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,

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

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

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

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

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.

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

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

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

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.

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

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

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

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

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

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

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

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.

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

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.

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.

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

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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.

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

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