FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS

ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Wednesday, January 23, 2008

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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.

DR. 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.

DR. 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.

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

DR. 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.

DR. TALAMINI: Mark Talamini, University of California, San Diego.

DR. KARWOSKI: Claudia Karwoski, team leader for risk management, Office of Surveillance and Epidemiology at FDA.

DR. 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.

DR. PHAN: Good morning. This is the Conflict of Interest Statement for the Gastrointestinal Drugs Advisory Committee. Today is January 23, 2008.

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

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

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.

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

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,

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

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

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

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,

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

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.

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.

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

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

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