3. If you only focus on GI-3, you do find the difference between 6 milligrams and 12 milligrams, and some data indicated that 6 milligrams is better based on GI-3. But if you're checking the endpoint for GI-2, in that case you're limited evaluation for flatus, and then you can see 12 milligrams compared to 6 milligrams, maybe 12 milligrams is better. That data I saw in my background package.

Like I said before, GI-2 only secondary endpoint for the first full Study 302, 308, 313, and 001. But doing the evaluation, we do recognize that the flatus is a very difficult endpoint to objectively assess, especially the method the sponsor used to assess the flatus. You know, you wake up the patient every two hours to ask do you have a flatus. And in this way, if you ask my personal opinion, I do consider the

GI-2 is a more objective endpoint.

And based on GI-2, I do feel 12 milligrams may be better dose for the further study, although the data do not show in that way. But I have no objection for the sponsor to choose 12 milligrams at a further study. That is Study 314; they only study for 12 milligrams.

DR. BUCHMAN: With the idea of trying to use the minimal effective dose, do you think another study comparing 6 and 12 milligrams would be necessary?

DR. HE: No. Probably -- I mean, if you do more studies, it's better -- we try to collect more data, but probably not necessary. The reason is there are five studies. If you include Study 306, a total of six studies. And though they did not show a significant dose response between 6 and 12, when you evaluate for the safety scenario, you do not see 12 milligrams increase significantly for a safety issue. Therefore, we do not have an

objection for the sponsor to choose which one they will go to further study, because Study 314 was only studied for 12 milligrams, you know. At this time point, we will focus on 12 milligrams.

DR. BUCHMAN: Dr. Rosing?

DR. ROSING: Yes. We've heard about Study 014, and the sponsor and Dr. Dannis has described the various characteristics and cardiovascular risk factors, et cetera, in the study. Unless I missed it, I haven't heard, though, what drugs those patients were on or those subjects were on in addition to the study drug; in other words, anti-platelet drugs, statins, diabetic treatment drugs, et cetera. Is there any reason to believe, or was it examined to see whether there was any skewing of the use of those drugs in the placebo versus the treatment groups?

DR. KORVICK: It might be appropriate to ask that question to the sponsor.

DR. BUCHMAN: Let's save that for the

afternoon then. Let's see, who was next here? Dr. Pasricha?

DR. PASRICHA: I have a question for Dr. He, also, which might require the sponsor's response as well. But just looking at the efficacy data by median and 75th percentile, the difference in the median is only -- looking at DOW, discharge order written, which is perhaps the most relevant parameter here, is only 0.3 days. And it's only when you get to the 75th percentile that you have a day difference. So is the interpretation correct then that the effect of this drug is really only valuable in the patients who are in the outliers, and it may not be as effective or as valuable in the majority of the patients or at least in the first five days to respond?

And then I guess a follow-up to that is, has either the sponsor or your group looked at differences in the profiles of patients, early responders versus the late responders, to try and see if there's some

marker that we can look at to identify which patients may best respond?

DR. HE: Yeah. You're definitely right. When we did the efficacy evaluation, initially we focused on the median. Right now, during my presentation, I chose three different time points: 25 percent, median, and 75 percent. I tried to give balanced data to show you all of the data.

To answer your question, the difference between median and the 75th percentile, roughly only 1 day difference. If you're looking for the time achieved for the median, roughly about four days. And if you're looking for the 75th percentile, roughly about 5 days.

And because this indication is POI post-surgery, it is very difficult to assess the early responder. Most of the patients, they take several days to recover GI function, you know? If you don't give a treatment, roughly five days. And if you try

to see the early time, like a 75th percentile, it is very difficult, because this disease -- the nature of the disease. Therefore, we later on -- initially, we only focus on median, but later on, I do agree to looking at the data at the 75th percentile.

Because the total of the hospital stay is seven days, and you want to evaluate the totality of the data. Therefore, you looking for the time point at 75th percentile may be okay even at the later, after disease. But there's still some -- the meaningful difference between the two groups. Therefore, either choose at Day 4 or Day 5, I have no personal feeling. Either way is okay.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: Yeah. I think one of the most important things that we have to do is figure out whether 014, why is it different? Is it a real difference?

And so I was looking at Dr. Dannis'

Slide 18, and I wonder if we could put that up. Yeah. So I'm trying to compare the results for Study 014 with these results, and these include 014, so I'm trying to subtract out the 014. But the problem is, I think that 008 and 684 involve the same patients. Some of the patients are the same. And so it looks like the N at the top isn't quite right, because I think that N was obtained by just adding the number of patients in those two as if they were separate people.

And the other thing I worried about with this slide, I want to make sure about this, is that could someone have a CVD event and then go into the extension study and have another one and be counted twice? I can't remember from the briefing document whether there was anyone in that category.

DR. DANNIS: Is this on? Okay. To answer your first question, the patients that went from Study 008 to 684 were only counted once, so that N should just be who was in 008.

And the second question was -- oh, there were no patients that were counted twice for events, either for Study 008 and 684. Any patient that had an event only had one and was counted once, especially in this side because this side is the patient's experience and serious cardiovascular events.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: So many surgeons have used the admittedly off-label use of ketorolac as a similar narcotic-sparing type of a strategy. It looked like in only Study 001 that was done overseas was that drug used. And I wonder if there was enough data in there to determine what the effect of that specific drug was on the outcomes of that study.

DR. HE: Study 001 is a large study. It includes more than 700 patients. They do have some difference between the North American study and Study 001, the European study. But I do believe to evaluate the primary endpoint for GI-2 or GI-3, Study 001 is still valid, which

should include those data for evaluation of GI recovery.

But -- because, according to the sponsor's presentation, you can see the difference between the North American and European clinical practice is different. And therefore, I personally agree for evaluation, DOW already for discharge or hospital stay, Study 001 may not provide so much information.

DR. KORVICK: As far as the concomitant drugs, that's I think the second time we've heard that question. I think that maybe the sponsor might have some backup slides to enlighten us later. Maybe this afternoon we can come back to that. We're not prepared to talk about that issue.

DR. BUCHMAN: As a follow-up question to that, virtually all -- we don't know all, but perhaps virtually all these patients were on a PCA pump postoperatively. Postop ileus, by definition, would be related to manipulation of

the bowel. Is the agency able or in need to differentiate between postoperative ileus from a bowel-related issue versus a narcotic-induced ileus? And are we talking about two potential different indications here?

DR. KORVICK: I think that's an interesting point that perhaps the group should discuss in a broad way. We're looking for feedback from you, and I think that we've seen the data and what the sponsor's proposed, so we'd be looking forward to that discussion later this afternoon.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: Yes, I had a question for Dr. Dannis. A lot of the questions we'll have to deal with this afternoon have to do with assessing the clinical meaning of these results, and for me, that ties both benefit and risk. You have clearly pointed out that although there wasn't a cardiovascular signal seen in the POI studies, the follow-up was limited and the extent to -- in fact, there were over 250

patients that didn't have any follow-up after discharge. Has the FDA done any sample size calculations of the kind of study that would need to be done to assess cardiovascular risk with a short-term administration?

I mean, it's conceivable that even a short-term administration could, since we don't know the mechanism, could have a long-term effect if you follow these people. And I just wondered if anyone could give us a sense of what type of a study would be required, and if you've looked at that.

DR. DANNIS: I think that's a very interesting idea, but at this point, we haven't yet come up with the answer to that question.

DR. BUCHMAN: Dr. Hennessy? Oh, I'm sorry, Dr. Richardson.

DR. RICHARDSON: I have a question that I think follows a little bit on what Dr. Kramer had asked, and that is I think relating to the FDA's impression of cardiovascular risk and whether this changed

over time. Were the bowel resection studies completed before the questions of cardiovascular risks were known? And when these questions surfaced, did the agency feel that these patients needed to be re-consented?

DR. HE: For your first question, yes, during the end of the first review cycle, we did not have identify any specific safety issues. We issued an approval letter purely because of the advocacy issue.

Cardiovascular events were identified after we issued the approval letter, that is during the second review cycle, after the sponsor submitted the second NDA. During that period, we identified the imbalance cardiovascular events during the interim analysis for that 12-month safety study. And that is why the study for the POI program is not designed to capture those kinds of events.

DR. RICHARDSON: But what about the question of re-consenting patients once that

risk surfaced? I mean, that would have demanded a little bit more in the way of follow-up.

DR. KORVICK: I believe for Study 14, we had discussions with the sponsor where we discussed the follow-up and the safety issues for the continuation of that study since it wasn't clear if we would see more events in the long term, and they were close to completing that study. So there were, I believe, re-consents, and there were also attempts to better define for the patients still in that Study 014 more close follow-up. But I think the sponsor can tell you more closely the timetable, but a lot of those patients had completed a significant proportion of the study. So I think that there were mechanisms put in place and we had these kind of discussions.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I have a question for Dr. Dannis regarding the safety analysis of cardiovascular events. The Kaplan-Meier curves, et cetera, that you presented look a bit

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concerning, but they're based upon the non-adjudicated data. In cardiovascular trials, we usually use adjudicated data, recognizing the difficulties in investigators and the variability in sites assessing -- particularly myocardial infarction or non-mortal endpoints, which have a great degree of objectivity.

So there's clearly precedent with the regulatory agencies for accepting adjudicated data's endpoints.

Now, I recognize that this is a post hoc adjudication, but then again, the cardiovascular endpoints were all post hoc anyhow. They weren't primary endpoints. So I'm curious why you chose to do all of your analyses with the non-adjudicated data, and if you feel that there's a problem with the adjudicated data. Because at least from the sponsor's presentation, the adjudicated data looks much more reassuring.

DR. KORVICK: We used the non-adjudicated data, but I think that the

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differences were small. And I'm not sure that there were that many differences in the different ways that you did the analysis, and that's the data we had at-hand at the time.

DR. LINCOFF: Perhaps I can address that because this I think is a key point and I'm not trying to perseverate on something relatively small.

But if you look at your Slide, I guess, 15 -- it's really 14 and 15, and compare it to Table 35 that's presented on page 98 of the sponsor's packet -- or sponsor's form. So if you look at the actual number of events, any cardiovascular -- now, the denominator's slightly different, but I think relatively small differences and I'm not completely clear. I mean, it's 1,800 as compared to -- 1,807 in the active treatment group compared to 1,728. But if you look at the total number of any cardiovascular events adjudicated, it's 13 versus -- I'm sorry, 26 versus 9, and that's 26 versus 4 for the

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non-adjudicated. And that reduces the difference quite substantially for the non-adjudicated.

If you look at ischemic cardiovascular events, it's 13 versus 6 as compared to 14 versus 3.

That, again, because of the differences in the treatment groups, virtually eliminates the difference in the point estimates.

So now, other cardiovascular events were more similar, but -- so, again, it turns out to be -- actually it's 14 adjudicated as compared to 8 non-adjudicated, 3 in the placebo compared to 2 non-adjudicated for the other events, non-ischemic. So at least for ischemic events and for total events, the adjudication does change the point estimates and the relative risks substantially.

So again, I think that the adjudication process should be valid. Certainly the people participating in it and

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the methodology that they reported sound to be valid and appropriate, similar to what we would use in a cardiovascular trial. And so I'm concerned that the non-adjudicated data may give us a somewhat skewed result, estimate of the cardiovascular risk.

I'm also interested, on a related note, there's been concern about whether or not longer-term follow-up of the short-term POI studies would have shown a later cardiovascular event. I'm unaware of any precedent for a short-term drug that led to long-term cardiovascular risk. I'm certainly happy to -- be pleased to know of a precedence that exists, but I don't know of any where a five- to seven-day drug then leads to an incremental risk of events out beyond an immediate post-drug observation period.

DR. DANNIS: I just want to make sure that you're comparing -- this table is actually patients experiencing the events. So there's

another table, I think the next slide, which is events. I'm not sure if those numbers are more similar.

DR. LINCOFF: So that's what I was comparing to Table 35. They have all -- any event, which seems to be what you have on your previous, but perhaps if we just look at -- so that's patients. But if -- so then, if you look at your next slide, so ischemic events, 14 versus 3. Adjudicated ischemic events were 13 versus 6. Now, that makes a big difference. Because 13 versus 6 comes out .7 percent versus .7 percent.

DR. DANNIS: What we discovered while doing these analyses is the sponsor did their analyses, adjudication did their analyses, and when we looked at what we had, which was somewhat limited because we just had narratives, we had -- we didn't have complete information. We actually at times got different results. However, what we found were that even though the results were somewhat different, they were put

in different categories and moved around a little bit, the end result was really the same. And I think it's really difficult when you don't have complete information to have a really great investigation of what went on, but we did do the analysis. And because the end result really wasn't that different, we didn't want to kind of fight over who had angina and who had this because it just seemed like the end result was the same.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I want to follow up on the cancer signal. Since the majority of patients in the POI study were being operated on for colon cancer or GI cancer, and given the concern about cancer, if there's any data on survival of these patients -- they're presumably all in a registry of some sort and we should be able to get long-term at least cancer-related outcome data on these patients, and if the agency is thinking of trying to obtain that information, it'd be helpful.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: Yeah, again, I want to go back to the comparison of 014 with the other studies. And I notice that the FDA made some different comparisons. One was versus the non-cancer OBD trials, and the other one combined cancer and non-cancer. And I'm wondering whether you think that's reasonable to combine the cancer and non-cancer. It seems like those are quite different.

DR. HE: For combined non-cancer and cancer patients, we combined them according to the duration of treatment. For the long-term therapy, for the long-term safety data, we have very limited information, because they are both cancer and the non-cancer patient treated, duration is longer. Therefore, we want to do different analyses to see if that more days are still so the signal or not. That is one way we do our safety analysis, so that is why we pooled them together. But we also do the separate analysis, and that is why we put them in here

differently.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: I just wanted to follow up on Dr. Kramer and others' comments about having a short duration of therapy and then maybe having a long-term effect. And I'm just kind of surprised when Dr. Dannis presented the follow-up. In person with the investigator, the patients had so little contact.

I would think that after a bowel resection, you would come back and see the surgeon in person. So I thought that there must be data out there on a follow-up visit and how they're doing. And if there was any -- if you ask the sponsor to go back, even though it's not standardized and it's retrospective, to go back and look at some of the data.

And then also, I was thinking that in the opioid bowel dysfunction, most of the trials are short-term, and they may have had follow-up later on in a month or two that you

could collect that data, or patients who would rollover in the extension study who had drug. And then, I don't know if there's any of these people that had drug on a short-term study, rolled over in the extension study and had placebo. There's probably not that many of them, but I mean, that's a way to follow them, also. But there's probably ways to collect some of that information out there.

DR. DANNIS: Yes. That was one of the questions that I actually had for the sponsor in one of our meetings. I think that what I was presenting was the official protocol-defined visit, where the official information was collected. I'm sure that most of -- if not all actually, probably every single person who had a bowel resection was followed up, and I'm sure that that information is somewhere.

However, I don't know if it was collected in a standardized way and whether we have entire information on all the patients.

DR. BUCHMAN: Dr. Talamini?

DR. CHANG: You could probably get that, though, couldn't you? I mean, that might be something good to look at.

DR. DANNIS: Yes.

DR. BUCHMAN: Dr. Talamini? Last question, Dr. Kramer. Did you have a question? Dr. Epstein?

DR. EPSTEIN: Yes, I have a question for Dr. Chakraborti. The mu-opioid receptor, can you describe where that is in the body? Is it in the smooth muscle? Because you mentioned the Purkinje fiber study that the sponsor did, but was there any evidence of any effect on arteries? I know we use morphine, too, in patients with congestive heart failure, et cetera, so I wondered about that.

MR. CHAKRABORTI: Mu-receptors are distributed in several organs and tissues. But the -- I'm sorry, I did not follow your question there.

Can you tell me one more time?

DR. BUCHMAN: The question was where the opioid receptors are located, what part.

MR. CHAKRABORTI: Yeah. Opioid receptors are almost located and distributed all over the body, including the CNS. But for this particular compound, they also did a distribution study in rats, a radiographic study, and this drug was not distributed. And I've gone to the central nervous system because I did not cross the (inaudible) barrier walls, so -- because of its structure. So it was mainly distributed in the gastrointestinal tract, and actually locally acting on probably the GI mu-opioid receptors in the gut, and that's all.

DR. BUCHMAN: Was there any data on systemic absorption and concentrations of the drug in the bloodstream?

MR. CHAKRABORTI: Yes. In the toxicology studies, there was about 6 percent -- about 10 percent absorption following oral administration of this drug.

DR. BUCHMAN: And do you have any concern with that in terms of opiate receptors elsewhere outside of the CNS?

MR. CHAKRABORTI: They have done in pharmacology studies -- the CNS effects, first of all, in 70 (?) pharmacological studies there is no CNS effects of alvimopan in rats at tested doses, up to 2 milligrams per kilograms. Besides that, they have actually demonstrated in a pharmacological study in mice where the mice were actually treated with morphine and it causes the morphine-induced (inaudible) -- I'm sorry, the (inaudible) morphine-induced infusion of the (inaudible) transit. But it did not cause any effect on the (inaudible) acid-induced. Our writing reflects that is actually morphine was exhibited in that, but it did not actually cause any effect to that. So the (inaudible) for that particular central effect was about 8.7 milligrams per kilogram compared to the morphine's (inaudible) effect was about 0.7. And that gives us a

peripheral-to-central ratio of about 127. So that demonstrated pretty much that it actually acts through a peripheral mechanism, so the central action is not our concern.

MR. DESEGTER: To answer your question, we don't have any concern about other peripheral opiate receptors.

DR. BUCHMAN: Could you identify yourself, please?

MR. DESEGTER: Yeah, I'm Shoshan Desegter. I'm the pharmacologist here at FDA. And to answer your question, we don't have any concerns about other peripheral opiate receptors because in toxicology studies, there is no target organs identified even at high doses.

DR. BUCHMAN: We're going to take a break for lunch here. We'll be back at 1:00 p.m. For the committee, downstairs in the lunch room, there is an area that's roped off with tight security just for committee members.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

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

(1:00 p.m.)

DR. BUCHMAN: Okay, good afternoon. I hope everybody enjoyed their lunch.

The original schedule has for an open public forum as we typically do at these sessions, although no one from the public has registered. So therefore, we're going to dispense with that. That gives us an extra hour of discussion, and I think there are some important points that we need to address that are going to be used before we get to the questions.

I'd like to reintroduce Joyce Korvick, who will address some of the concerns that were raised this morning about the cardiovascular risk profile from Entereg.

DR. BEITZ: I'll just read sort of a summary of where we are after this past hour of sort of discussion regarding the different analyses that have been presented.

So we essentially don't differ very

greatly from the sponsor on the categorization of the individual patients in terms of cardiovascular events. But what I think what we're seeing with the different analyses that have been presented today, some instability in the data and in the risk estimates that we're wrestling with and that we're going to ask you to wrestle along with us. And that's kind of where I'd leave it at this point.

DR. BUCHMAN: Thank you very much. What we're going to use this next period for is, there are a lot of questions that committee members had left for the sponsor. So we're going to allow those to be addressed at this point. And the sponsor can also add some additional information as a rebuttal, if you will. And if we have time in the hour, we'll allow for a re-rebuttal.

So with that, I'd like to call on Dr. Hennessy, if he recalls his questions from this morning.

DR. HENNESSEY: Great, thank you. I have two questions. One has to do with the size of the population that's likely to be exposed to the drug if it's approved. So one obvious population is people who have had gut surgery. How large a population is that likely to be per year? And also, it seems likely that the drug would be used for non-gut surgery. For example, orthopedic surgery, where there's lots of opiate use after surgery. And I'm wondering if the drug is used off-label, how large the population of people that is likely to get it off-label.

DR. BUCHMAN: Please identify yourself when you speak for the transcriber.

DR. JACKSON: This is David Jackson from Adolor. I'm going to ask Dr. Senagore to address the question about numbers of potential surgical patients.

DR. SENAGORE: Anthony Senagore, Spectrum Health, Grand Rapids, Michigan. The labeling is requesting for colectomy, and national numbers are somewhere in the range of

about 400,000 per year for all diseases. And of that, still in this country, about 90 percent of those are done by open surgical techniques. So, it would be about 350,000 to 360,000 patients. In terms of the off-label, I'll leave that to the sponsor to discuss.

DR. BUCHMAN: Thank you. Dr. Epstein?

DR. EPSTEIN: Yes, my question to the sponsor is, was there any sub-analysis done of patients with diabetes? One of the biggest clinical problems we face is individuals with diabetes having a significant risk to develop prolonged motility disorders. And I wonder if there was any look at the data regarding diabetes, and how that impacted on the trial and the clinical endpoints.

DR. JACKSON: Thank you. Dr. Techner? There are significant numbers of patients in the database who did indeed have diabetes.

DR. TECHNER: If I could just have the slide on baseline cardiovascular risk factors and POI population. I think that's an

interesting question. And one of the things we have looked at is the proportion of patients who in fact did have diabetes. And I think what you can see here is that somewhere between 10 and 14 percent, whether it be the overall population we're looking at or the bowel resection population only, had recorded baseline comorbidity of diabetes.

So proportionally, it was about the same across treatment groups. We did not look at the treatment effect specifically in that subgroup. However, one would suspect that it if that was a factor in any way, shape, or form, it would be affecting both the placebo and the alvimopan treatment groups similarly. The other thing is, I believe what you're referring to is not really a narcotic-induced condition. And again, alvimopan is a highly selective mu-opioid receptor antagonist.

DR. EPSTEIN: Yes. And I guess nevertheless, those patients do have a higher

tendency to get postoperative ileus regardless. And I wonder if the clinical effect would be stronger in that population or if you have any data? Do you have any data on that particularly?

DR. TECHNER: We do not have data on that. But that's certainly something we could look at in the future.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: As sort of a related question to that, can you please clarify whether the outcomes were analyzed with your modified intention to treat equally all patients whose discharge was potentially delayed for non-GI problems as well, or only included GI-related?

DR. TECHNER: No, our analyses included all patients, regardless of whether they were readmitted or their hospital stay was prolonged for a GI or non-GI event.

DR. PASRICHA: So was that a significant proportion of patients whose discharge was delayed because of non-GI

complications?

DR. TECHNER: I believe that I would really have to say that the majority of patients, the primary reason for a delay discharge was unresolved ileus, which is, as you've heard from Dr. Senagore, consistent with what surgeons see in practice.

DR. PASRICHA: I guess what I'm trying to see is if the effect was even larger if you carved out the non-GI complications.

DR. TECHNER: We did not look at the data that way. But again, this is certainly something we could look at in the future.

DR. BUCHMAN: Dr. Talamini, you had a question regarding the use of ketorolac and other -- perhaps a group of patients that did not receive narcotics?

DR. TALAMINI: Yes, so my question was, particularly in the European study, where that drug was indeed used, whether you had enough data to analyze that group separately, and if so, what the effects were. Again,

because in context, I think in this country, many surgeons use that as a strategy to reduce overall opioid postoperative use and get the patients out of the hospital a little bit more quickly. So it's a similar strategy.

DR. TECHNER: How about -- I think the way we'll answer your question is twofold. I'll address it from a data perspective, and then I'd like to have Dr. Senagore address it from what is commonly used in practice today. You are correct, in the European study -- in the non-U.S. study, I should say, the range of opioid use and opioid-sparing technique was broad. It varied from country to country. So we would have countries, for example, where we saw virtually no opioids being used. And in those situations, as you would expect, the effect of Entereg was minimal to countries where the use of opioids was comparable to what we see in the States.

So I think -- and this goes back to an earlier question -- is there a threshold,

if there is virtually no opioid on board, then we would not expect this drug to have much benefit.

I'd like to ask Dr. Senagore to come up just to address common practice with respect to pain management in these patients.

DR. BUCHMAN: You know what? Before Dr. Senagore addresses us, I just want to follow up on your comment with regard to a question I had earlier --

DR. TECHNER: Sure.

DR. BUCHMAN: And something that we'll perhaps discuss a little bit later. But what is the sponsor's feeling in terms of the labeling? Is this really a postoperative ileus that you're treating? Or in view of your most recent comment, perhaps that's incorrect. Perhaps it's a narcotic-induced, specifically a narcotic-induced postop ileus that you're treating. And is that more appropriately the indication that you seek?

DR. TECHNER: You know what? I think

that Dr. Senagore can address that as well. And I think this goes back to what is the etiology? What are the mechanisms involved in ileus? So Tony, if you would address that, please.

DR. SENAGORE: Yeah, I think probably the 001 study gives us guidance on that, because there are truly no regimes that are devoid of narcotic administration in patients undergoing major laparotomy. But as I discussed, the etiology of ileus is multifactorial. So it may be that the group that gets an NSAID is actually abrogating the effects of the inflammatory component that leads to ileus, and now you're seeing an added benefit from blocking the narcotic component. So even in Europe, patients still do get modest doses of narcotics, of which you did see benefit in the 001.

DR. BUCHMAN: Dr. Kramer?

Dr. KRAMER: Judith Kramer from Duke. Actually, my question is for Dr. Senagore as well, but it's very similar. It's really a follow-up on what Sean raised. And my question

is, as a surgeon who is very familiar with this drug, would you expect that if this were marketed, that surgeons would prescribe it to prevent and treat postoperative ileus plus other types of abdominal surgery besides bowel resection?

DR. SENAGORE: Well, if you look at the data, at least for laparotomy, what operations lead to the highest rate of postoperative ileus, it really is bowel resections, both large and small. And so for our general surgical community, that would be the most common indication. Could this drug be advantageous in other operations that use high doses of narcotics, like spinal surgery or total joint reconstruction? It's plausible, but I don't know that we have data at this point to say that.

DR. BUCHMAN: Would you foresee the use of this medication in a postoperative ileus in a patient that had a abdominal aortic aneurism repair or had other baseline

cardiovascular risk issues?

DR. SENAGORE: Again, I don't think that there's data to say convincingly that it would work there, but certainly if you pull the expectation that, again, these patients have a major incision, high doses of narcotics, it's plausible to believe there would be a benefit in that population as well.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I'd just like to continue the same line of questioning I was discussing with the adjudicated endpoints. I wonder if you have any more data that you can show us specifically for Study 14 with the adjudicated endpoints? I mean, given really that Study 14 is the reason that we're having I think all of this discussion on the cardiovascular endpoints, and that there is a small number of events that differ between the adjudicated and the non-adjudicated that nevertheless changed the odds ratios fairly substantially. And the point estimates, which

is, of course, a good indicator of the instability of these estimates in the first place with small numbers. But how much of the data that was in the table, that is in your book, and that you had shown, how much of that? Could we see that for 14, which is really where most of the analyses that the FDA has done with the unadjudicated data focused on? What can you show us in terms of breakdown, the components of the ischemic endpoints, et cetera?

DR. JACKSON: Let's try and get to it.

Dr. Camm?

DR. CAMM: Thank you very much, Dr. Lincoff. First of all, I'd like to see the data for the adjudicated events, the ischemic events, for the entire OBD database, and I think that's in OC 44. This is the data of the adjudicated events for the whole OBD program. Now, I mean by that not exactly the same population as Dr. Dannis analyzed, because it didn't include the clinical pharmacology studies, and it didn't include the idiopathic

chronic constipation study, so it's strictly the OBD population. It changes the denominators slightly, and I think you recognized that when comparing the graphs.

So here are the results expressed in terms of events and patients, and this relates to ischemic events. And I should point out at this point that the ischemic composite that was assigned prior to doing this analysis was somewhat different to the FDA ischemic composite, because it contained, in addition to myocardial infarction, unstable and new angina, and stroke, it also contained ischemic heart failure and TIA and sudden cardiac death and cardiac arrest, which was deemed to be ischemic in origin.

So you can see here that any ischemic event, in terms of events, was 8 versus 14 for the whole program. And the number of patients was 6 versus 13. That is roughly equivalent. But you can see that there is a numerical imbalance in terms of

acute MI, which was contributed to very largely by the GSK014 study, and that in percentage terms was 0.24 with placebo and 0.44 with patients.

New onset unstable angina also showed potentially an imbalance, at 0.12 percent versus 0.22 percent. But as you can see, the numbers are very small, and any oscillation in terms of the assignment would make a big difference to the ratios in either the acute MI or in terms of the new onset or unstable angina.

I'm not sure whether you also have a slide for the GSK014. Do you have that available? Here, you can see just in the number of studies, one by one, going from 011, 012, 013, and 014, the difference between placebo and alvimopan with respect to ischemic cardiovascular events. And you can see in 014, it was 9 versus 0 ischemic events when adjudicated by the IDMC.

And I think I shouldn't go past

this point without remarking on the fact that zero events in the placebo group is pretty unusual, given that this group of patients was relatively high risk for cardiovascular events. And the events seen with alvimopan are not necessarily out of context with chronic opioid bowel disorder.

So those, I think, answer the question that you put to me.

DR. BUCHMAN: Ms. Corkery-DeLuca?

MS. CORKERY-DELUCA: Yes, my comment and question would be related to Dr. Lincoff's. Looking at the diabetes population, I think one of the more popular upcoming surgeries is bariatric, a bowel resection to alleviate diabetes. So who handles that?

Who's in charge?

DR. JACKSON: Well, I'm going to have a surgeon answer the question for you.

DR. SENAGORE: I don't do that surgery anymore, but that population actually has a very, very low rate of postoperative ileus. In

fact, if you look at the U.S. data, I think probably the mix today is probably 90 percent or greater laparoscopic versus open. And the rate of ileus is very low. The length of stay is under two days in the U.S. for that operation.

MS. CORKERY-DELUCA: So it would be a move forward.

DR. SENAGORE: Well, again, I'm not sure that this drug would be an advantage in that population, because they're laparoscopic, very small incisions, and they're home so quickly that they're on to other alternative treatments.

DR. BUCHMAN: Are you suggesting, then, that the drug be limited to use in patients with open bowel surgeries?

DR. SENAGORE: I guess I can leave that to the sponsor to comment on what they're asking for on the labeling.

DR. BUCHMAN: Dr. Proschan?

DR. PROSCHAN: I just wanted to follow up on the question previously, because I don't

think that was quite what Dr. Lincoff asked for, at least it's not what I was thinking. Because what you didn't show was the MI, patients with MI, in the 014 adjudicated. And I'm wondering if you have that slide and that information?

DR. BUCHMAN: Do you have that, Eric?

DR. MORTENSEN: Eric Mortensen, GSK. I'll see if we have a slide to bring up. But essentially, I can say to you is that all seven of the myocardial infarctions that occurred in 014 were positively adjudicated. I mean, I wouldn't bother showing the slide. Essentially, and as I noted before, they all occurred in patients who were then confirmed to have had pre-existing cardiovascular disease.

DR. BUCHMAN: Dr. Cullen?

DR. CULLEN: Joe Cullen from University of Iowa. One question on the postoperative ileus studies: Were the use of prokinetics, like Reglan on a scheduled basis, or antiemetics or suppositories allowed in the study protocols? And if so, was there

equivalence between placebo and drug?

DR. TECHNER: In order to address your question, let me answer it in two ways. One, in general, the prophylactic use of antiemetics, et cetera, generally was as per hospital standard. So in general, we did not restrict to any significant extent across the board the use of those medications. However, if we look at the use of those medications, in other words, all medications where we feel their use may have in some way, shape, or form impacted GI function, 5HT3s, metoproclamide, erythromycin, laxatives, cathartics, 5HT4, and any other antiemetics, I think you can see here that it was very well-balanced across treatment groups. So if there was some effect, we would basically expect it to be a wash between a placebo and the alvimopan treatment.

DR. BUCHMAN: A related question. Electrolyte abnormalities have been demonstrated quite frequently to have a role in the development and prolongation of postoperative

ileus. I would assume that you have data on potassium, magnesium, and calcium in these patients, and if so, were they similar between groups?

DR. TECHNER: We do have that data in our adverse event database, and they were similar across treatment groups.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: Just one possible confounding variable with the cardiovascular events. I wonder if you can tell me about the geography of Europe? Was this Western Europe-limited or was it all of Europe?

DR. MORTENSEN: I'm not sure. What do you have in mind? What kind of a subissue is it?

DR. LEVINE: I'm specifically asking if there are any -- if Eastern Europe investigators were involved in this.

DR. MORTENSEN: In Study 001 or in the 014 study?

DR. LEVINE: In any of the non-U.S.

Studies.

DR. MORTENSEN: Can I have the slide that shows the distribution of sites for 014? What I'll start out just by noting is I didn't mention in my core presentation that of the seven events, that five were Cluster II sites. We don't know what it means, but we have known that three of those events did occur at a site in Glasgow, which is a region that is particularly marked to have a very high rate of cardiovascular disease incidence.

We did have sites also -- I'm still not seeing the slide coming up -- we did have sites extended across Eastern Europe, but we did not have anything in the Soviet Union. Are you done with the slide? Number 14. We did include sites in both Eastern and Western Europe, but we did not include the former Soviet Union countries.

DR. LEVINE: I'd like to know the number of the total subjects that were in Eastern Europe versus Western Europe.

DR. MORTENSEN: We'll be happy to get that information. I am sorry I don't have that information for you.

DR. LEVINE: Was it a small number? Was it a modest number? Can you give us some idea?

DR. MORTENSEN: The total number of patients randomized from Eastern Europe was relatively small. The majority of the patients overall for the entire 14 study, the majority came from the United States. I don't have --

DR. LEVINE: No, I'm talking about the non-United States studies.

DR. MORTENSEN: No, I understand it. I'm just saying that the total composition for 014 -- did you say 001 or 014?

DR. LEVINE: Either one, actually. I'd like to know the numerical number approximately of the Eastern European investigators versus the Western European investigators, for possible obvious reasons.

DR. MORTENSEN: Okay. I don't have

that answer for you immediately for 014. I will be happy to get that information by the time of the second review. I'm not sure, Lee, if you have a slide that speaks to the issue in 001.

DR. TECHNER: Let's see if this potentially answers your question. How about let's look at the slide of opioid use by country. Yeah, that should do it.

So on Study 001, here is a list of countries involved. What you see here is the proportion of patients that came from that country, and this is really the use of PCA opioids within the first 48 hours by country. So the purpose of the slide is a bit different, but at least it gives you a breakdown of where the patients were divided across countries. You see certainly, if you were in Greece, that might be a bit of an issue.

DR. BUCHMAN: Dr. Kramer, did you have a follow-up question on that?

DR. KRAMER: Yes, I just had a

follow-up question. The sponsor is pointing out that three of the patients were at a single site in Glasgow, and there was a high incidence of cardiovascular disease. But is there any reason to think that there weren't also placebo patients of equal balance in that site? Was that site somehow randomized such that they were all alvimopan?

DR. MORTENSEN: No, we actually --

DR. BUCHMAN: Please state your name for the record.

DR. MORTENSEN: Eric Mortensen, GlaxoSmithKline. No, we did look to see whether or not the two sites that represented the majority of the myocardial infarctions showed perhaps any alteration imbalance. There was no evidence of an imbalance with regard to randomization. We simply mention this to note that it is a somewhat unusual clustering and we cannot rule out potentially differences in regional practice in terms of the number of patients with high risk that may have been

randomized at the trial.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: Hi. I have an efficacy question and a safety question. The efficacy question is about whether the treatment effect is clinically meaningful. And I would think that the unmet need is more of these patients with prolonged postoperative ileus, and I suppose that's your 75th percentile where you show a one day earlier discharge. To me, that seems clinically meaningful.

I don't think a half-day seems clinically meaningful, but I was wondering how the sponsor determined that. Is that based on a survey with surgeons or with patients or a cost-effective analysis? How is that determined? That's the first one.

The safety issue is really based on this issue about neoplasm. And I was wondering if, like in colitis, immune cells release opioids, and I don't know for tumors if the opioid receptors, the mu-opioid

receptors, had some kind of tumor-inhibiting effect, like it's believed that endorphins may help cancer patients. But is there any studies, either by the FDA or sponsor, that people know of where the mu-opioid receptor plays a role in tumor inhibition or growth, and might that blocking that receptor may play a role in enhancing tumor growth?

DR. TECHNER: Lee Techner, Adolor. Let me address the first part of your question, the efficacy part. And I'm going to do it, if you don't mind, in two ways. I'll present our thoughts, a bit about our thoughts, and then I'd like to have either actually Dr. Senagore or Dr. Delaney come up and give you their clinical perspective. May I have my slide showing GI-2 recovery, the Kaplan-Meier curves, please?

I think one of the important things to consider here is that when we set out to design these trials and evaluate these patients, we really wanted to look at the 10-day period where we knew things were

happening. They were recovering from their ileus, if you will. And so we followed them along this period. And I think what you can see here is that clearly, regardless of whether patients are down in this part of the curve or up in this part of the curve, which really corresponds to about Day 5 or 6, which, as I think you've heard from Dr. Senagore, is the period of time where that red flag starts to go up in their heads, that the alvimopan curve is always to the left of the placebo curve.

And so yes, we do see what appears to be the most robust difference at around the 75th percentile, Day 5 and 6, which I think is very clinically appropriate. But we also see that patients all along this curve are doing better.

And so I think certainly from our perspective, we feel that if we can get patients to achieve GI recovery earlier so that they can eat earlier, so that their

nutritional status improves, they're up and around earlier, that to us likely is very important to the patient and likely important to these guys.

So how about if we bring Dr. Delaney up here and allow him to address this from his perspective?

DR. DELANEY: Conor Delaney, Case Western Reserve University. Actually, one day is probably quite a clinically meaningful endpoint. That's something that's really evolved over the last decade in this type of research. First, from the patient's point of view, obviously every day less in hospital is a nice thing for them. And from the institution's point of view, it's useful as well. You have not only that bed available, but you have the opportunity to bring someone else into that hospital bed. The one day is useful, and it's become valid enough that it's now really the endpoint that's been used for many of the other studies that we do on postoperative ileus,

looking at different types of postoperative care pathway. So one day has become reproducibly an effective endpoint for that reason.

DR. BUCHMAN: One day is 24 hours. Hospitals don't function like cheap hotels where you pay by the hour. So is one day 24 hours; is that the same as 22 hours? Is that the same as 25 hours?

Or in the current billing structure, if we're going to save money and get people out earlier, it seems to me that we're really stuck at 24 hours here. Because otherwise, if they're there for 24 hours and 30 minutes, they've paid for that second day.

DR. DELANEY: Right. And I think that's a very important point to raise, whether it's 12 or 18 or 20 or 22 or 24. I think what we see with all the multiple types of data analysis that have been presented is that whatever way you look, whether it's recovery of GI-2 or GI-3 or discharge order written or average mean length of stay, which you also saw

presented, it approximates one day. What I think you have to remember when you look at the Kaplan-Meier curves is that it's not a shift to the left for one day for every patient, but it's particularly the patients who have the longer complicated postoperative ileus that were improving.

So yes, maybe for a certain percentage of the patients, they only go home or are ready to have a discharge order written two hours earlier, and no, that's not going to matter much for the hospital. But for the patients who really make the difference to shifting that mean, or the patients who stay seven days instead of nine, and that's opportunity for the hospital, but particularly important for the patient. And then the other spin on it is that they end up being less likely to be readmitted with ileus symptoms. So I think the effect is seen in multiple places.

DR. BUCHMAN: If we contrast that 75th

percentile to the mean and median data, if indeed there's this full-day benefit for the 75th percentile, which is quite different from that which we see with a mean or median patient, to me that suggests that there are patients on the other end who actually stay longer with the Entereg medication.

Have you evaluated -- what's the 25th percentile group, for example? Is there a longer stay in some of those patients? Because how do we see such a difference between the 75th percentile and the mean? And also, how do you explain the difference between the mean and median? The median, of course, would alleviate the outlier data.

DR. TECHNER: Let me see if I can address that question for you. Can I please see the core slide that I showed the committee on the Kaplan-Meier curves for discharge order written, please? Very much like the GI recovery curves that I showed you, the same pattern applies to the discharge order written curves.

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And so I think what you're seeing here -- and remember, as I discussed before, we see this cyclical pattern in these curves just as a result of the pattern of when discharge orders were written clinically.

But I think you see the same thing. And that is that all time points, from about between Day 2 and Day 3, which is when some patients do get out -- now, we don't know if these folks are coming back with unresolved ileus. Maybe they were discharged too early; we don't know that. But from here all the way through the entire 10-day observation period, the alvimopan curve stays to the left of the placebo curve. So there is no point along here where we see patients receiving Entereg doing worse than placebo. So I think that addresses one point.

I think the other point that I'd like to make is, you mentioned the difference between the median, et cetera. Can we just please leave that up? Thank you. Okay. I

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see what you're trying to do. You know, again, I think when you look at the median versus when you look at the means, you're looking at two different measures. The median, you're looking at one time point across this entire early perioperative recovery period.

And it may be that at that particular point in time, the curves are either very close together or they're either very far together, and that's going to have an impact on your median. And that's why, from our perspective, we believe that the mean, the Kaplan-Meier mean, meaning the difference between these two treatment groups over the entire 10-day observation period, is more appropriate for looking at what Entereg is really doing with respect to either GI recovery or discharge order in this particular population.

And the third thing I'd like to add, in follow-up to Dr. Delaney's statement,

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is that we don't know who's going to be here and who's going to be here. And I think that's the biggest dilemma that these guys face, not only from a GI recovery perspective, but also from a discharge perspective.

I think if you asked Drs. Delaney or Senagore to predict which one of their patients is going to have earlier GI recovery or later GI recovery or earlier discharge or later discharge, they will tell you they cannot do that. So I think that's also an important item to remember.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I'm not exactly sure how to ask this, but the construct that we're dealing with today is built upon the belief that once a patient is having bowel movements after an anastomotic procedure, that they're okay and they can go home. And all the surgeons in the room have been trained to believe that because we believe that once the bowel's functioning,

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the anastomosis is okay. That probably isn't really true.

And the reason I bring it up is that that right now is what keeps patients in the hospital, and if that turns out not to be true, there will be a push to send bowel anastomosis patients home when they're on liquids, much like your hysterectomy patients went home when they were on liquids, which would change this whole idea of this drug only being given when patients are in the hospital.

I wonder if you've thought about that or anticipated it, because there are some early studies of bowel surgery patients going home before they have their first bowel movement.

DR. TECHNER: I think that's an important question. And I think I'd like to ask Dr. Delaney to respond to that from his clinical perspective. I can tell you that certainly, in our studies, in polling all of these surgeons as

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to what criteria they use to discharge their patients -- now understand, this spans a period of time between 2001 and 2006 -- consistently, consistently, their definition of GI recovery usually includes both tolerating solids and the occurrence of a bowel movement.

So I'll let Dr. Delaney address that for you.

DR. DELANEY: Conor Delaney, Case Western. I think Dr. Techner has really partly addressed your answer. But I think we also have to remember that the GI-2 or GI-3 endpoint includes tolerance of diet. And while yes, there are protocols to discharge patients early from hospital while they're just on liquids, first, it certainly would be routinely accepted and it would be quite an aggressive discharge policy to follow.

And second, that that depends on the patient's being able to adequately tolerate oral intake sufficient to be able to maintain hydration at home. So this would

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suggest that this is still going to help from that point of view. It's not just passing a bowel movement, but also being able to tolerate diet earlier, that this medication can help that.

And then finally, the concern with being too aggressive about discharging people is that they may be more likely to be readmitted. And so that's perhaps I think why many people do wait for GI function to occur before they discharge patients. And again, this is somewhere this may be able to help us in practice.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: Judith Kramer from Duke University. I'd like to follow up on Dr. Buchman's question again concerning if you could go back to that slide, CA 38, where you're trying to show the medians in the different studies. If I understood your presentation correctly in the packet, 314 and 313 are major efficacy studies in your application.

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Is that correct?

DR. TECHNER: That is correct. And the reason, because they contain either all, or mostly all, bowel resection patients.

DR. KRAMER: Bowel resection, right. The next slide, the one that has the actual individual studies.

DR. TECHNER: The actual mean, median, et cetera.

DR. KRAMER: That's CA 38.

DR. TECHNER: Yes. Go ahead and put that up.

DR. KRAMER: I'm concerned about the representation of how you counted the median there. If we just look at Studies 313 and 314, the median difference from placebo is 7.8 and 6 hours; is that correct?

DR. TECHNER: That is correct.

DR. KRAMER: And the mean is clearly affected by outliers, and the 75th percentile by definition are the outliers. So I just feel like when we consider the risk and benefit, we

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really need to consider how many patients we're asking to take this drug with an unknown cardiovascular risk, I would say at this point, in order to obtain the benefit in the patients at one end of the spectrum. So I don't think we should discount the median benefit. So if you line up all the numbers, it's right in the middle, and the most common kind of response is going to be on order of magnitude less in terms of the clinical meaning of it.

DR. TECHNER: Let me address your question two ways, if you would. I'll give you just a brief perspective for myself. And then I'd actually like Dr. Koch to come up and give you a perspective of the mean, the median, et cetera, from a practical standpoint. I think that we certainly are not discounting the median. And in no way, shape, or form, and if it came across that way, I will certainly apologize, that the median is not valid statistically. I think what we're trying to say is in order to evaluate the effect, the

treatment effect of alvimopan in this population, we believe that the mean is one important measure that we focus primarily on, and that the median, and at the 75th percentile, provide additional information to support the mean based on the differences between the two treatment groups.

So we're not dismissing the median. We're trying to look -- and as a matter of fact, we're trying to present you with all the data. But I think maybe it would help to have a little more of a perspective from Dr. Koch as far as the practicalities of looking at medians and means to help you understand this maybe a little differently.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina. Can we go back to CA 31, with the area filled in? So as you can see, Kaplan-Meier curves wiggle. And when you pick a particular quantile like the median, you make pick a quantile where they are randomly somewhat closer together, or you may

even pick one up down here, where they may be randomly somewhat further apart. So picking a single quantile to emphasize isn't really that much different than picking a particular time point, like 72 hours in comparing proportions, or 96 hours in comparing proportions, or 120 hours in comparing proportions.

The different hours along the time course are arbitrary landmarks, although some may be more meaningful than others. And there has been some mention here that five days was a meaningful landmark along the time course. And some quantiles may be of more interest than others. And we've had discussion of the 25th percentile, the 50th percentile, which is the median, and the 75th percentile.

Now, we also have been emphasizing more the difference between the means than the means per se. When you have a time-to-event curve, the mean is actually the area under the Kaplan-Meier survivorship

curve or non-event curve. And when you have two groups that you're comparing, the difference in means is the area between the Kaplan-Meier curves. Now, when we work with the difference in means, we're actually looking at the horizontal distance between the curves at every quantile, and then averaging them together as we move up. And we're taking into account what the differences are at every quantile and averaging them together.

The difference in means is actually an underestimate of what the actual difference is, because the difference in mean estimate is truncated at 264 hours. So it is not leveraged by outliers beyond 264 hours. It actually is a truncated mean calculated through 264 hours. And because alvimopan is still better through 264 hours, the estimates that you're seeing for the difference in means is actually an underestimate of what the means would be if you went the full

distance.

So the main advantage of the mean is that it's basically integrating all of these horizontal distances between the two curves at their respective quantiles together, and producing what can be interpreted as the average amount of benefit that a patient might expect, comparing one of the arms to the other arm.

DR. BUCHMAN: In terms of -- leaving this up for a minute, the number needed to treat, I think there's been some perhaps misunderstanding of that.

It was suggested that this was to get the average 75th percentile patient out early. But what's actually the number needed to treat from the get-go, with an intent-to-treat analysis to get the median patient out 24 hours earlier?

Did you understand my question?

DR. TECHNER: Sort of.

DR. BUCHMAN: Let me rephrase it then.

DR. TECHNER: Go ahead.
DR. BUCHMAN: Simply, what is the number needed to treat? How many patients from an intent-to-treat analysis have to be given the medication in order to get a single patient out 24 hours earlier, regardless of which percentile they fall into?
DR. TECHNER: I think in order to answer your question, let's look at the responder analysis for discharge order written, and I believe that will provide a range of NNTs that you can use to judge. As you remember, we did do a responder analysis. And if you recall, that responder analysis was based on patients who achieved the endpoint of interest between any of Postsurgical Days 3 through 8, and then had no subsequent reports, adverse event reports of ileus, that either led to prolonged hospitalization or readmission within seven days of discharge.
No, sorry. Wrong slide. Why don't you go back to my core slide? Percentage of

patients discharged by Postsurgical Day 7. I think that's what I was looking for; I'm sorry. Yes.
So I think when we look across the studies, using that responder definition I just defined, we can see here that the NNTs to get patients out, in the pooled data for bowel resection only, within seven days ranged from five to nine. And this is across each of the individual trials. And so this is looking at responders in the pooled data from each individual study. And I think what you can see, one, is a higher proportion of alvimopan responders. And when you look at the absolute difference between these in each study, the NNTs you get are between five and nine.
DR. BUCHMAN: Dr. Hennessy?
DR. HENNESSY: Thank you. Given that alvimopan, at least as far as we know, doesn't save any lives, and given that the size of the potential market is at least 400,000 patients

per year even if it's used strictly on-label, I'm wondering whether you think a safety database and POI of about 2,600 patients is adequate to address the safety signal of MI?
DR. JACKSON: Dr. Alexander, may I ask you if you would respond to that question for Dr. Hennessy?
DR. ALEXANDER: John Alexander from Duke University. The patient population that's enrolled in these clinical studies, and in fact, the patient population that undergoes elective bowel resection surgery is at generally relatively low risk for cardiovascular events. And so the perioperative myocardial infarction rate in this population is likely to be less than 1 percent.
So even enrolling substantially larger numbers of patients on the orders of 10- to 20,000 in a safety database is unlikely to eliminate or exclude modest increases -- 25, 50 percent increases -- in myocardial infarction with alvimopan. So

with rare cardiovascular or other safety events, there's a real challenge in low-risk populations of excluding them, even with large safety databases.
In the totality of evidence from the POI population studies, and the analyses that we've gone over quite extensively from the OBD populations, there's risk, there's possible risk, increased risk of myocardial infarction that showed up in one OBD population study that -- where there was no such signal for MI or any other rare event in the POI studies or in the other OBD studies.
DR. BUCHMAN: Dr. Epstein?
DR. EPSTEIN: Yes, question for Dr. Techner. Dr. Epstein from Annapolis. Could we go back to slide CA 31? In this pooled study or, for that matter, in 314, for example, did you get a chance to look at the different age brackets by decade? Perhaps to see if -- you know, elderly patients obviously are less mobile and they may have more of an ileus, so your

effect may be greater in that population. I'm just wondering if you had a chance to look at that group and see if there was any clinical difference maybe by decade.

DR. TECHNER: We did, and it brings up I think a very interesting point. So we broke down the population for you here. This is looking at GI-2 by age in the pooled North American trials: Less than 65 years, greater than or equal to 65 years, and greater than or equal to 75 years. I think what you can see here is that regardless of where we cut the age group, we see consistent benefit throughout. And yes, the numbers are not quite as large, but we tend to see somewhat of a more robust response in patients that are elderly.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I had a couple of questions, one of them related to preclinical data.

Do you have any preclinical data on the effects of this drug on vascular tone?

Have you done isolated blood vessels and seen if there's any change in vasomotor activity? I know you looked at blood pressure in intact animals. But have you specifically looked at that, because that's one of the preclinical screening tests for --

DR. JACKSON: Yes, I'm going to ask Dr. Garver to address that preclinical question.

DR. GARVER: Deanne Garver, a non-clinical consultant to Adolor. There have been no systematic studies done for localization of the mu-receptors in the cardiovasculature itself. There's some limited data with respect to the distribution in heart, which is largely kappa- and delta-receptors, and not the mu-receptor.

DR. BUCHMAN: Dr. Proschan?

DR. PROSCHAN: Yeah, I'm a statistician, so I'm trying to get the clinical understanding in terms of the mean and the median and so forth. And I'm thinking, from a clinical standpoint, to me as a statistician, it

makes sense that what you'd really want to reduce the time in are the patients in whom there's a problem. So a patient who only stays for one day, it doesn't matter as much whether you reduce their time.

On the other hand, someone who takes five or six days, maybe it's a lot more important to reduce their time. And likewise, if you went to the other extreme and took people -- I know the maximum here is only 10 days, but if you had data going out to 30 days, then maybe a one-day difference wouldn't be very important. So it seems to me that the 75th percentile actually might be fairly reasonable in terms of clinically important. But this is coming from a non-clinician.

And the other thing I wanted to ask about was this decision about going to GI-2 instead of GI-3. You know, I'm worried that that hindsight may have been driven by results a little bit. And I'm wondering if

you're so convinced that GI-2 is really the better endpoint, then why did you decide on GI-3 at the beginning of some of those studies?

DR. TECHNER: You know, the clinical development program for Entereg really spanned almost seven years, a long seven years. And we're still here. And I think, to be quite frank with you, it's a learning experience. I mean, we have to understand a couple of things. One, there is no precedent here. There's no guidance document to tell a sponsor how to develop a drug to manage postoperative ileus in patients undergoing bowel resection.

So in essence, Adolor and GSK kind of were carving the path. And so we really relied on I think two very important things -- three important things. One, our data as we accumulated it. Two, our surgeons, our anesthesiologists, our statisticians, our physicians who really helped us understand the condition, and what

really matters from their perspective and from the patient's perspective. And third, the FDA, who we've been collaborating with over this entire period of time.

And I think when we looked at everything, the data, what's important to the surgeons, what's important to the patients, what really gets to the treatment effect of alvimopan, and our ability to really assess that so that we can be able to give you data that you feel confident in making your decision, it really came down to GI-2. And that really is the honest answer. It was a learning experience. We took input from everybody, and that's how we got there.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I just had a couple of questions about the cancer signaling, because I remain a little concerned about that. Dr. Dannis mentioned that there was a fairly large difference in the Karnofsky scores between the two groups receiving the drug and the

placebo in the OBD study; is that correct? And if you correct for that variable, do you still see a risk, an increased risk for cancer? Because there's a question over this immune surveillance may be related to that effect and it's not truly a drug effect.

DR. BUCHMAN: Microphone, please?

DR. DANNIS: I'm not sure we looked into that.

DR. PASRICHA: And the question of the sponsor is, it's probably been at least two years since you've completed the study or enrolled your last patient in the study; is that correct?

DR. JACKSON: No, 014, the data are not quite as mature as that. And we did -- if you'd like an answer from the sponsor to that question, I think we can provide it.

DR. PASRICHA: What I would like to see, especially since most of these patients were treated for cancer, with this new information on the signaling, I'd like to see

some information on two-year survival after exposure, even though brief, to this drug. And that should not be very difficult to get.

DR. MORTENSEN: Eric Mortensen, GSK. Let me first speak to your direct question about the multi-event analysis, and I'll ask us to put that up.

Understandably, we wanted to know why we were seeing this gross imbalance, the 20 versus 30 that we saw in the continuum of 008, 101, 684. And so in conjunction with our external consultants, we suggested that we had to consider that, given that we had not made any effort, because that was not the objective of the study, to try to balance patient Z severity or prognostic factors, that we should investigate some very well -- clinically well-established prognostic factors for death and disease progression in patients to see whether or not we really had balance between the treatment groups.

Now, what I'm showing here, this first, just looking at the initial unadjusted hazard ratio for the risk of death in the continuum of 008, 101, 684, and we see there's a 2.1 alvimopan to placebo, again, broad confidence in embracing one because we're talking about small numbers here. The next steps were then to look at the influence of those factors that were thought to potentially be related to what we saw as the imbalance.

Again, we note we had a numerical increase in the number of patients who had with non-small cell lung cancer in the alvimopan treatment group. And we saw here that we ended up doing this in a sequential step stages of looking at a multi-variant model, and that actually showed the most significant risk factor for patients' death. So imbalances based upon their underlying diagnosis would potentially significantly impact the outcome of patients.

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But in addition, we also then looked at two other factors. One is Karnofsky score. Now, Karnofsky scores are a patient performance score that is I guess commonly used in many oncology studies. And what we found is that each additional 10-point decrease in Karnofsky score is associated with additional worsening of patient's outcome and greater probability of the patient being moribund.

And so we see that for each 10-point decrease, we then see a hazard ratio increase of 1.5. And I'm emphasizing that because it's not saying that it was an arbitrary cut. Each cut, from 100 to 90 to 80, you're seeing each of those cuts, and if you then have the increase in those patients in the treatment group, a progressive worsening of their outcome. And then, a similar number of metastatic sites for their cancers. And again, there's a numeric increased number of patients with more

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metastases, and that the treatment group, that was also as you see here, seen to be positively associated with an increased risk for death.

So when we adjusted the studies for the proportion of patients with these differences between the alvimopan group versus placebo, we actually saw that we had a decrease in the adjusted hazard ratio to 1.4. Again, with a wide confidence level, but at least that gave us some confidence that the factors that we were told by external experts in oncology that might very well be influencing the outcomes of our study seem to be borne out.

I was going to give a quick factual answer to the earlier question that was asked. There was an earlier question about the distribution of patients in 014, and I just wanted to just very quickly get back to that and answer your question. Briefly, 65 percent of the patients in 014 were from

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the United States. A total of 85 percent of the patients overall were from the United States, Canada, and the U.K. We then also had a small number of patients contributing from other sites, fewer than 1 percent from either Poland or Hungary.

And then we had fewer than 3 percent of patients coming from New Zealand, Australia, Hong Kong, and Taiwan. So it was largely a study conducted in the U.S., Canada, and U.K.

DR. JACKSON: This is David Jackson, Adolor. In regard to the second part of your question, we do not have, obviously, two-year follow-up on those patients. But we've talked extensively about the IDMC and the consideration of the cardiovascular effects of that drug. Obviously, there was no place for an IDMC and that the neoplasmic findings were after the study was finished.

We did, however, convene a panel of expert oncologists, one of whom is present

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today, and would I'm sure be very happy to provide his thoughts if you'd like to hear them.

DR. FUCHS: Hi. I'm Charlie Fuchs, medical oncologist and cancer epidemiologist at the Dana-Farber Cancer Institute in Boston. And our group did look at the evidence in its totality to look at the relationship between this drug and cancer risk, and thought about sort of several of the major criteria that one considers when thinking about cancer risk.

First, there really was not a plausible biological mechanism by which this opiate antagonist would contribute to cancer risk. None that we're aware of. The question was asked earlier about the presence of mu-receptors on cancer cells. I'm not aware of that. In fact, in terms of looking at opiate antagonists and opiates on immune surveillance, there is limited evidence, but would suggest that opiates sometimes reduce NK cell activity, whereas antagonists might

increase it. Now, I think that's purely speculative, but doesn't suggest that one impairs immune surveillance. So bottom line is, first, we didn't see clear biological plausibility for a relationship with this drug and cancer.

Secondly, as you've seen, the genotoxic studies and the animal studies delivered over two years failed to demonstrate any clear carcinogenicity of the compound.

Thirdly, the time course seems implausible. Namely, the idea that cancers could develop in a matter of weeks to months is unlikely with any agents.

And then finally, the histology. We're clearly looking at a panoply of cancer histologies.

And when assigning risk, one usually expects to see a specific tumor histologic type. And as you saw in the data, we're not seeing any clear pattern. So in

sum, we're really not seeing any convincing evidence that would link alvimopan with cancer risk.

Finally, with regard to the POI indication, we're looking at seven days of exposure to the drug, and I'm not aware of any precedent where a drug that doesn't have any genotoxicity or carcinogenicity would lead to cancer risk with a seven-day exposure.

DR. BUCHMAN: As chair, I'm going to take the prerogative to ask the last question for this session. Given that we're dealing with a benign condition here, vis-a-vis I'm not aware of a single case report of anyone dying from postop ileus; furthermore, I'm not aware of any data that would suggest that leaving hospital 22 hours earlier also decreases nosocomial infections, C. diff, or anything else that we've discussed, and you haven't shown that actually in your study that you showed a positive benefit there, we need to limit exposure to the drug

given the potential complications however minimal they be because we have to consider a cost-benefit analysis. Do you think you should be required to do a single dose, a preoperative dosing study -- in other words, 6 or 12 milligrams one time only preoperatively as the only dose, another study?

Do you think you should be required to do that? And if not, why not?

DR. TECHNER: Before I answer your question, I'd like to, if you don't mind, make one point of clarification, because I think it will help in you understanding the response.

DR. BUCHMAN: My question is predicated on the answer to my previous question, where you illustrated the continuous difference between the curves at all points, even as soon as two days postoperatively.

DR. TECHNER: Let me start by clarifying something, and I think it was a point actually that Dr. Chang raised, and also Dr. Dannis.

And I think we -- and I think Drs. Senagore and Delaney can speak better than I to this, agree that virtually all of these patients are being seen by their surgeon within generally two to four weeks. And actually, I can tell you that we polled all of our sites, and the vast majority of our surgeons see their patients back for their first follow-up visit within two to four weeks. Per all of the protocols, the sites were required to report any serious adverse events that occurred between the last dose of study drug and 30 days following that time point.

In addition, we had monitors visiting these sites routinely, scouring through the hospital records, the clinicians' medical office records, and any other medical records that were available, to ensure that anything that looked like an adverse event was captured. And the sites were instructed to report any adverse events, including

serious adverse events, that occurred during that period of time. So we believe that the database that FDA currently has would include those events that occurred basically from the onset of study through 30 days post last dose. So I just wanted to clarify that to give you a perspective of follow-up.

Dr. Schmith from GSK?

DR. SCHMITH: Hi, Ginny Schmith from GSK. I wanted to comment on the idea that a single dose preoperatively would work. And I would argue that I do not believe that it would, and I'd like to show you a plot as to why.

Dr. Techner had told us originally that the time above the KI for the mu-opioid receptor was longer with a 12-milligram dose than with a 6-milligram dose. Okay? And this data comes from POI patients. Okay. We have collected samples in POI patients, and they do have higher concentrations than we would expect to see in healthy volunteers, because they have higher viability because

they do have a decreased GI transit and more time for the drug to be absorbed. Okay? But as you can see, this is a over a 12-milligram dose over a 12-hour period. So they're above the KI for 12 hours. They're not going to be above the KI for five days.

DR. BUCHMAN: But if you prevent the development of a postop ileus, why would you need to give it for five days? If you don't have a postop ileus at Day 1, you're not going to suddenly get one at Day 5.

DR. TECHNER: I will address that, and I will also ask Dr. Senagore to address that as well. I think we discussed the fact that ileus is multifactorial. Opioids are definitely a key component. So as long as a patient is receiving opioids, the risk that ileus is prolonged is high. And therefore, we believe that if you only gave one dose preoperatively and the patient continued to get opioids, then in essence, that preoperative dose effect, the chance to mitigate the effect of those opioids,

would be lost. And this is not that dissimilar from administering antibiotics to prevent wound infection, and other prophylactic measures that we use in order to reduce the chance that a patient will get a certain condition.

DR. BUCHMAN: That goes back to a question I had a few hours ago. And that is, is it what you're really treating here is not a postop ileus at all, that you're treating narcotic-induced ileus? I can tell you from dealing with a lot of patients with complicated GI surgery, those that stay the longest are those that have a trigger finger. They can't get their finger off of the PCA pump. And they may stay a couple of weeks in the hospital with a postop ileus. And so that also then brings up the issue of using it more than seven days.

But the most important issue is, are you seeking an indication that perhaps doesn't truly exist or that you weren't really treating? That you're treating a completely different indication, being a

narcotic-induced ileus.

DR. TECHNER: I think this is the way I would respond to that. If the standard of care in this country was to manage postoperative pain with no narcotics, then I don't believe we would feel this drug would have a benefit. I do not believe that that is the standard of care here.

DR. BUCHMAN: You can answer the other question when we get to some of the questions. Dr. Krist, you had one question. Then we've got to move on to the questions.

DR. KRIST: Well, maybe my question is better to be brought up as we address these questions. What I'm really looking for is reassurance that we don't need to be worrying about looking at long-term safety issues for the short-term indication of the medicine. And I know we've been trying to talk about this, and we've been skirting around that topic when we're looking at the incidences of cancer and MI and those types of things. But the picture that I

keep coming back to that has me uncomfortable is I hear consistent information about efficacy.

The clinical significance, we could talk about, and as Alan, you brought up we don't see reductions in mortality and DVT and nosocomial infections, but we do see consistent reductions in nausea and postop ileus and earlier discharge from the hospital.

But I also hear a drug that would apply to 400,000 people that you can't predict who's going to need it, so you've got to give it to everyone. It's something that I would envision a surgeon would just do. You wouldn't really discuss it with the patient, because there's bigger things to think about, like your cancer resection and other things like that that patients are dealing with. So I feel like there's a lot of importance for making sure that this is safe.

And on one hand, I heard

Dr. Lincoff earlier say, well, why would a drug that you give for seven days cause an MI three to six months later. So we see these spikes in the folks on the long-term use of the medication. And I can buy that, but on some level, the people in the short term are getting more of the drug. They're getting 120 to 168 milligrams, where the people on the long-term dose -- if you're looking 40 days to 120 days out, they getting 40 to 120 milligrams of the medicine.

And then in the risk management plan, I don't see anything to even go back or look at or think about -- if you give it for a short period of time, are there these long-terms complications that we saw the spikes of? Cancer, I can buy more as a short-term dose. You can have an increase in cancer 6 to 12 months later. That certainly is plausible. MI, I have a more difficult time with.

But I'm just looking for some

reassurance and trying to figure out, well, why don't we need to worry about looking at that longer time period for the short-term administration? I know it wasn't the plan and it came up afterwards, after these spikes appeared. But before releasing a drug and saying it's safe and potentially exposing a lot of people to it, it seems like an important thing that we need to figure out.

DR. BUCHMAN: So your question is if we use similar cumulative doses, why don't we look at the data the same? Is that the question that you're asking?

DR. KRIST: The cumulative dose, I didn't mean to -- it's not an issue of the cumulative dose.

It was more of an issue of on one hand, we're saying, well, if you give it short-term, in the studies we see, we don't see risks of MI in the POI studies. But as Sean was bringing out, we probably don't have power to see that at least short term.

The thing I'm concerned about is our follow-up is 14 days, and the spikes in the chronic use folks occurred at 40 to 120 days. The issue of the dose was just -- the positive towards the POI studies is, well, it's only five to seven days people get it as opposed to 60 to a year's worth of days that they get it. But the negative is the cumulative dose might be more in the short-term POI patients in the studies.

DR. JACKSON: David Jackson from Adolor. I'd love to make you comfortable in that regard, obviously. In part, I'd like to answer your question with providing an answer to a comment that came from the left side of the committee table earlier. And I apologize, I can't remember whether it was Dr. Lincoff or Dr. Talamini. But the size of this acute care safety database at 4,000 patients is actually rather large for a short-term administered product. Okay?

DR. KRIST: Short term.

DR. JACKSON: So we have a lot of data. The second point I would offer is that in the OBD data, the risk, whatever it is, whatever that signal, if it is a signal, means, is largely confined to one single study. Those other studies which looked at a significant number of patients for three months did not see that imbalance. So although we don't understand perhaps the meaning of the signal right now, if it is such, we have a preponderance of data in which we don't see anything.

DR. KRIST: But that one study was the main one that followed people for a year. The other one stopped at three months, right?

DR. JACKSON: Yes, but the myocardial infarctions were all seen in the first four months.

There was nothing seen at all in the last six months of that study.

DR. KRIST: Not necessarily true, though, for the cancer risk, of course.

DR. JACKSON: Absolutely not, but

again, as I think my colleague Dr. Mortensen tried to indicate, there is a very good chance that a large number of those cancers were present at the time of introduction into the study.

DR. KRIST: Likewise, there's no methodologic reason to say that we shouldn't be considering Study 14. Even though it all occurred in that one study, there's no -- when you look at that study compared to the other studies, there's no explanation as to why it occurred in that one study compared to the others.

DR. JACKSON: There is indeed not, and we have looked very hard for that.

DR. BUCHMAN: Unfortunately, we're going to have to move on and catch up here. We're going to move on to the questions that the agency has posed to the committee. Some of these will be questions that the committee will actually vote on, and I will announce those as we get to them.

The first question is a non-voting question, and we'll spend about 10 to 15 minutes on this, less if we need. And the question is, for the record, for the assessment of efficacy in clinical trials of postoperative ileus, GI-2 and GI-3 have been utilized to measure times for recovery of upper and lower GI function.

What do you consider a minimal acceptable treatment difference as measured by GI-1 or GI-3 for alvimopan relative to placebo? Specifically, do you think 12 hours is sufficient? Twenty-four hours, 36 hours, a month, 12 years? We need you comments on this.

Dr. Pasricha?

DR. PASRICHA: I just think we need to clarify what time points or what percentile we're talking about. Are we talking about the means for the whole -- are we talking about differences in means?

DR. BUCHMAN: That's a good question

here. Are we talking about the mean, median, or 75th percentile?

DR. KORVICK: I would think that anyone that responds to this question should specify what's the most meaningful to them, and why and how much. So you can pick whichever one you think is meaningful to you.

DR. PASRICHA: So I'd like to say in general that reducing postop stay by 24 hours on an average patient is meaningful. But if you're talking about an operation or a procedure that results only in 3 days hospitalization and you can reduce that by 12 hours, that might be meaningful, also. So in part, it depends on the denominator, which is one of the reasons we asked the question. But if you just take sort of this dumb average that we have, five days and so on, I think 24 hours would be considered a meaningful endpoint.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I would say as one of those surgeons on the committee who's watched

lots of patients go through this, I think for me, 12 hours in terms of the GI-2 endpoint or 12 hours in terms of being able to leave the hospital would be significant.

I'd like to add one quick comment to follow up on what you said, Dr. Buchman. The surgeons in the room know when we finish most operations, the small bowel is peristaltic. So there is this definition. You know, in our minds, we have this ileus thing when we close a patient. When we close a patient, the small bowel's functional. The colon usually isn't, the stomach usually isn't, but the small bowel is. It'd be fascinating to know by ultrasound what's really going on with the bowel at all these time points, but we don't.

DR. BUCHMAN: Dr. Levine? Dr. Epstein?

DR. EPSTEIN: Yes, just to expand a little bit on what Dr. Talamini said. And as we've been going through this discussion and

talking a lot about the safety, we've also gone, and Dr. Chang has made the comments, on more of a pharmacoeconomic argument, which is kind of unique in my experience on panels. But nevertheless, it's an important thing to discuss. And just by way of my background, I've served as president of a medical staff and on a board of a 700-physician hospital for more than a decade. So we wrestle with these issues from the pharmacoeconomic every day. And we also have the P&T committee, which would then consider this drug because it's going to be a hospital drug.

And a lot of our time is spent trying to get the hospital bed days -- our mean hospital bed days are around 3.16 days, trying to get it from 3.23 days down to 3.16 days, and that is a huge number. It has everything to do with reimbursement to the hospital, quality indicators, and on and on.

And even if you look at this drug, if you gave it to the 500 patients or so that

had a bowel resection, if you could save one hospital bed day or even half a bed day, which is significant, or 12 hours, you're talking about 55 bed days. That's very substantial. It's not only you're getting the patient out of the hospital early and saving money, but you're putting somebody in the hospital on that day and you're able to do more surgeries.

I don't know about the hospitals or the places where everyone else works, but we have a very, very critical bed shortage on a daily basis. And this is a common problem throughout our area. So this would have a significant pharmacoeconomic impact if we could save even 12 hours on our postoperative patients. So from that standpoint, I think this drug would be very beneficial if we could make that change in our time of stay.

DR. BUCHMAN: Dr. Talamini and Dr. Epstein, if the nurse called you at home, and actually both of you are probably rounding

at midnight, and the patient eats dinner, solid food -- and of course, we don't know what solid food tolerance means. They ate a hot dog, they ate a whole sandwich, they ate one piece of toast. But if they call you at midnight and say, well, the patient ate, can they go home now, but the patient's asleep now, would you send them home or would you wait until 8:00 in the morning? And so basically that's just a joke that didn't go over very well to illustrate my point, does 12 hours really make a difference clinically?

DR. TALAMINI: This is Dr. Talamini again. I believe that it does, because most surgeons, at least academic surgeons, which is what I've been and lived with, really think of these things twice a day: Once for the morning and once for the evening. So if you hear from the house staff in the afternoon bowels are moving, patient's eating a diet, you'll say go on home, and we'll have a bed fresh early the next morning.

DR. EPSTEIN: Just to --
DR. BUCHMAN: Dr. Krist?
DR. EPSTEIN: I'm sorry.
DR. BUCHMAN: Oh, I'm sorry, Dr. Epstein.
DR. EPSTEIN: Just to reiterate on that. The protocol that we have in place in our hospital is we have a 24-hour team in the hospital, a discharge team. We have cars standing by ready to get you out of the hospital. It does not matter if it's New Year's, Christmas Eve, a blizzard.
Our ER is -- we just built a brand-new hospital and our ER is stacked up with people in the hallways down the halls. We don't have room for these people, and it's really a troubling situation. But the point is that every hour makes a difference. And we can't even transfer a patient to another hospital. We have the same problem throughout the metropolitan area. So yeah, it's a big difference, and 12 hours is

enormous.
DR. BUCHMAN: Dr. Krist?
DR. KRIST: Now, I practice more at a community hospital, and I'm not sure that things happen in anything other than 24-hour increments, even though people want it to do, and we have bed shortages as well. But maybe this is where it helps us a little in thinking about whether we're talking about the mean or the 75th percentile. Because really, as you were talking earlier, for an individual patient, I think what's more clinically significant is 24-hour increments. But if you're talking about mean for the overall group of patients who had the surgery, maybe 12 hours for that mean would be important, because that represents people who are getting out one or two days as well as people who are getting out an hour or two.
Whereas if I look at the 75th percentile, more of the extreme of the people staying longer, maybe I want that to be more around 24 hours as opposed to the 12 hours.

So that's how I might rationalize and interpret the overall population mean versus the 75th percentile.
DR. BUCHMAN: And of course, we saw a mean of six to seven hours in this study. So okay, well, we're going to move on to Question No. 2.
DR. PASRICHA: The mean was about 15 or something.
DR. KRIST: The 75th percentile mean was closer to a day.
DR. BUCHMAN: Were you referring to the overall mean or the mean for the 75th percentile?
DR. KRIST: Well, the overall mean was more like 15 hours.
DR. BUCHMAN: Fifteen. Fifteen, you're correct.
DR. KRIST: And the 75th percentile one was 24 hours.
DR. BUCHMAN: Yep, you're correct. We're going to move on to Question No. 2. And

keep in mind Question No. 2 is actually a voting question, and we'll have up to 30 minutes to discuss this. The question is, do you consider the efficacy results from the submitted POI studies to be clinically meaningful, and explain which of the endpoints, that's GI-1 -- or GI-2, GI-3, date of writing the order for discharge, or ready for discharge, or perhaps some other outcome that you feel is important? And which studies are you relying on to support your conclusion?
Comments from the committee?
Dr. Kramer?
DR. KRAMER: I think before we actually discuss this, we should get to the question that you raised about what the actual indication is here. Because what bothers me in terms of determining efficacy is that essentially you have a situation where this drug has been shown to be effective when you required opioid patient-controlled analgesia. And if I got it right, I think when the surgeon,

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Dr. Senagore, described the care pathways being instituted across the country now, some of the newer approaches, I think one of the things you listed in general, not in these studies, included opioid-sparing techniques. That was excluded from these studies, with the exception of the one in Europe.

So in order to determine whether or not this is efficacious, we have to say what are we really doing? Are we minimizing the effect of opioids, and should it have that indication? Should it be tied to use in a situation where you're administering PCA? So you interpret the results accordingly. So that's the comment I want to make.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I think it's very hard to look at the data and tease out what's opioid-induced and what's non-opioid-induced in the setting of postoperative ileus. So I'm not sure that clinically that would be very helpful for us to do that. I think you can clarify the

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context in which you're asking for efficacy, which is I guess the context in which they're asking for the label.

And in my opinion, I think it is clinically meaningful, the data. And I'm relying on the GI-2 and the DOW endpoints to support that. And I think we see it in all the studies that have been presented.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I just wanted to -- actually, Slide CA 37 shows that the mean difference is more like 18 hours. Now again, I don't -- you know, I'm not a clinician, so I'm probably the wrong one to be commenting on this. But it seems to me that it's appropriate that as you go out to the 75th percentile, you're getting a bigger difference, a whole day; as you're down in the lower amounts of time, maybe 12 hours is really important.

You know, if you're talking about the difference between three days and two and a half, that may be very important. And then

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when you integrate across all time points, it seems to me that 18 hours is pretty long as well. So once again, from a non-clinician standpoint, it seems like the results are pretty good.

DR. BUCHMAN: Dr. Rosing, do you have any comments on this particular question?

Dr. Cullen?

DR. CULLEN: I think the results are efficacious. I think that the GI-1-2 study and the DOW as mentioned previously are what I look at. And I think getting a patient out in a day at 75th percentile is really significant.

DR. BUCHMAN: Dr. Krist, anything to add to your previous comments?

Dr. Levine?

DR. LEVINE: I just want to ask Dr. Cullen, we agreed that in the 302 and some of the other studies where we had total abdominal hysterectomies, that this was going to only look at postoperative ileus, not in the gynecological surgery. On the other hand, if

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you can save a half a day or a day in total abdominal hysterectomy, it may be cost-effective. My question is, can we guesstimate if this would be utilized on or off -- in the hospital on- or off-label by gynecological surgeons for cancer surgery, where there's total abdominal hysterectomy, when we don't have data in that area shown in the presentation?

DR. BUCHMAN: Ms. Corkery-DeLuca, any comments?

MS. CORKERY-DeLUCA: I haven't heard enough negative to think --

DR. BUCHMAN: Use your microphone, please.

MS. CORKERY-DeLUCA: Pardon me. I haven't heard enough negative comments to say that it would not be.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: Richardson, Mayo. I have a comment, and perhaps Dr. Talamini and some of the other surgeons can answer this for

me. I know that at our institution, more and more bowel resections are being done laparoscopically, and that has shortened up the stay substantially. And I guess I'm wondering, if you're looking for this narrower indication, that is using this particular drug only in the situation of the open laparotomy, is this going to be relevant as practice evolves?

DR. BUCHMAN: Dr. Chang?

Dr. Talamini, go ahead.

DR. TALAMINI: Should I respond?

DR. BUCHMAN: Go ahead. But this is going to be your one time to respond, so make it a full one.

DR. TALAMINI: I think that the data's pretty clear that right now the majority are open surgery. I think over time, though, those numbers will shift and it's an unanswered question.

I would say in terms of my answering of Question No. 2, the endpoints that are key to me are GI-2 and Ready,

because GI-3, flatus, patients just can't explain most of the time, and discharge order depends on another human being in the chain. So those are the data points that are important. And I think that this is significant based on those endpoints.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: I would say I like what Dr. Krist said about the mean being 12 hours and at the 75th percentile, it's 24 hours. But I would go by GI-2 because it is objective. I don't feel like Ready or discharge orders -- that's more subjective and it's based on -- it could be variable. But obviously, the results support the GI-2 endpoint, so I definitely think this is efficacious.

DR. KRAMER: I'd like to say that I do think that it's efficacious for -- I agree that GI-2 makes sense, although it does bother me that it looks like it was a post hoc decision after the data was looked at, but it does make sense. But I think the statement must specify

that this is in the context of opioid PCA.

DR. BUCHMAN: I'd have to say who am I to question the surgeon's judgment when to send their patient home, although I don't infrequently do that.

If I was the patient at 4:00 a.m., and you're going to send me home, I'd beg you to not wake me up first, and secondly, to wait until 8:00 a.m. But given that there is a feeling around the table from our surgeons that 12 hours is clinically important for ready for discharge, then I would have to say I think that that is efficacious as well.

The problem with the written order for discharge is it suffers from exactly the same problems as actually going home, because it's a red flag for insurance companies. If I know a patient from out of state, for example, is ready to go home on Friday and they can't get picked up until Monday, I'm not going to write that order. So it suffers from exactly the same problems. So ready to

discharge is important. We're talking about a benign condition, but if we can get the patient out earlier and basically save money -- that's the only thing we're talking about here is potentially saving money -- then I'm going to concur with my surgical colleagues.

Dr. Hennessy?

MR. HENNESSY: Thanks. I would say that the endpoint is clinically meaningful, but only marginally so. It's right at the cusp.

DR. LINCOFF: As a non-GI specialist, I would say that I think this endpoint is very clinically meaningful from other conditions. A day in the hospital or a half a day in the hospital, I think is relevant, particularly a day or a half a day of having an unpleasant condition, like an NG tube or nausea. So from that standpoint, I think that even a half a day would be clinically relevant.

In terms of the endpoints, I think that the GI-2 is the hardest endpoint, in

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that it's most linked to an objective finding. But I also believe that the DOW and Ready are very important as well, in particular because they're concordant with the more mechanistic endpoint, and because this is a blinded trial.

So for all the limitation -- these are blinded trials. So for all the limitations inherent in the physician's decision of when he's going to discharge and if he's got people wandering around at night ready to kick people out into the cars or not, but whatever these are, they apply to both groups, and they model clinical practice. So for the very question of relevance, where GI-2 is science, DOW and Ready are clinical relevance and relevance in medical practice. And so I think they're all meaningful. They all support each other.

And I think together it's a very -- as much as I hate to use this overused word -- robust findings, set of

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findings, that there is efficacy for this drug.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: Yes, I agree with my colleagues so far. And even just modeling Dr. Talamini's hospital, the number of surgeries he does, if you apply some numbers to this, it's a very substantial clinical savings, cost savings, time savings, that would outweigh any cost of the medicine and its delivery.

DR. BUCHMAN: Dr. Talamini had his chance, but he begs me for one more. We have time, so go ahead, Dr. Talamini.

DR. TALAMINI: The only thing that I would add to the differentiation that you're bringing up, Dr. Buchman, is having personally had a PCA after a very painful operation, it is the Rolls Royce of pain control. And if this does ameliorate or make that easier to use, I think that's a consideration.

DR. BUCHMAN: We're actually now going to vote on this as a committee. And the way the

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voting procedure is going to go is I'm going to read the question for the record, but then all committee members who are going to vote yes, I'm going to ask them to raise their hand. Now, unfortunately, you're going to need to keep your hand up in the air until Dr. Phan has recognized that she has recorded your vote.

Separately, we will then -- I will then ask for those that are voting no, and finally, those who abstain. And remember to keep your hand up until it's acknowledged. Not quite the secret ballot that we're used to.

So the question again is do you consider the efficacy results from the submitted POI studies to be clinically meaningful? All those that say yes, please -- I'm sorry, we have an interruption.

DR. KRAMER: Can I just ask a clarification?

DR. BUCHMAN: Yes.

DR. KRAMER: Can we specify that

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this -- since all the studies require PCA, that this is the setting in which we're making the statement?

DR. BUCHMAN: Well, I think you can make a comment, but as far as voting goes, the question stands as is. You can certainly abstain if you feel that it's an incomplete question.

Any comments from the agency? Would they like to see that any differently?

DR. KORVICK: I agree with what you just said.

DR. BUCHMAN: So all of those that feel that the efficacy is clinically meaningful, please raise your hand. Oh, please -- now that you have your hand up, that was just an exercise. Now you have to actually state your name and say yes. And we're going to start with Dr. Talamini.

DR. TALAMINI: Talamini, yes.

DR. EPSTEIN: Epstein, yes.

DR. BUCHMAN: And you can put your

arms down. The war's over after you've voted.
DR. LINCOFF: Lincoff, yes.
MR. HENNESSY: Hennessy, yes.
DR. BUCHMAN: Buchman, yes.
DR. CHANG: Chang, yes.
DR. BUCHMAN: Losing hands over here. Put them down after you've been recorded.
MS. CORKERY-DeLUCA: DeLuca, yes.
DR. LEVINE: Levine, yes.
DR. PASRICHA: Pasricha, yes.
MR. PROSCHAN: Proschan, yes.
DR. KRAMER: Krist, yes.
DR. CULLEN: Cullen, yes.
DR. ROSING: Rosing, yes.
DR. BUCHMAN: All those that vote no, that the efficacy has not been shown, please raise your hand. All those who are abstaining? Please state your name.
DR. RICHARDSON: Richardson, abstention.
DR. KRAMER: Kramer, abstention.
DR. BUCHMAN: With that, we're going

to --
MS. PHAN: So we have 13 yes, no nos, and 2 abstains.
DR. BUCHMAN: Thank you, Dr. Phan. With that, we're going to move on to Question No. 3, which is a non-voting question. The question is: based on currently available data, do you have concern for the use of alvimopan 12-milligram capsules in the short term, that is seven days or 15 doses, for the patient following a partial large or small bowel resection with primary anastomosis with regard to the following: Cardiovascular events, neoplastic events, and/or bone fractures?
If you noticed I only call on anybody, put them in the hot seat if it's a voting question, so this is a free-for-all here.
If you have a comment, please make it. Dr. Hennessy?
MR. HENNESSY: So yes, I do have concerns with regard to cardiovascular events.

I think that a meaningful signal for cardiovascular events, and in particular MI, was raised for other studies. I think that the studies in postoperative ileus were too small to address that. I think there's a potential mechanism underlying the potential signal, and that is mu-opioid agonism can reduce arrhythmias, so blockage would reduce that reduction of arrhythmias. Given the number of patients that are likely to see this drug, I don't think that that safety signal has been adequately addressed.
DR. BUCHMAN: Dr. Proschan?
MR. PROSCHAN: Yes, I also had concerns. I was -- you know, for me, the two big questions are, is 014 really different than the others? And is the OBD different from POI? And when I look at -- I did my own statistical test to see if the results were different in 014 compared to the other trials, and I got something that was statistically significant, showing that there's a difference between 014

and the other OBD trials. Now, I don't know why that is, so it's hard for me to dismiss GSK014, because that's the one that had most of the MIs.
You're taking a trial that had more of the information and trying to dismiss that. I have a real problem with that. In particular, you're estimating the odds ratio better in that trial than you are in all of the other trials in terms of variability.
The other thing that bothered me was that it wasn't just MI. If you look in 014 in the briefing document, it looked like it was arrhythmias, it looked like it was other cardiac events. So that, to me, suggests that this is not really just a chance finding, those two factors.
As far as POI versus OBD, I did my own statistical test and I did not get a statistically significant difference in the odds ratios for those two classes of trials. And so that suggests that maybe the harm, if you believe that there's harm, in OBD might

also apply to POI, and we just don't have enough events to detect that. So I did have those concerns.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I would say that I have concerns. I don't have concerns regarding bone fractures. I don't think I have concerns about the neoplastic events, because looking at each individual case, they're all over the board, and many of them really just make no sense to me in terms of long-term use of the drug in that study.

I do have concerns about cardiovascular events, which I think are somewhat allayed by the comments here today that nobody can point to a short-term drug like this creating a longer-term cardiovascular event. So I have concerns, but I think they've largely been addressed.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I do have concerns, in particular about the cardiovascular events. And

it's not just short-term exposure causing long-term effects, but I would say that the follow-up in the short term was really inadequate. Granted, at the time these studies were done, it was not known that there was a signal -- a signal would later show up in this OBD population. But I think we have to keep in mind that this was passive adverse event reporting, and we know how doctors collect that information. It's not an active solicitation of cardiac events.

But furthermore, a very large percentage of these patients were not followed when they left the hospital, that there's -- if I read the slide correctly, I think it was 257 patients did not have any further information. And that is not even short-term follow-up. I mean, they could have had an event at 10 days or 2 weeks. And my understanding, even though the metabolite is less potent than the parent drug, that the metabolite would have been present past the

time these patients were observed, a large percentage of the patients were observed. So I don't think we have adequate information to say that there's even no relatively short-term problem in the POI population.

So I do have a concern, and I think that given that this benefit -- it's really striking. The FDA is not allowed to make decisions based on financial information or cost savings, but now our clinicians are making those decisions based on saving hospitals money.

But our patients are being asked to take this drug, I suspect without, as Dr. Krist said, I suspect without a lot of informed consent about what the potential downsides are. Everyone has acknowledged that it's really for those patients who are going to have a problem. But since we don't know who they are, all the patients have to take it. That's when you get into trouble later on, retrospectively, if you do discover

the signal is real, that you have mud on your face or egg on your face, however you want to say it. So I have a concern.

DR. BUCHMAN: I had some concern as well in terms of the long-term data. I don't think we can ignore the long-term data, because if we look at corticosteroids, for example, well, you say seven days' worth of corticosteroids, there's no increased risk of bone fractures, but with cumulative use, there certainly is. And it's the cumulative dose of corticosteroids that have the greatest effect on the risk of fracture.

So if we look at the long-term data, the cumulative dose that those patients have at a very small dose, but for a long period of time, is very similar to the much larger dose used for a very short period of time. And indeed, it may be -- we don't know this, but it may be the cumulative dose is what's most important. Because many of these patients that have an operation will be

re-operated on in the future, and do they get the medication again or are they allowed it once in a lifetime?

If we look at a Crohn's patient, for example, within five years of having a strictureplasty, they've got a 40 percent risk of being back in an operation again. Patients who -- an ideal obviously with IBD patients, but patients who have had an IPAA, within five years have a greater than 50 percent chance of being in an operation again because of a bowel obstruction from adhesions. And do they then get this medication again? Patients who have had 30 abdominal surgeries, they get 30 weeks of this medication, that may prove to be a significant risk. We don't have the information on that, obviously.

Dr. Pasricha?

DR. PASRICHA: I think everybody on this panel has some degree of concern about the cardiovascular risks. The question is what do

we do about them? And we have three options: We either don't let this drug come on the market or we do prospective trials, which you've already heard are going to require tens of thousands of patients and probably not answer the question; or we put in place a very strict risk management surveillance program, which are really the three options that we have here. I think a priori, we cannot necessarily come to any conclusion about how severe the risk is going to be based on the data we have.

DR. BUCHMAN: Dr. Rosing?

DR. ROSING: Yes. As a cardiologist, I would come at this with a little different approach.

First of all, I don't think there's any evidence in the short-term study that there was any cardiovascular risk at all. And even though there's a question -- Dr. Hennessy raised the question of arrhythmias, this was a blinded study and there were no arrhythmias. And just as

Dr. Lincoff couldn't think of any mechanisms to cause long-term myocardial infarction, I can't think of any reason once they're off the drug that these people should be having arrhythmias from a drug that's given over a very short period of time. So we're really talking about this concern about cardiovascular problems on the basis of this 014 study, which seems to me to have a lot of problems associated with it and doesn't make a whole lot of sense from a cardiology standpoint.

You raised the question, Dr. Buchman, of the cumulative effect, but even that breaks down, because once you get out beyond 60 or 70 days, there was no cumulative effect. That curve was perfectly flat. So it seems to be an isolated effect in a very brief period of time. There is probably -- and it doesn't even reach statistical significance apparently.

I think there's information we

don't have. I brought up the question of other drugs, but I didn't bring the question up a second time because I was convinced that the problem is not the seven or the nine events. The problem is the zero events, that if you take a patient population with these risk factors, including age, which the average age was in the sixties, you'd be very surprised over the course of a year, with an intervention such as surgery and other stresses, that you wouldn't come up with at least one or two or more events.

So as a cardiologist, I think I'd be less concerned and be willing to accept the short term use of this drug.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I still feel the same way I felt before when I had my little rant. And I disagree some, in the sense that, to me, what's different here is that it's not that it's questionable as to whether there's risks long term and beyond 14 days. I'll take it a step

further than what Dr. Kramer said. We need to look at it past 14 days. There's no systematic data collection beyond the short term use of the medicine.

And even building on some of what Jay said, I am concerned about, well, what would it take to evaluate this? But if you look at the Study 014, to at least see this blip, it didn't take that many people to see the blip. Now, it's not enough people to reach statistical significance, but it's enough to raise safety concerns, which I think is different than looking at an efficacy outcome.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: So I guess our role here is really to focus on the cardiovascular, "our" being the cardiologists. And I'm trying to put that in the context of what I would expect from other therapies and be concerned about.

I really do think there is a difference between long- and short-term

therapy. Cumulative effects have impact with some types of therapies, and corticosteroids are obviously an example of that, because the effect on bone may be cumulative.

But if we think about mechanisms of ischemic cardiovascular events, it's either progression of atherosclerosis, plaque instability, thrombosis, vasoconstriction. And it's hard to postulate how a short-term therapy would lead to a long-term risk.

Now, that only goes so far. Obviously, theory and pathophysiology are important up to a point, but in the end, you have to go by what your empiric data is. And so what we have here is empirically not a hint of any signal in short term, albeit with incomplete follow-up, but for what we have, no imbalance, virtually no events in this short-term follow-up.

And in long-term follow-up, in a study that was one-third of the total patients tested for this OBD indication,

albeit the longest study, one-third of the patients showing what appeared to be a numeric excess ended up being seven events.

Those events, that excess, if it existed -- because it didn't in the adjudicated, although that's with mixing of the MI being mixed with less severe unstable angina, et cetera. So if we just say we're going to talk about MI and we're not going to care about the others, even though they're mechanistically similar so you would have expected them all to trend in the same direction, but if you say we're just going to talk about MI, then what we're talking about is in the first three to four months of this large study, this study with one-third of all the patients in the OBD, you had these excess events.

In two-thirds of the patients in the other studies whose follow-up range from one to three months, that same period, that three to four months, you didn't see any

excess. In fact, there was almost a countervailing less -- numerically less than the active drug arm.

So it's not to say it isn't real. The reality is we don't know what we would see if we duplicated this 14. But it's not a strong signal. It's a signal that gives us a lot of question of stability with one or two events in either direction, with one or two extra events in the placebo group that one would have expected based upon the patient population. And so it's a very weak piece of evidence. And it's a piece of evidence that I'd have trouble hanging my hat on even for an approval of a long-term indication.

But certainly to then go back and say I've got a very short-term indication for which we have no signal at all and we can't mechanistically calculate -- or we can't mechanistically postulate why there should be, I have a lot of trouble.

So the long and short is, for the

short-term indication that we're talking about, even though the dose is much higher, of course, I don't have a concern for cardiovascular risk.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I'd like to shift the conversation to something that Dr. Pasricha raised, which is what are we to do about this? I mean, we can talk all afternoon, and part of the reason we're talking so much is because there's a lot of missing information, and you can only go so far with mechanistic discussions. But the question is what are our options?

I think there are a couple of options that maybe you didn't list that -- I didn't see in the plans outlined by the sponsor, if this drug were to be approved, any suggestion that there even be a registry of all patients that are taking this drug with follow-up, or that there be any observational studies in large health plan databases or any -- you know, as this drug is

on the market, if we just depend on passive reporting, we're going to be in the same situation we're in right now in the future, which is we will not have any information to add to the database. So I'm disappointed that there isn't some plan to actively solicit cardiovascular safety in the long term, and I'd like to see that laid out, I would suggest.

DR. BUCHMAN: Dr. Proschan, did you have a comment?

MR. PROSCHAN: I didn't have my hand up, but now that you called on me, I will say something.

DR. BUCHMAN: You stuck your light on.

MR. PROSCHAN: And that is that I think the argument that there are not enough placebo events, exactly the same argument was made in the cardiac arrhythmia suppression trial. It's not that these drugs are killing people. It's those -- you know, placebo patients aren't dying enough.

So I think that often happens in clinical trials, that the placebo event rate is lower than you thought it would be.

DR. BUCHMAN: I think that was worth including you.

We're going to move on. Oh, was there one other? Dr. Epstein?

DR. EPSTEIN: Yes, I just wanted to say that the three things that were asked, the cardiovascular events, I agree there was no signal in the short-term study. And to be able to do a follow-on study, that just statistically based on the numbers, even that you saw in the long-term OBDs, would be very impractical.

And I've often heard about these registries and things at various panel meetings, but that's a huge thing to require for something with a very small signal. So I don't necessarily follow along with that.

And again, the other thing we were asked is neoplastic. I agree with everyone else that there was a very scattered signal,

and again, not short term.

And the bone fractures, I don't know, was the floor more slippery in those -- no. But that didn't seem to have any real signal. So I don't see anything in the pooled data on the short-term studies that would indicate that there's any particular concern, particularly in regards to the cardiovascular.

DR. BUCHMAN: We're going to move on.

Dr. Pasricha, last point and then we're going to move on.

DR. PASRICHA: No, no, just for the record, I want to clarify. On the bone fractures thing, I think that was the only signal that was actually statistically significant, wasn't it? That is the only one with a 95 percent confidence interval that did not cross -- so actually, I think as far as the long-term data is concerned that is -- if I remember correctly, that is the most robust signal that we had amongst the three. I just

don't think it translates into a seven-day course of medication.

But I want to make sure that we have the record straight on that. Is that correct?

DR. KORVICK: Can you repeat your question?

DR. PASRICHA: The clarification was whether the fracture risk was statistically significant. If I recall from Dr. Dannis' presentation, it was. I just want to make sure we have that on the record.

DR. BUCHMAN: I think the lower was .99, which was still -- is my memory correct. that it actually kind of approached 0 as well?

MS. CASTILLO: This is Sonia Castillo, FDA. For Study 014, it was significant. For the non-cancer and cancer population combined, it was not. Let's see, for the combined cancer and non-cancer population, confidence interval, 95 percent, for the relative risk was .6 to 2.3. And for the Study 014, confidence interval was

1.1 to 10.4.

DR. BUCHMAN: Dr. Hennessy?

MR. HENNESSY: A very quick comment. I think that the way to address a safety signal is to do a study, even if it's difficult. Saying that we wouldn't require one because it's difficult essentially says that we're dismissing the safety concern. I'm uncomfortable doing that, particularly for a drug that is not life-saving, but is dollar-saving.

DR. BUCHMAN: We're going to move on to --

DR. KORVICK: We would be interested if the chair would be willing to ask the members to vote on the first bullet of whether or not they think that there is an issue for the short term use for cardiovascular.

DR. BUCHMAN: Absolutely. We can do that as an official vote. So let's do that now, and I'm going to read the question.

Based on currently available data, do you have concerns for the use of alvimopan

12-milligram capsules in the short term, that is seven days or 15 doses, for patients following partial large or small bowel resection surgery with primary anastomosis with regard to the cardiovascular events, neoplastic events, and/or bone fractures?

Just the cardiovascular?

DR. KORVICK: Please.

DR. BUCHMAN: Did you want three separate votes or no?

DR. KORVICK: I think we've got a lot of input on the other, but the first one seems to be an issue.

DR. BUCHMAN: So just for cardiovascular events. Can I have a show of hands for all those that do have concern with the cardiovascular risk profile?

Please keep your hands up and state your name and then you can put it down.

Dr. Krist, do you want to start?

DR. KRIST: Krist, yes.

MR. PROSCHAN: Proschan, yes.

DR. PASRICHA: Pasricha, yes.

DR. RICHARDSON: Richardson, yes.

DR. CHANG: Chang, yes.

DR. KRAMER: Kramer, yes.

DR. BUCHMAN: Buchman, yes.

MR. HENNESSY: Hennessy, yes.

DR. BUCHMAN: All those that vote no? Keep your hand up until you say your name and your vote's recorded.

We'll start over here, Dr. Talamini.

DR. TALAMINI: Talamini, no.

DR. EPSTEIN: Epstein, no.

DR. LINCOFF: Lincoff, no.

DR. LEVINE: Levine, no.

DR. CULLEN: Cullen, no.

DR. ROSING: Rosing, no.

DR. BUCHMAN: Any abstentions?

MS. CORKERY-DeLUCA: DeLuca, abstained.

DR. BUCHMAN: The state of Florida is calculating the vote.

MS. PHAN: We have eight yes, six no, and one abstain.

DR. BUCHMAN: We're going to move on to Question No. 4, which is a voting question.

Do we want to take a break? We need a potty break, I guess.

Okay, let's take a break. I forgot about that. I was so excited about how we were moving along here. So let's take a 15-minute break -- actually 13 minutes. If everybody could be back here at 3:15 sharp, we'll move on to Question No. 4.

(Recess)

DR. BUCHMAN: If I could have everybody's attention, please. There is one comment that I want to clarify for the press.

First off, I am going to give a brief chair summary of each of the questions at the end of today. But for those from the press that want to scram and not wait to see if I have a surprise up my sleeve, in regard to the vote that we had on Question No. 3, it

was not originally designed to be a voting question. We changed that. But what we voted on, as a committee, was only whether we had concern about the cardiovascular risk effects. We did not vote on whether we had concern about neoplastic events or bone fractures, although obviously those were discussed.

We're going to move on to Question No. 4, which is a voting question. Do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients with partial large or small bowel resections with primary anastomosis?

I'm going to start, actually, on this side with Dr. Talamini, what comments you have.

DR. TALAMINI: I want to just speak for a moment to the potential benefits of a strategy like this. Certainly the economic argument is there, and it's easiest to fall into

and look to the economic argument because it's easily quantified. But as a surgeon, I would also say that lying in a hospital bed for 12 or 24 additional hours with a bloated belly and not eating is not a healthy condition. It's much harder to quantify what is not healthy about that and measure it.

But I think most of us who take care of patients on a daily basis know empirically that that is not a healthy thing, and that if you reduce that by some percentage, you're improving the patient's overall care. So I just wanted to get away from this idea that the only thing sitting on the benefit side is economic. I don't believe that that's true.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: As a treating clinician who deals with a lot of patients with ileus, it is a very unpleasant condition. And if you can shorten that, I think, for the patient's benefit, you've really made a great improvement

in their overall outcome of health. And whether it's 12 hours or 24 hours, that's very significant.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I agree with that, and I want to emphasize that -- although we brought up the financial issues, I don't think that that's the key here at all. I mean, what we do in medicine is to make people live longer or to prevent unpleasant things in terms of make them feel better, and this is the latter, and I think it's very real.

DR. BUCHMAN: Dr. Hennessy?

MR. HENNESSY: While I'll agree that there is a clinical benefit to the patient rather than just to the hospital, and I'll admit that I don't see patients, it seems to me from looking at the numbers that the benefit can be characterized as modest or even marginal. And this is a drug that clearly doesn't save lives, and for which there's a significant signal of a cardiovascular risk from a randomized trial.

And in my mind, the benefit does not outweigh the risk while that concern has not been addressed.

DR. BUCHMAN: I would echo Dr. Hennessy's comments in that we're looking at a benign condition. And clearly, I think the drug, as we discussed earlier in this session, does have some efficacy and has physiologic effect. It's not very great, but it is statistically and perhaps marginally clinically significant.

We're asked to make a risk-benefit analysis here. We're dealing with a benign condition with fairly marginal but clinically significant effects of a drug. So therefore, it really can't tolerate any potential for significant side effects. And my concern is that the denominator, that is the risk potential, not necessarily the risk, but the risk potential, does at a minimum slightly outweigh the potential benefit for the patients.

Dr. Kramer?

DR. KRAMER: I would love to see a study that compared the effects of this drug in PCA-controlled analgesia after a bowel resection to an alternative pathway that was a postop pathway that involved opioid-sparing techniques, such as what occurred in the European study. I don't think we've demonstrated that this should be -- have a blanket indication for bowel resection surgery; I think it should -- as I've said many times before, bowel resection surgery in the setting of PCA. And I echo the comments of Dr. Buchman and Hennessy. I would not say yes to this question based on my concerns about risk, and the fact that it has been studied only in the setting of PCA.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: I think this is a really tough question, but when I brought the cost effective, that was just one example of measuring clinical meaningfulness. I mean, I take care of -- it's all about how they feel.

It's not really about that much more. But so I obviously think that's very important.

I think this is tough because I do have concerns, but I feel that the signal really is more in the long-term data, and it's a different patient population. So I would feel more comfortable if there was some monitoring of the patients that did get the drug. I feel very uncomfortable just giving it to anybody.

Just because you brought this up a couple times, Judith, is that there is a study on alvimopan in chronic constipation with no opioids and it didn't show efficacy, so I don't know how well it will help. And this is a different patient population, even if you didn't give opioids after a surgery, but I'm not sure how efficacious the drug would be if you're not on an opioid.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: I guess I'm troubled, as everyone else seems to be. Clearly, there

are some benefits to the various parties that are involved in this. The sponsor, obviously. The hospitals I think certainly can benefit from this. I think if you look at the patients, though, I think that benefit is much more difficult to describe.

I was quite taken by the effects of this with respect to use of PCA or not. I'm particularly interested in the effects of ketorolac in this group. Unfortunately, I don't see anybody who is a generic maker of ketorolac out there promoting that drug for this indication, so that I don't think we'll ever see that type of study find the light of day.

I'm also troubled by the fact that the number needed to treat -- if you combine the GI-2 and GI-3, which I think realistically, one probably should do because I don't see that there's a great deal of difference in those criteria, it seems to me that the number needed to treat is probably

around 10 patients to see one patient benefit. In medical oncology, at least, a 10 percent response rate would be regarded as a failure. And I don't see that the overall benefits are adequate for the patients.

I'm also troubled by the fact that the RiskMAP doesn't include any sort of input from the patients in this, but we'll wait until we get to that.

DR. BUCHMAN: Ms. Corkery-DeLuca?

MS. CORKERY-DELUCA: JoEllen DeLuca. As a patient that's had a lot of bowel surgery, I'll tell you, every day out of the hospital is a good day. And I protest mightily when I have to go in. And if I'm your patient and you're going to be doing an NG tube, you're going to be in for the fight of your life.

I didn't feel that the cardiovascular events -- to me, the GSK seemed to be more of a risk than the Entereg. The bone fractures, when you start picking up with age, when we start looking at people

being age 65 and up, that to me was what made me say I think I should abstain.

Because I am a patient, I don't know enough, but bone fractures are something that -- you're lying down, you're hitting 65, you're hitting 70, you're hitting 75, and I think that you're going to be much more likely to stand up and fall and injure yourself that way than perhaps even a cardiovascular event.

The overall benefits, even reading between the lines I think that some of the questions have been answered. And looking back towards an answer, at least in my mind, looking back toward how hospitals will handle this, I'm still not sure when gut surgery moves from doing one large bowel resection to another for another comorbidity factor, whether we're -- who's going to handle that.

But as a patient, I think sometimes we have to make strides when we can make strides. And the overall risk, to me, made

me say maybe this is a time when we should make a stride with a drug that is looking small and then -- even if we have to revisit it later. I mean, there is not anything else like this.

And I'm not just looking from my hospital's bottom line. They don't need another 12 hours. And I've been in the hospital for a weekend because the surgeon didn't make it. He had too many things to do and didn't make it on Friday before closing time and the nurses were gone, so I had to stay until Monday. So I think we can argue the 12 hours or the 24 hours, but the reality is, it's who -- which of the nurses got the paperwork ready or not. So I think the 12 hours or the 24 is sufficient for most general purposes. And my hospital is fairly large, so it's not a matter of just being a little community hospital.

So that's how I would feel. I think that the risk for a patient, that a lot

of us that have been in the hospital a lot for bowel resections, would say it's worth it.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: I'm more on the fence than ever, but I would say that, no question about it, as Dr. Hennessy and others point out, the hard data is marginal, modest, whatever you want to call it. It's not very, very significant. Again, I'm unimpressed, or relatively unimpressed, that there's a dose response data shown that's very significant between 6 milligrams and 12 milligrams.

On the other hand, there's no question, not only for the patient, but for the physician and everyone else, it is a big difference in seeing patients like this, if they can get that tube out in 12 hours or 24 hours. And the patients feel better, it's important, and I think we're going to have to have very strict risk management control here, but I definitely feel that probably the

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patient outweighs it here than just the cost-effectiveness. And I think for the patient's sake, I would probably agree that the benefits marginally overcome the negatives.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I'd like to start by reinforcing the concept that while the discussion may have been a little heavy on the health care costs of this drug, I don't think that's what's driving the decision. I want to make sure that at least that's on the record.

Dr. Buchman, you mentioned that this is not a life-threatening condition, and that is true. But as somebody who's made a career of looking after patients who have chronic nausea, I can tell you next to dying, nausea is probably the most bothersome symptom that patients have. And if you can make a difference in that, it's a big advance.

So I would just like to say that,

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and in that context, I actually was a little struck that the sponsor has not gone beyond some very simple measures and not, for instance, included any surrogate measures of quality of life or global sense of helping in their outcome. And I just -- maybe this is the time to ask them whether they have any data that actually looks beyond the objective points, such as we saw with GI-2. But also got a global sense from the patients if they had any questions that might actually reinforce what we're saying here.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I agree with the comments that this is -- as far as the potential harm, I mean, this is no slam dunk. I am persuaded that the signal is real for OBD. Even that's not a slam dunk, but I am persuaded that that's real. I don't see a reason to throw out 014. And so I'm more persuaded than not that that's real.

Now, the question then becomes is

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POI -- is that similar? And the answer to that is I just don't know. And that's what bothers me is maybe that's right. Maybe you have to be on this drug long term to feel any harm, to have any problems. But I just don't know that and I don't have strong evidence that that's the case. I have some suggestion that that's the case, but I don't have strong evidence.

So for me, the benefit of reducing by one day versus the potential for an MI or something else is enough.

Maybe I'm just a 'fraidy cat, but that's enough to make me think, no, I wouldn't. I think the risks outweigh the benefit.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I'll echo what some of the others have said. And the way I think about it with this question, we're asked to do a benefit-to-risk analysis. And I think, if you look on one level, quality of life-type

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measures, clearly having a postoperative ileus, having increased nausea and vomiting, having an NG tube, are significant things.

And I think we've seen relatively clear data suggesting that this medication reduces those risks.

And we do see decreased nausea and vomiting, in a sense, when you look at the adverse events. And people are more likely to stop placebo than the intervention drug because of nausea and vomiting. And then if you look at quality of life risks, like how people feel and those types of side effects, this medicine seems beneficial.

Where I get lost is looking at major morbidity and mortality. And as Dr. Hennessy has pointed out, in the studies, we don't see reduction in mortality from the medication. We don't see reduction of thromboembolic disease or nosocomial infection, and those significant things. It could happen from a reduced hospital stay,

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and that's where I think there's benefit. But we don't see that in our studies. We don't even see a signal of that. And to me, the significant morbidity/mortality risks is a black box and we can't answer that. And because it's a black box, that makes me more afraid overall about the benefit-to-risk ratio.

DR. BUCHMAN: Dr. Cullen?

DR. CULLEN: As a surgeon, what a patient complains about, there's really basically three things postoperatively they complain about: pain, which you can take care with a PCA or something else; an NG tube, if they have one, which is a miserable experience, and their study shows that it reduces the incidence of reinsertion; and then the distention, they're not feeling very good because they're distended, nausea, and vomiting. And the study demonstrates that it's efficacious in that respect. So I think the benefits of the medication are there.

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The stress of surgery is -- it's not like running a marathon, but it is a stressful situation on the cardiovascular system and the pulmonary system. So you're adding a medication to this already stressful system and you're not seeing an increased risk of cardiac events. So in the short term, I understand everybody's concerns, but I don't see the increased risk.

And then finally, my concern with this drug is if it was approved in a hospital, that my orthopedic surgery colleagues would use it and my vascular surgery colleagues would use it, and anybody who had anything done would use it, where it wasn't -- the studies didn't show an efficacy in those type of operations. And that's a concern I have in the back of my mind.

But those other two things I mentioned, unless you've been a patient sitting in a hospital with an NG tube, you don't know how miserable that is.

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DR. BUCHMAN: So it looks like the surgeons and gastroenterologists are going to have to duke it out in the parking garage after the meeting.

Dr. Rosing, as a cardiologist, what are your feelings in terms of the risk-benefit analysis here?

DR. ROSING: I think the gastroenterologists are also going to have to battle the cardiologists, along with the surgeons. I've heard from the patient advocate, I've heard from some of the gastroenterologists, and certainly both of the surgeons. I've read the data and I think there is some benefit that arrives from this drug beyond the economic benefits. And I really don't see any risk from the short-term studies at all. I do respect some of my colleagues' concerns, though, and I think it would be reasonable to ask the sponsor to implement some form of long-term monitoring for this drug.

DR. BUCHMAN: I would just add one

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last comment before we come to a vote. There was an interesting paper a couple of years ago that looked at all the drugs ever approved by the FDA. And as I recall, not the difference between the effect of placebo and study drug, but the benefit over placebo was actually only 20 percent. But if we look at NG tube reinsertion in this study, the difference was -- sure, the difference was 43 percent, but the real difference was 11 percent versus 6 percent.

Let's put it in perspective. We're looking at small numbers in terms of risk. We're looking at small numbers in terms of benefit.

So with that, I'm going to ask are there any other comments from the committee, any rebuttals or re-rebuttals?

Dr. Epstein?

DR. EPSTEIN: Just one comment. I'd like to point out we've heard about ketorolac as a opioid-sparing drug. And as a

gastroenterologist, if you want to talk about risk, start putting a lot of people on ketorolac and you'll see a lot of risk.

DR. BUCHMAN: Don't tell people that. That's how we make money.

DR. EPSTEIN: And the other thing is, just in terms of cardiac -- we've heard from Duke, we've heard the adjudicated data, we've heard from our cardiologists, we've seen no signal in any of the combined short-term studies. We're dealing with the fact that the placebo happened to have a zero number, and so we're dealing with a little bit of the tyranny of small numbers here. And I think it's a leap of faith to think that there's a big cardiac risk in the short term. That's just my opinion, based on the global cumulative data that we've heard today.

DR. BUCHMAN: I'm going to go ahead and read the question and then we're going to go for our vote.

The question again from the agency

is, do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients following small or large bowel resections with primary anastomosis?

All of those that feel that the benefit outweighs the risk, please raise your hand, and keep them up until you state your name.

Let's start over here with Dr. Rosing.

DR. ROSING: Rosing, yes.

DR. CULLEN: Cullen, yes.

DR. PASRICHA: Pasricha, yes.

DR. LEVINE: Levine, yes.

MS. CORKERY-DELUCA: DeLuca, yes.

DR. CHANG: Chang, yes.

DR. LINCOFF: Lincoff, yes.

DR. EPSTEIN: Epstein, yes.

DR. TALAMINI: Talamini, yes.

DR. BUCHMAN: All those that vote no, state your name.

MR. HENNESSY: Hennessy, no.

DR. BUCHMAN: Buchman, no.

DR. KRAMER: Kramer, no.

DR. RICHARDSON: Richardson, no.

MR. PROSCHAN: Proschan, no.

DR. KRIST: Krist, no.

MS. PHAN: We have nine yes and six no, no abstain.

DR. BUCHMAN: We're going to move on to Question No. 5, which is also a voting question. If alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks?

Explain what features of the proposal would be most desirable.

Dr. Rosing, let's start with you.

DR. ROSING: I think we can refocus on the questions that have been raised about the long-term effects, even though it's short term use of this drug. And I think that the features of the proposal that are not adequate would be

that I think there should be some form of long-term monitoring for the three signals that were identified in Study 014, namely cardiovascular complications, fractures, and neoplasia.

DR. BUCHMAN: Dr. Cullen?

DR. CULLEN: I agree with Dr. Rosing. I think specifically the cardiovascular effect should be monitored long term.

DR. BUCHMAN: And Dr. Proschan? All right, Dr. Krist, I'm sorry I forgot you.

DR. KRIST: I don't think that the risk management plan is adequate. We have a big black box on long-term safety, and the plan doesn't do anything to address that.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I don't have a good sense of whether it would be adequate or not, so I really don't know.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I'd like to see a surveillance program for cardiovascular risk.

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And secondly, I'd like to make sure that as far as possible, we've put restriction on off-label use for now. And that means perhaps more narrowly define the target population that this is really indicated.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: I definitely agree with the latter point. I also feel that there should be a much stricter approach in our past meetings with an already approved drug disparity. We noted that we used the touch phone. I think something in that line is really necessary for follow-up here. I think we have to be -- it would answer the question for short term and otherwise if we had a very strong type of risk management program, which we didn't hear from yet -- about from the sponsor.

DR. BUCHMAN: Ms. Corkery-DeLuca?

MS. CORKERY-DELUCA: I'm JoEllen DeLuca. For the long-term risk, I would like to see something more done about that. I think we owe it to the people who look for what the FDA

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approves and not approves to say that there are risk factors. And for me, particularly, the cardio and the osteo.

And I didn't know, how can we monitor this? I don't know that. But that is a question for me. And the off-label use, it goes back again to my question about letting the horse out of the barn. If it goes then to bariatric or if it goes to then to another use entirely that we're not discussing today, who does that? Who is going to monitor that? I don't know.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: I think we need to provide patients with a little more information on this. The RiskMAP talked about getting some sort of verbal consent from patients as they're being wheeled into the OR, and I don't think that's adequate. I think people have to have some written information that they can digest, say 24 hours before their procedure. I think the idea of having some health care provider

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walk up to them when 10 other people are asking them to initial the site of their operation in the preop area and -- oh, by the way, we want to give you this drug. We're a little uncertain about the cardiac risks on this, but trust us and everything will be all right -- I don't think that's an adequate way of addressing that. I think patients have to have more information and some input into this decision.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: There's parts of this that I like, that it is restricted to bowel resection and they're making sure it's only for hospitals. I think that they've put some things in here that are very good. I guess I'll have to think about the emergency surgeries. Sometimes you can't always give the patient all that information or they really don't care. But I do think that not only just looking at long-term monitoring, I think they should look at some predictors if someone comes in, like baseline characteristics of age or gender or

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cardiovascular risk factors, and cancer or not cancer.

I think there are some things that may -- information they can get to figure out who may have the greater benefit over risk than others.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I think the proposed risk management program is predicated on process measures of assuring that it only be used in the inpatient setting and not outpatient. I agree with the comments that have been made that I think we need to go beyond that and look at clinical endpoints. As I've said many times, I believe the indication should be specified that it be given in the context of opioid PCA.

And I agree with the comments about trying to more carefully prevent off-label use. I'm concerned that once this is available, that anybody doing surgery where they think there's a chance of ileus might prescribe it, and therefore, increasing the

population potentially at risk.

I agree with the idea of trying to get consent. I realize this is challenging, but I think that patients should be informed. And I was concerned -- I heard a presentation recently within the last year by a wholesaler about what the impact of all these various risk management programs is having on their ability to function. They're an industry, I've learned from this presentation, that operates in a very slim margin of ability to manage, and really, the main brunt of this program is put on the wholesalers. So I agree with the FDA's comments that it really shouldn't be the wholesaler trying to sort out who gets this drug, and that the sponsor should take on some of that cost and responsibility.

DR. BUCHMAN: Quite frankly, I think that the RiskMAP proposed by the company was done haphazardly, and it looks like very little time was really put into it. It's very, very

short on specifics. Now, that can all easily be corrected, but I am quite surprised that we've come to the point of having a meeting here. You've had this drug under development for seven years. You've known about these risks, at least since last November, that you didn't come up with a more specific plan other than, well, wholesalers will going to control this. The Pittsburgh Pirates are not going to finish in last place next year because they're going to play better. You really need to have more specifics. You need to define things. "Acute care hospital" was mentioned only once. Otherwise, it's always "hospital." Hospital has various definitions, even including veterinary hospitals.

So I think you need to supply definitions. You need to have an algorithm, a framework of exactly how this is going to work, what are your check and balance systems? I mean, really, I mean, you guys can do a better job at this, putting this

together than we can as physicians, and I'm just disappointed in what I saw.

MR. HENNESSY: Sean Hennessy. I think that this drug needs additional study to characterize its cardiovascular risks. I'm not convinced that it needs a risk management action plan. Reading from Dr. Weaver's Slide 8, when should a RiskMAP be considered? When the risks are serious and preventable. When safe and effective use calls for specialized health care skills or settings. When a RiskMAP encourages appropriate use increase benefits relative to risks. Products in a class of product with similar risks that require a RiskMAP. I don't think any of those criteria apply to this drug.

The drug is going to be used in lots of patients, more so than can probably be accommodated by the more stringent risk management action plans that we've seen, like clozapine and patient registries to prevent pregnancies. So in my view, the risks need to be characterized in the context of one of

more epidemiologic studies, but they aren't typically part of risk management action plans. And I don't think that a risk management action plan will be effective for reducing the risks unless there are particular patient populations who can be identified who have better or worse risk-benefit balances. And in the absence of a benefit of the RiskMAP, then it's just added cost and added inconvenience.

DR. BUCHMAN: I just want to clarify my response. The RiskMAP here primarily, as I see it, is towards prevention of off-label use, because the concern here was in the long-term patients, again, the chronic opiate users. And there needs to be a clear way in which -- because it's very difficult to regulate off-label use for anything. And this is going to have to be a better attempt to keep it out of the hands of the narcotic addicts, those on methadone, patients in nursing homes, and all these sorts of thing. So I just wanted to

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clarify my remark.
Dr. Lincoff?
DR. LINCOFF: I think we need to be realistic about the prospects of useful data from follow-up long-term epidemiologic studies. Such studies are notoriously limited in their ability to look at treatment effects, and we've got to be realistic. If we force a 10,000-patient registry of the next 10,000 patients on-label to get this drug, and we see and event rate, we're going to have an event rate. And we're going to have no idea if that event rate is higher than it would be if patients didn't get the drug.
And we're not going to be able to look at risk factors for treatment effect. We're going to be able to look at risk factors for cardiovascular events, but we've got better registries in existence right now to do that. So if there's really that much concern about what the long-term cardiovascular events are as a consequence of

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giving these drugs, then the drug shouldn't be approved.
I personally don't believe that. But I also don't believe that the resources should be diverted toward elaborate registries and epidemiologic studies that aren't going to test causation. You can't test causation with observational studies, and that's really what we want to know. So I think efforts should be directed instead toward, as several people have said, trying to make this drug used only as the label does describe.
And I, too, am a physician, not a pharmacist or a manufacturer who can best design those systems, but I suspect they probably can be designed, especially since we are trying to make a wall between outpatient and inpatient, which seems to me to be a relatively discrete setting that's easier than some of the more difficult drugs.
As for consent, I think consent is

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important up to a point, but realize, we use a lot of drugs without much in the way of consent that carry much more in the way of danger -- drugs for atrial fibrillation and some antibiotics, et cetera.
Hospitals institute programs with their pharmacies to require approval of specialists, et cetera, before it's given. But in reality, there are a lot of drugs that have much more evidence of danger that we use without elaborate methods of consent, et cetera. So I think the main issue should be to try to assure that these drugs are used within the label.
DR. BUCHMAN: Dr. Epstein?
DR. EPSTEIN: I basically second what Dr. Lincoff said. We have a very large number of trial patients in the pooled data set from the short term, and there was no increased cardiovascular signal, and that is the intended use. I think that the RiskMAP should include an order that states -- basically from the

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physician that states simply, for use in a patient undergoing bowel resection, to limit it.
I think the biggest concern would be, as mentioned by Dr. Cullen, that the orthopedist or some other surgeons might want to use the drug off-label. So I think that's where we should focus the RiskMAP specifically.
DR. BUCHMAN: Dr. Talamini?
DR. TALAMINI: I would make a couple of points. I would say the risk management plan is not adequate because it's currently just an outline. And I would encourage the FDA to predicate approval on that being filled out to their satisfaction.
Having said that, I think the consent issue would be extremely difficult, for the same reasons that Dr. Lincoff already outlined. I've got a hunch that the preoperative antibiotics that we give are probably more dangerous than this drug, and we just don't have the means to ask consent

for every single drug that we give during surgery.

I also know that the story of post-approval studies is not an encouraging one. So my suggestion would be to be very focused there. And from a point of ignorance, I might suggest looking into the NSQIP database, which is becoming ever bigger and more robust, as a potential means to try to answer this question post-approval, if it's approved.

DR. BUCHMAN: Dr. Kramer, you wanted to clarify your comment?

DR. KRAMER: Dr. Hennessy's comments made me realize I did want to clarify what I was at least suggesting. I'm personally seeing the RiskMAP as a method of limiting the use until we have more information. And I would actually agree that post-approval epidemiologic studies, while not addressing causation, can identify safety signals. And I think that in an era where we're starting to put together distributed

safety networks, in the order of being able to accumulate 50 million patient lives to look at things, we have several pilot programs going on right now across multiple collaborative centers in this country, and I think we can get information with a control group to try to understand some of these safety signals. And I don't think we should be ostriches just because it's challenging. If there's any concern, we should look. And if it's no concern, then it's a waste of money, but --

DR. BUCHMAN: Okay, Dr. Korvick?

DR. KRIST: I just wanted to --

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I just wanted to quickly clarify my answer, too. That's the drawback of going very early on in this. I mean, I agree with both of these comments. I don't think a RiskMAP is going to address this and we need more research. I do worry -- and I wasn't going to say anything until you started talking, Dr. Kramer, I mean, I do worry about response

for follow-up for a short term use drug. I can see just methodologically that people are going to have low incentive to respond to having used the drug for five days. So I mean, it depends on the methodology used, if you use an existing database or something. But that's some of the fear that I have with some post-surveillance trying to figure this out -- or post-approval trying to figure it out.

DR. BUCHMAN: Dr. Korvick, with your permission, I'm going to split this into two different votes, with two different questions. The first question being, is a RiskMAP necessary? And the second question being, whether the RiskMAP proposed by the Adolor Corporation is adequate.

Is the agency in agreement with that, or would you just like the single vote as originally planned?

MR. PROSCHAN: Didn't we already vote?

DR. BUCHMAN: No, that was in another life.

DR. KORVICK: I think we'd prefer to go with the way that it's written.

DR. BUCHMAN: You heard the commander in chief. We're going to go with one single vote. And so that means that you're voting at the same time as to, A, if you think a risk management plan is necessary; and also whether you think the risk management plan as proposed is adequate.

So all those in favor that the risk management plan is necessary, and as proposed is adequate, please raise your hand.

DR. EPSTEIN: Point of order.

DR. BUCHMAN: Okay, go ahead.

DR. EPSTEIN: I'm sorry, Mr. Chairman, can you read the question as written? Because I'm confused about "is necessary" or "adequate."

DR. BUCHMAN: I'm going to reread the question then and just going to delete the last sentence. So if alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is

adequate to address the potential risk?
So we're not voting on whether you think they need to have a plan, you're voting on whether you think the plan that they have proposed is adequate, just so that everybody understands that. Okay?
DR. KORVICK: That's correct.
DR. BUCHMAN: So all those who think it's adequate, please raise your hand, for a yes vote.
All those that think it's inadequate, for a no vote, please raise your hands.
Please state your name.
Dr. Talamini, why don't you start?
DR. TALAMINI: Talamini, no.
DR. EPSTEIN: Epstein, no.
DR. LINCOFF: Lincoff, no.
MR. HENNESSY: Hennessy, no.
DR. BUCHMAN: Buchman, no.
DR. KRAMER: Kramer, no.
DR. CHANG: Chang, no.

DR. RICHARDSON: Richardson, no.
MS. CORKERY-DELUCA: DeLuca, no.
DR. LEVINE: Levine, no.
DR. PASRICHA: Pasricha, no.
DR. KRIST: Krist, no.
DR. CULLEN: Cullen, no.
DR. ROSING: Rosing, no.
DR. BUCHMAN: All those abstaining, please raise your hand. State your name.
MR. PROSCHAN: Proschan, abstain.
DR. BUCHMAN: Are we going to announce the vote here?
MS. PHAN: We have no yes, 14 no, and 1 abstain.
DR. BUCHMAN: We're going to move on to the final question of the day. This is a non-voting question. Based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short-term and long-term clinical trials with alvimopan?
Dr. Lincoff?

DR. LINCOFF: That's easy. This is the situation we all wish we were in, is knowing the risks prospectively beforehand. I mean, I think for short-term trials as well, for any trial it's fairly clear that we want to prospectively, not passively, but actively gather cardiovascular endpoints, and cancer and fractures, but particularly cardiovascular. By accepted definitions to do that, not by adverse event reporting, but by, at routine visits, a follow-up to explicitly ask patients, and then to fill in more detail as we typically do in cardiovascular trials if a positive response, or if there are triggers to suggest that there was an event.
And for short-term studies, that that follow-up be for at least 30 days after the last administration of drug. And for long-term studies, one could argue three to six months, depending upon how long term after the last administration of drug.
DR. BUCHMAN: Are you suggesting a

formal Phase IV trial?
DR. LINCOFF: To me, Phase IV -- the definition of Phase IV varies from person to person.
Some mean it to say drugs approved, and so any trial you do from that point on is Phase IV, even if it's randomized. And if that's the case, then, yes.
But if we're talking about, for example, another indication, the OBD indication, is that Phase IV or is that Phase III? Because it's a different indication. I don't know. But I'm talking about in a randomized trial format, any trial that is ever done from this point forward. And certainly none of us have seen the data for OBD, but if one were to want to come forward with an indication for the OBD, one would probably want better data than exists already, no matter how good the efficacy signal is.
DR. BUCHMAN: Dr. Pasricha?

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DR. PASRICHA: I just wanted to clarify this because, I mean, are we talking about studies required for approval or post-approval studies? I'm not sure whether this is linked to the previous question.

DR. KORVICK: I think it's now after you've given your answers that you've given and where we find ourselves today. We've had a wide-ranging discussion on a lot of issues. So this is your opportunity for each one of you, if you feel, to register in what area you would like to see what works. So it could be short term, if you still think they need to do something. It could be longer term, as someone else said. So if you could just qualify what you mean, and we'd find any advice helpful.

DR. BUCHMAN: And Dr. Lincoff has suggested two very different mechanisms, one being a Phase IV study on this particular indication. Should this drug be approved in this particular population? And the second being, either in addition or instead of that,

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for any future trials, Phase III or Phase II, in other potential indications.

Dr. Talamini, you had a question?

DR. TALAMINI: I completely agree with that. And I'm probably on thin ice here, but I think consideration is doing -- expanding the study to a group of patients that don't have bowel resective surgery, but do require high doses of narcotics postoperatively, and see what the benefits and potential cardiovascular risks might be in that population, where there may be equal or even greater potential benefit.

MR. HENNESSY: I would recommend a large randomized trial for cardiovascular safety endpoints. That would probably be best accomplished in a group at high risk for cardiovascular outcomes, since the problem of low numbers in the denominator won't be much of an issue. Given the size of the potential market, that should take relatively little time to accumulate the number of patients.

DR. BUCHMAN: Dr. Lincoff?

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DR. LINCOFF: I'd like to add to those last two comments because I think they're excellent for several reasons. First of all, these are groups which there still remains equipoise, because we don't have data. So the problem with doing pure Phase IV in the same populations, of course, everybody says, well, I already know it works, so how can I ethically randomize to a placebo? And you could say it's on the basis of safety, but it's much harder.

But if you expand the indications to other groups for whom there is logic that the high-dose narcotics would -- there would be a benefit, you then truly have equipoise and you could be focusing, for example, on vascular surgery or elderly patients undergoing orthopedic surgery. So that would be a very good trial from the standpoint of the science, the potential indication for the company, because of expanding it, and the opportunity to prospectively -- still in a short-term study, because I don't know if

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you're ever going to pursue OBD -- but in the short-term study, gain much more data that can then be extrapolated backward in terms of cardiovascular safety.

DR. BUCHMAN: Dr. Levine? Okay, then just turn your mike off.

Ms. DeLuca?

MS. CORKERY-DELUCA: Are you saying, Dr. Lincoff, the 30-day trial that you had mentioned before, to follow up with the 30 days? What is your time limit?

DR. LINCOFF: Yeah, I was thinking 30 days after the last drug administration.

MS. CORKERY-DELUCA: Would this be paid from the cost of the drug as it enters the market? How is this going to be paid for?

DR. LINCOFF: These would be paid for by the sponsor, who stands to make a profit in the future.

MS. CORKERY-DELUCA: That's what I'm asking.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I was just saying, I'd be able to do the study you were talking about, randomizing people for the postoperative indication on the PCAs with equipoise. Because to me, there's still enough of a question that -- and I as a patient would be willing to be randomized for that. Because that's an important question that effects the overall risk-to-benefit ratio.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: Proschan. Yeah, I think the problem with doing a trial in people who are at high cardiovascular risk is that if you show that there is a problem, then that doesn't answer the question for those who aren't at high cardiovascular risk. Now, I know Dr. Lincoff believes that it will not come out that way and that may very well be true, but I'm just saying if it does come out that way, then there's still an open question for people who aren't at high cardiovascular risk, is it fine?

DR. PASRICHA: And I'll have a very

hard time getting that study approved through an RB using a drug for which a stated contraindication is high-risk cardiac already for your first approval. So I think you're going to have to structure it in a way that gets around -- assuming this is a post-approval study.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: First, I didn't know that we were going to suggest that the contraindication to the use of drug would be high cardiovascular risk, because I don't know that we've seen that. The cardiovascular risk was not a prerequisite, or did I miss it in the inclusion/exclusion criteria for entry into the trial?

But that aside, I would think that if you properly designed a trial with perhaps stratification according to whether or not a patient is at high risk and set a criteria, but enroll both high- and low-risk, again the issue is other surgeries. So there's the

payoff for the company and the motivation to do it, is to expand the indication. Because otherwise, there's no motivation. All they can do is downside. If a drug's approved and then they're going to do another study in the same indication, then all they can do is lose.

But if you have the potential for expanding an indication and you have both low- and high-risk patients, you get science, you get safety data, and they potentially get a reason to sponsor a study. So I think if you -- I mean, it's not straightforward, but if you think about it, you could probably satisfy all the criteria for a good design of another study and still get some information that we need.

DR. BUCHMAN: Dr. Hennessy?

MR. HENNESSY: The flipside of that is, if the drug is used extensively for off-label purposes, then the company gets its cake and eats it, too, because they don't have

to do the studies to show that it's safe and effective in the other groups, but they get the sales because of the off-label use, which, my prediction is likely to happen.

DR. BUCHMAN: It looks like we're going to finish early. So because we do have a few extra minutes here I want to see if anybody from the committee has any additional questions, either for the sponsor or for the FDA, or just some comments they want to make themselves.

If not, I'm going to give a brief chair summary of the six questions that we had.

The first question was a non-voting question. For the assessment of efficacy of clinical trials of postoperative ileus, GI-2 and GI-3 have been used to measure times for recovery of upper and lower GI function. What do you consider a minimum acceptable treatment difference, as measured by GI-2, GI-3, for alvimopan relative to placebo?

The committee felt that either a

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12- or 24-hour difference was considered to have clinical efficacy, and that GI-2 and ready for discharge were the most important endpoints.

This also included Question No. 2, which was, do you consider the efficacy results from the submitted POI studies to be clinically meaningful?

So Question No. 3 was based on currently available data. Do you have concerns for the use of alvimopan 12-milligram capsules in the short term use, that is the seven days or 15 doses, for patients following partial large or small resection surgery with primary anastomosis with regard to the cardiovascular events, neoplasic events, and bone fractures?

The committee felt that there was some concern for the cardiovascular risks, although these risks were not adequately addressed. But certainly there was some potential concern. The major concern was

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that follow-up was inadequate. Cumulative dose might be important, especially with repeated doses, but we have no data to either support or deny that.

Risk analysis for the most part was based on a single long-term study, and there appeared to be weak signals for these three problems. Nevertheless, the cardiovascular, neoplastic, and bone risks cannot be discounted. And that if the drug was approved, there was clear opinion on the committee that some sort of process would need to be put in effect to be able to monitor these specific potential side effects.

Question No. 4 was, do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients following large or small bowel resections?

There was some concern with efficacy as demonstrated in the trial,

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especially if the patients were not on opiate. Although the consensus of the committee was that there were benefits, even if these benefits were relatively marginal and mostly financial.

There is a potential for risk. There was some concern expressed in the committee that these risks might be real, although might not be applicable to short term use.

It was fairly unanimous that there was small benefit and small risk, although the risk was not zero.

Question No. 5, if alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks?

The unanimous decision of the panel was that the risk management plan was not adequate at all. However, it was also brought up as to whether a risk management

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plan was even really necessary and whether, if the drug was approved, such a plan should be oriented towards more specific prevention of off-label use.

And finally, Question No. 6, based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short-term and long-term clinical studies of alvimopan?

It was the general consensus of the committee that prospective longer term safety monitoring studies for adverse events would be necessary. These could take the form of one of two mechanisms: either A, a Phase IV type trial to monitor the risk-benefit ratio -- or I should say, just the risks of these specific and perhaps other potential events in patients that end up receiving the drug; or to implement a more thorough and long-term follow-up in any future studies for potential future indications.

So with that, I'm going to adjourn

our meeting. Thanks for coming.

(Whereupon, at approximately 4:09 p.m., the MEETING was adjourned.)

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