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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BUCHMAN: Dr. Pasricha?

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

DR. BUCHMAN: Dr. Proschan?

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

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

differently.

DR. BUCHMAN: Dr. Chang?

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

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

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

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

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

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

DR. BUCHMAN: Dr. Talamini?

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

DR. DANNIS: Yes.

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

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

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

Can you tell me one more time?

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

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

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

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

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

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

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

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

DR. BUCHMAN: Could you identify yourself, please?

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

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

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

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

(1:00 p.m.)

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

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

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

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

So we essentially don't differ very

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

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

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

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

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

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

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

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

DR. BUCHMAN: Thank you. Dr. Epstein?

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

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

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

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

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

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

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

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

DR. BUCHMAN: Dr. Pasricha?

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

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

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

complications?

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

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

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

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

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

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

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

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

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

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

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

DR. TECHNER: Sure.

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

DR. TECHNER: You know what? I think

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

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

DR. BUCHMAN: Dr. Kramer?

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

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

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

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

cardiovascular risk issues?

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

DR. BUCHMAN: Dr. Lincoff?

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

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

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

Dr. Camm?

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

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

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

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

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

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

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

And I think I shouldn't go past

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

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

DR. BUCHMAN: Ms. Corkery-DeLuca?

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

Who's in charge?

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

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

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

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

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

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

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

DR. BUCHMAN: Dr. Proschan?

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

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

DR. BUCHMAN: Do you have that, Eric?

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

DR. BUCHMAN: Dr. Cullen?

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

equivalence between placebo and drug?

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

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

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

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

DR. BUCHMAN: Dr. Levine?

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

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

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

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

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

Studies.

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

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

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

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

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

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

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

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

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

DR. MORTENSEN: Okay. I don't have

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

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

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

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

DR. KRAMER: Yes, I just had a

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

DR. MORTENSEN: No, we actually --

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

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

randomized at the trial.

DR. BUCHMAN: Dr. Chang?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BUCHMAN: If we contrast that 75th

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

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

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

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

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

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

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

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

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

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

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

DR. BUCHMAN: Dr. Talamini?

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

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

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

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

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

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

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

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

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

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

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

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: Judith Kramer from Duke University. I'd like to follow up on Dr. Buchman's question again concerning if you could go back to that slide, CA 38, where you're trying to show the medians in the different studies. If I understood your presentation correctly in the packet, 314 and 313 are major efficacy studies in your application.

Is that correct?

DR. TECHNER: That is correct. And the reason, because they contain either all, or mostly all, bowel resection patients.

DR. KRAMER: Bowel resection, right. The next slide, the one that has the actual individual studies.

DR. TECHNER: The actual mean, median, et cetera.

DR. KRAMER: That's CA 38.

DR. TECHNER: Yes. Go ahead and put that up.

DR. KRAMER: I'm concerned about the representation of how you counted the median there. If we just look at Studies 313 and 314, the median difference from placebo is 7.8 and 6 hours; is that correct?

DR. TECHNER: That is correct.

DR. KRAMER: And the mean is clearly affected by outliers, and the 75th percentile by definition are the outliers. So I just feel like when we consider the risk and benefit, we

really need to consider how many patients we're asking to take this drug with an unknown cardiovascular risk, I would say at this point, in order to obtain the benefit in the patients at one end of the spectrum. So I don't think we should discount the median benefit. So if you line up all the numbers, it's right in the middle, and the most common kind of response is going to be on order of magnitude less in terms of the clinical meaning of it.

DR. TECHNER: Let me address your question two ways, if you would. I'll give you just a brief perspective for myself. And then I'd actually like Dr. Koch to come up and give you a perspective of the mean, the median, et cetera, from a practical standpoint. I think that we certainly are not discounting the median. And in no way, shape, or form, and if it came across that way, I will certainly apologize, that the median is not valid statistically. I think what we're trying to say is in order to evaluate the effect, the

treatment effect of alvimopan in this population, we believe that the mean is one important measure that we focus primarily on, and that the median, and at the 75th percentile, provide additional information to support the mean based on the differences between the two treatment groups.

So we're not dismissing the median. We're trying to look -- and as a matter of fact, we're trying to present you with all the data. But I think maybe it would help to have a little more of a perspective from Dr. Koch as far as the practicalities of looking at medians and means to help you understand this maybe a little differently.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina. Can we go back to CA 31, with the area filled in? So as you can see, Kaplan-Meier curves wiggle. And when you pick a particular quantile like the median, you make pick a quantile where they are randomly somewhat closer together, or you may

even pick one up down here, where they may be randomly somewhat further apart. So picking a single quantile to emphasize isn't really that much different than picking a particular time point, like 72 hours in comparing proportions, or 96 hours in comparing proportions, or 120 hours in comparing proportions.

The different hours along the time course are arbitrary landmarks, although some may be more meaningful than others. And there has been some mention here that five days was a meaningful landmark along the time course. And some quantiles may be of more interest than others. And we've had discussion of the 25th percentile, the 50th percentile, which is the median, and the 75th percentile.

Now, we also have been emphasizing more the difference between the means than the means per se. When you have a time-to-event curve, the mean is actually the area under the Kaplan-Meier survivorship

curve or non-event curve. And when you have two groups that you're comparing, the difference in means is the area between the Kaplan-Meier curves. Now, when we work with the difference in means, we're actually looking at the horizontal distance between the curves at every quantile, and then averaging them together as we move up. And we're taking into account what the differences are at every quantile and averaging them together.

The difference in means is actually an underestimate of what the actual difference is, because the difference in mean estimate is truncated at 264 hours. So it is not leveraged by outliers beyond 264 hours. It actually is a truncated mean calculated through 264 hours. And because alvimopan is still better through 264 hours, the estimates that you're seeing for the difference in means is actually an underestimate of what the means would be if you went the full

distance.

So the main advantage of the mean is that it's basically integrating all of these horizontal distances between the two curves at their respective quantiles together, and producing what can be interpreted as the average amount of benefit that a patient might expect, comparing one of the arms to the other arm.

DR. BUCHMAN: In terms of -- leaving this up for a minute, the number needed to treat, I think there's been some perhaps misunderstanding of that.

It was suggested that this was to get the average 75th percentile patient out early. But what's actually the number needed to treat from the get-go, with an intent-to-treat analysis to get the median patient out 24 hours earlier?

Did you understand my question?

DR. TECHNER: Sort of.

DR. BUCHMAN: Let me rephrase it then.

DR. TECHNER: Go ahead.

DR. BUCHMAN: Simply, what is the number needed to treat? How many patients from an intent-to-treat analysis have to be given the medication in order to get a single patient out 24 hours earlier, regardless of which percentile they fall into?

DR. TECHNER: I think in order to answer your question, let's look at the responder analysis for discharge order written, and I believe that will provide a range of NNTs that you can use to judge. As you remember, we did do a responder analysis. And if you recall, that responder analysis was based on patients who achieved the endpoint of interest between any of Postsurgical Days 3 through 8, and then had no subsequent reports, adverse event reports of ileus, that either led to prolonged hospitalization or readmission within seven days of discharge.

No, sorry. Wrong slide. Why don't you go back to my core slide? Percentage of

patients discharged by Postsurgical Day 7. I think that's what I was looking for; I'm sorry. Yes.

So I think when we look across the studies, using that responder definition I just defined, we can see here that the NNTs to get patients out, in the pooled data for bowel resection only, within seven days ranged from five to nine. And this is across each of the individual trials. And so this is looking at responders in the pooled data from each individual study. And I think what you can see, one, is a higher proportion of alvimopan responders. And when you look at the absolute difference between these in each study, the NNTs you get are between five and nine.

DR. BUCHMAN: Dr. Hennessy?

DR. HENNESSY: Thank you. Given that alvimopan, at least as far as we know, doesn't save any lives, and given that the size of the potential market is at least 400,000 patients

per year even if it's used strictly on-label, I'm wondering whether you think a safety database and POI of about 2,600 patients is adequate to address the safety signal of MI?

DR. JACKSON: Dr. Alexander, may I ask you if you would respond to that question for Dr. Hennessy?

DR. ALEXANDER: John Alexander from Duke University. The patient population that's enrolled in these clinical studies, and in fact, the patient population that undergoes elective bowel resection surgery is at generally relatively low risk for cardiovascular events. And so the perioperative myocardial infarction rate in this population is likely to be less than 1 percent.

So even enrolling substantially larger numbers of patients on the orders of 10- to 20,000 in a safety database is unlikely to eliminate or exclude modest increases -- 25, 50 percent increases -- in myocardial infarction with alvimopan. So

with rare cardiovascular or other safety events, there's a real challenge in low-risk populations of excluding them, even with large safety databases.

In the totality of evidence from the POI population studies, and the analyses that we've gone over quite extensively from the OBD populations, there's risk, there's possible risk, increased risk of myocardial infarction that showed up in one OBD population study that -- where there was no such signal for MI or any other rare event in the POI studies or in the other OBD studies.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: Yes, question for Dr. Techner. Dr. Epstein from Annapolis. Could we go back to slide CA 31? In this pooled study or, for that matter, in 314, for example, did you get a chance to look at the different age brackets by decade? Perhaps to see if -- you know, elderly patients obviously are less mobile and they may have more of an ileus, so your

effect may be greater in that population. I'm just wondering if you had a chance to look at that group and see if there was any clinical difference maybe by decade.

DR. TECHNER: We did, and it brings up I think a very interesting point. So we broke down the population for you here. This is looking at GI-2 by age in the pooled North American trials: Less than 65 years, greater than or equal to 65 years, and greater than or equal to 75 years. I think what you can see here is that regardless of where we cut the age group, we see consistent benefit throughout. And yes, the numbers are not quite as large, but we tend to see somewhat of a more robust response in patients that are elderly.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I had a couple of questions, one of them related to preclinical data.

Do you have any preclinical data on the effects of this drug on vascular tone?

Have you done isolated blood vessels and seen if there's any change in vasomotor activity? I know you looked at blood pressure in intact animals. But have you specifically looked at that, because that's one of the preclinical screening tests for --

DR. JACKSON: Yes, I'm going to ask Dr. Garver to address that preclinical question.

DR. GARVER: Deanne Garver, a non-clinical consultant to Adolor. There have been no systematic studies done for localization of the mu-receptors in the cardiovasculature itself. There's some limited data with respect to the distribution in heart, which is largely kappa- and delta-receptors, and not the mu-receptor.

DR. BUCHMAN: Dr. Proschan?

DR. PROSCHAN: Yeah, I'm a statistician, so I'm trying to get the clinical understanding in terms of the mean and the median and so forth. And I'm thinking, from a clinical standpoint, to me as a statistician, it

makes sense that what you'd really want to reduce the time in are the patients in whom there's a problem. So a patient who only stays for one day, it doesn't matter as much whether you reduce their time.

On the other hand, someone who takes five or six days, maybe it's a lot more important to reduce their time. And likewise, if you went to the other extreme and took people -- I know the maximum here is only 10 days, but if you had data going out to 30 days, then maybe a one-day difference wouldn't be very important. So it seems to me that the 75th percentile actually might be fairly reasonable in terms of clinically important. But this is coming from a non-clinician.

And the other thing I wanted to ask about was this decision about going to GI-2 instead of GI-3. You know, I'm worried that that hindsight may have been driven by results a little bit. And I'm wondering if

you're so convinced that GI-2 is really the better endpoint, then why did you decide on GI-3 at the beginning of some of those studies?

DR. TECHNER: You know, the clinical development program for Entereg really spanned almost seven years, a long seven years. And we're still here. And I think, to be quite frank with you, it's a learning experience. I mean, we have to understand a couple of things. One, there is no precedent here. There's no guidance document to tell a sponsor how to develop a drug to manage postoperative ileus in patients undergoing bowel resection.

So in essence, Adolor and GSK kind of were carving the path. And so we really relied on I think two very important things -- three important things. One, our data as we accumulated it. Two, our surgeons, our anesthesiologists, our statisticians, our physicians who really helped us understand the condition, and what

really matters from their perspective and from the patient's perspective. And third, the FDA, who we've been collaborating with over this entire period of time.

And I think when we looked at everything, the data, what's important to the surgeons, what's important to the patients, what really gets to the treatment effect of alvimopan, and our ability to really assess that so that we can be able to give you data that you feel confident in making your decision, it really came down to GI-2. And that really is the honest answer. It was a learning experience. We took input from everybody, and that's how we got there.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I just had a couple of questions about the cancer signaling, because I remain a little concerned about that. Dr. Dannis mentioned that there was a fairly large difference in the Karnofsky scores between the two groups receiving the drug and the

placebo in the OBD study; is that correct? And if you correct for that variable, do you still see a risk, an increased risk for cancer? Because there's a question over this immune surveillance may be related to that effect and it's not truly a drug effect.

DR. BUCHMAN: Microphone, please?

DR. DANNIS: I'm not sure we looked into that.

DR. PASRICHA: And the question of the sponsor is, it's probably been at least two years since you've completed the study or enrolled your last patient in the study; is that correct?

DR. JACKSON: No, 014, the data are not quite as mature as that. And we did -- if you'd like an answer from the sponsor to that question, I think we can provide it.

DR. PASRICHA: What I would like to see, especially since most of these patients were treated for cancer, with this new information on the signaling, I'd like to see

some information on two-year survival after exposure, even though brief, to this drug. And that should not be very difficult to get.

DR. MORTENSEN: Eric Mortensen, GSK. Let me first speak to your direct question about the multi-event analysis, and I'll ask us to put that up.

Understandably, we wanted to know why we were seeing this gross imbalance, the 20 versus 30 that we saw in the continuum of 008, 101, 684. And so in conjunction with our external consultants, we suggested that we had to consider that, given that we had not made any effort, because that was not the objective of the study, to try to balance patient Z severity or prognostic factors, that we should investigate some very well -- clinically well-established prognostic factors for death and disease progression in patients to see whether or not we really had balance between the treatment groups.

Now, what I'm showing here, this first, just looking at the initial unadjusted hazard ratio for the risk of death in the continuum of 008, 101, 684, and we see there's a 2.1 alvimopan to placebo, again, broad confidence in embracing one because we're talking about small numbers here. The next steps were then to look at the influence of those factors that were thought to potentially be related to what we saw as the imbalance.

Again, we note we had a numerical increase in the number of patients who had with non-small cell lung cancer in the alvimopan treatment group. And we saw here that we ended up doing this in a sequential step stages of looking at a multi-variant model, and that actually showed the most significant risk factor for patients' death. So imbalances based upon their underlying diagnosis would potentially significantly impact the outcome of patients.

But in addition, we also then looked at two other factors. One is Karnofsky score. Now, Karnofsky scores are a patient performance score that is I guess commonly used in many oncology studies. And what we found is that each additional 10-point decrease in Karnofsky score is associated with additional worsening of patient's outcome and greater probability of the patient being moribund.

And so we see that for each 10-point decrease, we then see a hazard ratio increase of 1.5. And I'm emphasizing that because it's not saying that it was an arbitrary cut. Each cut, from 100 to 90 to 80, you're seeing each of those cuts, and if you then have the increase in those patients in the treatment group, a progressive worsening of their outcome. And then, a similar number of metastatic sites for their cancers. And again, there's a numeric increased number of patients with more

metastases, and that the treatment group, that was also as you see here, seen to be positively associated with an increased risk for death.

So when we adjusted the studies for the proportion of patients with these differences between the alvimopan group versus placebo, we actually saw that we had a decrease in the adjusted hazard ratio to 1.4. Again, with a wide confidence level, but at least that gave us some confidence that the factors that we were told by external experts in oncology that might very well be influencing the outcomes of our study seem to be borne out.

I was going to give a quick factual answer to the earlier question that was asked. There was an earlier question about the distribution of patients in 014, and I just wanted to just very quickly get back to that and answer your question. Briefly, 65 percent of the patients in 014 were from

the United States. A total of 85 percent of the patients overall were from the United States, Canada, and the U.K. We then also had a small number of patients contributing from other sites, fewer than 1 percent from either Poland or Hungary.

And then we had fewer than 3 percent of patients coming from New Zealand, Australia, Hong Kong, and Taiwan. So it was largely a study conducted in the U.S., Canada, and U.K.

DR. JACKSON: This is David Jackson, Adolor. In regard to the second part of your question, we do not have, obviously, two-year follow-up on those patients. But we've talked extensively about the IDMC and the consideration of the cardiovascular effects of that drug. Obviously, there was no place for an IDMC and that the neoplasmic findings were after the study was finished.

We did, however, convene a panel of expert oncologists, one of whom is present

today, and would I'm sure be very happy to provide his thoughts if you'd like to hear them.

DR. FUCHS: Hi. I'm Charlie Fuchs, medical oncologist and cancer epidemiologist at the Dana-Farber Cancer Institute in Boston. And our group did look at the evidence in its totality to look at the relationship between this drug and cancer risk, and thought about sort of several of the major criteria that one considers when thinking about cancer risk.

First, there really was not a plausible biological mechanism by which this opiate antagonist would contribute to cancer risk. None that we're aware of. The question was asked earlier about the presence of mu-receptors on cancer cells. I'm not aware of that. In fact, in terms of looking at opiate antagonists and opiates on immune surveillance, there is limited evidence, but would suggest that opiates sometimes reduce NK cell activity, whereas antagonists might

increase it. Now, I think that's purely speculative, but doesn't suggest that one impairs immune surveillance. So bottom line is, first, we didn't see clear biological plausibility for a relationship with this drug and cancer.

Secondly, as you've seen, the genotoxic studies and the animal studies delivered over two years failed to demonstrate any clear carcinogenicity of the compound.

Thirdly, the time course seems implausible. Namely, the idea that cancers could develop in a matter of weeks to months is unlikely with any agents.

And then finally, the histology. We're clearly looking at a panoply of cancer histologies.

And when assigning risk, one usually expects to see a specific tumor histologic type. And as you saw in the data, we're not seeing any clear pattern. So in

sum, we're really not seeing any convincing evidence that would link alvimopan with cancer risk.

Finally, with regard to the POI indication, we're looking at seven days of exposure to the drug, and I'm not aware of any precedent where a drug that doesn't have any genotoxicity or carcinogenicity would lead to cancer risk with a seven-day exposure.

DR. BUCHMAN: As chair, I'm going to take the prerogative to ask the last question for this session. Given that we're dealing with a benign condition here, vis-a-vis I'm not aware of a single case report of anyone dying from postop ileus; furthermore, I'm not aware of any data that would suggest that leaving hospital 22 hours earlier also decreases nosocomial infections, C. diff, or anything else that we've discussed, and you haven't shown that actually in your study that you showed a positive benefit there, we need to limit exposure to the drug

given the potential complications however minimal they be because we have to consider a cost-benefit analysis. Do you think you should be required to do a single dose, a preoperative dosing study -- in other words, 6 or 12 milligrams one time only preoperatively as the only dose, another study?

Do you think you should be required to do that? And if not, why not?

DR. TECHNER: Before I answer your question, I'd like to, if you don't mind, make one point of clarification, because I think it will help in you understanding the response.

DR. BUCHMAN: My question is predicated on the answer to my previous question, where you illustrated the continuous difference between the curves at all points, even as soon as two days postoperatively.

DR. TECHNER: Let me start by clarifying something, and I think it was a point actually that Dr. Chang raised, and also Dr. Dannis.

And I think we -- and I think Drs. Senagore and Delaney can speak better than I to this, agree that virtually all of these patients are being seen by their surgeon within generally two to four weeks. And actually, I can tell you that we polled all of our sites, and the vast majority of our surgeons see their patients back for their first follow-up visit within two to four weeks. Per all of the protocols, the sites were required to report any serious adverse events that occurred between the last dose of study drug and 30 days following that time point.

In addition, we had monitors visiting these sites routinely, scouring through the hospital records, the clinicians' medical office records, and any other medical records that were available, to ensure that anything that looked like an adverse event was captured. And the sites were instructed to report any adverse events, including

serious adverse events, that occurred during that period of time. So we believe that the database that FDA currently has would include those events that occurred basically from the onset of study through 30 days post last dose. So I just wanted to clarify that to give you a perspective of follow-up.

Dr. Schmith from GSK?

DR. SCHMITH: Hi, Ginny Schmith from GSK. I wanted to comment on the idea that a single dose preoperatively would work. And I would argue that I do not believe that it would, and I'd like to show you a plot as to why.

Dr. Techner had told us originally that the time above the KI for the mu-opioid receptor was longer with a 12-milligram dose than with a 6-milligram dose. Okay? And this data comes from POI patients. Okay. We have collected samples in POI patients, and they do have higher concentrations than we would expect to see in healthy volunteers, because they have higher viability because

they do have a decreased GI transit and more time for the drug to be absorbed. Okay? But as you can see, this is a over a 12-milligram dose over a 12-hour period. So they're above the KI for 12 hours. They're not going to be above the KI for five days.

DR. BUCHMAN: But if you prevent the development of a postop ileus, why would you need to give it for five days? If you don't have a postop ileus at Day 1, you're not going to suddenly get one at Day 5.

DR. TECHNER: I will address that, and I will also ask Dr. Senagore to address that as well. I think we discussed the fact that ileus is multifactorial. Opioids are definitely a key component. So as long as a patient is receiving opioids, the risk that ileus is prolonged is high. And therefore, we believe that if you only gave one dose preoperatively and the patient continued to get opioids, then in essence, that preoperative dose effect, the chance to mitigate the effect of those opioids,

would be lost. And this is not that dissimilar from administering antibiotics to prevent wound infection, and other prophylactic measures that we use in order to reduce the chance that a patient will get a certain condition.

DR. BUCHMAN: That goes back to a question I had a few hours ago. And that is, is it what you're really treating here is not a postop ileus at all, that you're treating narcotic-induced ileus? I can tell you from dealing with a lot of patients with complicated GI surgery, those that stay the longest are those that have a trigger finger. They can't get their finger off of the PCA pump. And they may stay a couple of weeks in the hospital with a postop ileus. And so that also then brings up the issue of using it more than seven days.

But the most important issue is, are you seeking an indication that perhaps doesn't truly exist or that you weren't really treating? That you're treating a completely different indication, being a

narcotic-induced ileus.

DR. TECHNER: I think this is the way I would respond to that. If the standard of care in this country was to manage postoperative pain with no narcotics, then I don't believe we would feel this drug would have a benefit. I do not believe that that is the standard of care here.

DR. BUCHMAN: You can answer the other question when we get to some of the questions. Dr. Krist, you had one question. Then we've got to move on to the questions.

DR. KRIST: Well, maybe my question is better to be brought up as we address these questions. What I'm really looking for is reassurance that we don't need to be worrying about looking at long-term safety issues for the short-term indication of the medicine. And I know we've been trying to talk about this, and we've been skirting around that topic when we're looking at the incidences of cancer and MI and those types of things. But the picture that I

keep coming back to that has me uncomfortable is I hear consistent information about efficacy.

The clinical significance, we could talk about, and as Alan, you brought up we don't see reductions in mortality and DVT and nosocomial infections, but we do see consistent reductions in nausea and postop ileus and earlier discharge from the hospital.

But I also hear a drug that would apply to 400,000 people that you can't predict who's going to need it, so you've got to give it to everyone. It's something that I would envision a surgeon would just do. You wouldn't really discuss it with the patient, because there's bigger things to think about, like your cancer resection and other things like that that patients are dealing with. So I feel like there's a lot of importance for making sure that this is safe.

And on one hand, I heard

Dr. Lincoff earlier say, well, why would a drug that you give for seven days cause an MI three to six months later. So we see these spikes in the folks on the long-term use of the medication. And I can buy that, but on some level, the people in the short term are getting more of the drug. They're getting 120 to 168 milligrams, where the people on the long-term dose -- if you're looking 40 days to 120 days out, they getting 40 to 120 milligrams of the medicine.

And then in the risk management plan, I don't see anything to even go back or look at or think about -- if you give it for a short period of time, are there these long-terms complications that we saw the spikes of? Cancer, I can buy more as a short-term dose. You can have an increase in cancer 6 to 12 months later. That certainly is plausible. MI, I have a more difficult time with.

But I'm just looking for some

reassurance and trying to figure out, well, why don't we need to worry about looking at that longer time period for the short-term administration? I know it wasn't the plan and it came up afterwards, after these spikes appeared. But before releasing a drug and saying it's safe and potentially exposing a lot of people to it, it seems like an important thing that we need to figure out.

DR. BUCHMAN: So your question is if we use similar cumulative doses, why don't we look at the data the same? Is that the question that you're asking?

DR. KRIST: The cumulative dose, I didn't mean to -- it's not an issue of the cumulative dose.

It was more of an issue of on one hand, we're saying, well, if you give it short-term, in the studies we see, we don't see risks of MI in the POI studies. But as Sean was bringing out, we probably don't have power to see that at least short term.

The thing I'm concerned about is our follow-up is 14 days, and the spikes in the chronic use folks occurred at 40 to 120 days. The issue of the dose was just -- the positive towards the POI studies is, well, it's only five to seven days people get it as opposed to 60 to a year's worth of days that they get it. But the negative is the cumulative dose might be more in the short-term POI patients in the studies.

DR. JACKSON: David Jackson from Adolor. I'd love to make you comfortable in that regard, obviously. In part, I'd like to answer your question with providing an answer to a comment that came from the left side of the committee table earlier. And I apologize, I can't remember whether it was Dr. Lincoff or Dr. Talamini. But the size of this acute care safety database at 4,000 patients is actually rather large for a short-term administered product. Okay?

DR. KRIST: Short term.

DR. JACKSON: So we have a lot of data. The second point I would offer is that in the OBD data, the risk, whatever it is, whatever that signal, if it is a signal, means, is largely confined to one single study. Those other studies which looked at a significant number of patients for three months did not see that imbalance. So although we don't understand perhaps the meaning of the signal right now, if it is such, we have a preponderance of data in which we don't see anything.

DR. KRIST: But that one study was the main one that followed people for a year. The other one stopped at three months, right?

DR. JACKSON: Yes, but the myocardial infarctions were all seen in the first four months.

There was nothing seen at all in the last six months of that study.

DR. KRIST: Not necessarily true, though, for the cancer risk, of course.

DR. JACKSON: Absolutely not, but

again, as I think my colleague Dr. Mortensen tried to indicate, there is a very good chance that a large number of those cancers were present at the time of introduction into the study.

DR. KRIST: Likewise, there's no methodologic reason to say that we shouldn't be considering Study 14. Even though it all occurred in that one study, there's no -- when you look at that study compared to the other studies, there's no explanation as to why it occurred in that one study compared to the others.

DR. JACKSON: There is indeed not, and we have looked very hard for that.

DR. BUCHMAN: Unfortunately, we're going to have to move on and catch up here. We're going to move on to the questions that the agency has posed to the committee. Some of these will be questions that the committee will actually vote on, and I will announce those as we get to them.

The first question is a non-voting question, and we'll spend about 10 to 15 minutes on this, less if we need. And the question is, for the record, for the assessment of efficacy in clinical trials of postoperative ileus, GI-2 and GI-3 have been utilized to measure times for recovery of upper and lower GI function.

What do you consider a minimal acceptable treatment difference as measured by GI-1 or GI-3 for alvimopan relative to placebo? Specifically, do you think 12 hours is sufficient? Twenty-four hours, 36 hours, a month, 12 years? We need you comments on this.

Dr. Pasricha?

DR. PASRICHA: I just think we need to clarify what time points or what percentile we're talking about. Are we talking about the means for the whole -- are we talking about differences in means?

DR. BUCHMAN: That's a good question

here. Are we talking about the mean, median, or 75th percentile?

DR. KORVICK: I would think that anyone that responds to this question should specify what's the most meaningful to them, and why and how much. So you can pick whichever one you think is meaningful to you.

DR. PASRICHA: So I'd like to say in general that reducing postop stay by 24 hours on an average patient is meaningful. But if you're talking about an operation or a procedure that results only in 3 days hospitalization and you can reduce that by 12 hours, that might be meaningful, also. So in part, it depends on the denominator, which is one of the reasons we asked the question. But if you just take sort of this dumb average that we have, five days and so on, I think 24 hours would be considered a meaningful endpoint.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I would say as one of those surgeons on the committee who's watched

lots of patients go through this, I think for me, 12 hours in terms of the GI-2 endpoint or 12 hours in terms of being able to leave the hospital would be significant.

I'd like to add one quick comment to follow up on what you said, Dr. Buchman. The surgeons in the room know when we finish most operations, the small bowel is peristaltic. So there is this definition. You know, in our minds, we have this ileus thing when we close a patient. When we close a patient, the small bowel's functional. The colon usually isn't, the stomach usually isn't, but the small bowel is. It'd be fascinating to know by ultrasound what's really going on with the bowel at all these time points, but we don't.

DR. BUCHMAN: Dr. Levine? Dr. Epstein?

DR. EPSTEIN: Yes, just to expand a little bit on what Dr. Talamini said. And as we've been going through this discussion and

talking a lot about the safety, we've also gone, and Dr. Chang has made the comments, on more of a pharmacoeconomic argument, which is kind of unique in my experience on panels. But nevertheless, it's an important thing to discuss. And just by way of my background, I've served as president of a medical staff and on a board of a 700-physician hospital for more than a decade. So we wrestle with these issues from the pharmacoeconomic every day. And we also have the P&T committee, which would then consider this drug because it's going to be a hospital drug.

And a lot of our time is spent trying to get the hospital bed days -- our mean hospital bed days are around 3.16 days, trying to get it from 3.23 days down to 3.16 days, and that is a huge number. It has everything to do with reimbursement to the hospital, quality indicators, and on and on.

And even if you look at this drug, if you gave it to the 500 patients or so that

had a bowel resection, if you could save one hospital bed day or even half a bed day, which is significant, or 12 hours, you're talking about 55 bed days. That's very substantial. It's not only you're getting the patient out of the hospital early and saving money, but you're putting somebody in the hospital on that day and you're able to do more surgeries.

I don't know about the hospitals or the places where everyone else works, but we have a very, very critical bed shortage on a daily basis. And this is a common problem throughout our area. So this would have a significant pharmacoeconomic impact if we could save even 12 hours on our postoperative patients. So from that standpoint, I think this drug would be very beneficial if we could make that change in our time of stay.

DR. BUCHMAN: Dr. Talamini and Dr. Epstein, if the nurse called you at home, and actually both of you are probably rounding

at midnight, and the patient eats dinner, solid food -- and of course, we don't know what solid food tolerance means. They ate a hot dog, they ate a whole sandwich, they ate one piece of toast. But if they call you at midnight and say, well, the patient ate, can they go home now, but the patient's asleep now, would you send them home or would you wait until 8:00 in the morning? And so basically that's just a joke that didn't go over very well to illustrate my point, does 12 hours really make a difference clinically?

DR. TALAMINI: This is Dr. Talamini again. I believe that it does, because most surgeons, at least academic surgeons, which is what I've been and lived with, really think of these things twice a day: Once for the morning and once for the evening. So if you hear from the house staff in the afternoon bowels are moving, patient's eating a diet, you'll say go on home, and we'll have a bed fresh early the next morning.

DR. EPSTEIN: Just to --

DR. BUCHMAN: Dr. Krist?

DR. EPSTEIN: I'm sorry.

DR. BUCHMAN: Oh, I'm sorry, Dr. Epstein.

DR. EPSTEIN: Just to reiterate on that. The protocol that we have in place in our hospital is we have a 24-hour team in the hospital, a discharge team. We have cars standing by ready to get you out of the hospital. It does not matter if it's New Year's, Christmas Eve, a blizzard.

Our ER is -- we just built a brand-new hospital and our ER is stacked up with people in the hallways down the halls. We don't have room for these people, and it's really a troubling situation. But the point is that every hour makes a difference. And we can't even transfer a patient to another hospital. We have the same problem throughout the metropolitan area. So yeah, it's a big difference, and 12 hours is

enormous.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: Now, I practice more at a community hospital, and I'm not sure that things happen in anything other than 24-hour increments, even though people want it to do, and we have bed shortages as well. But maybe this is where it helps us a little in thinking about whether we're talking about the mean or the 75th percentile. Because really, as you were talking earlier, for an individual patient, I think what's more clinically significant is 24-hour increments. But if you're talking about mean for the overall group of patients who had the surgery, maybe 12 hours for that mean would be important, because that represents people who are getting out one or two days as well as people who are getting out an hour or two.

Whereas if I look at the 75th percentile, more of the extreme of the people staying longer, maybe I want that to be more around 24 hours as opposed to the 12 hours.

So that's how I might rationalize and interpret the overall population mean versus the 75th percentile.

DR. BUCHMAN: And of course, we saw a mean of six to seven hours in this study. So okay, well, we're going to move on to Question No. 2.

DR. PASRICHA: The mean was about 15 or something.

DR. KRIST: The 75th percentile mean was closer to a day.

DR. BUCHMAN: Were you referring to the overall mean or the mean for the 75th percentile?

DR. KRIST: Well, the overall mean was more like 15 hours.

DR. BUCHMAN: Fifteen. Fifteen, you're correct.

DR. KRIST: And the 75th percentile one was 24 hours.

DR. BUCHMAN: Yep, you're correct. We're going to move on to Question No. 2. And

keep in mind Question No. 2 is actually a voting question, and we'll have up to 30 minutes to discuss this. The question is, do you consider the efficacy results from the submitted POI studies to be clinically meaningful, and explain which of the endpoints, that's GI-1 -- or GI-2, GI-3, date of writing the order for discharge, or ready for discharge, or perhaps some other outcome that you feel is important? And which studies are you relying on to support your conclusion?

Comments from the committee?

Dr. Kramer?

DR. KRAMER: I think before we actually discuss this, we should get to the question that you raised about what the actual indication is here. Because what bothers me in terms of determining efficacy is that essentially you have a situation where this drug has been shown to be effective when you required opioid patient-controlled analgesia. And if I got it right, I think when the surgeon,

Dr. Senagore, described the care pathways being instituted across the country now, some of the newer approaches, I think one of the things you listed in general, not in these studies, included opioid-sparing techniques. That was excluded from these studies, with the exception of the one in Europe.

So in order to determine whether or not this is efficacious, we have to say what are we really doing? Are we minimizing the effect of opioids, and should it have that indication? Should it be tied to use in a situation where you're administering PCA? So you interpret the results accordingly. So that's the comment I want to make.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I think it's very hard to look at the data and tease out what's opioid-induced and what's non-opioid-induced in the setting of postoperative ileus. So I'm not sure that clinically that would be very helpful for us to do that. I think you can clarify the

context in which you're asking for efficacy, which is I guess the context in which they're asking for the label.

And in my opinion, I think it is clinically meaningful, the data. And I'm relying on the GI-2 and the DOW endpoints to support that. And I think we see it in all the studies that have been presented.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I just wanted to -- actually, Slide CA 37 shows that the mean difference is more like 18 hours. Now again, I don't -- you know, I'm not a clinician, so I'm probably the wrong one to be commenting on this. But it seems to me that it's appropriate that as you go out to the 75th percentile, you're getting a bigger difference, a whole day; as you're down in the lower amounts of time, maybe 12 hours is really important.

You know, if you're talking about the difference between three days and two and a half, that may be very important. And then

when you integrate across all time points, it seems to me that 18 hours is pretty long as well. So once again, from a non-clinician standpoint, it seems like the results are pretty good.

DR. BUCHMAN: Dr. Rosing, do you have any comments on this particular question?

Dr. Cullen?

DR. CULLEN: I think the results are efficacious. I think that the GI-1-2 study and the DOW as mentioned previously are what I look at. And I think getting a patient out in a day at 75th percentile is really significant.

DR. BUCHMAN: Dr. Krist, anything to add to your previous comments?

Dr. Levine?

DR. LEVINE: I just want to ask Dr. Cullen, we agreed that in the 302 and some of the other studies where we had total abdominal hysterectomies, that this was going to only look at postoperative ileus, not in the gynecological surgery. On the other hand, if

you can save a half a day or a day in total abdominal hysterectomy, it may be cost-effective. My question is, can we guesstimate if this would be utilized on or off -- in the hospital on- or off-label by gynecological surgeons for cancer surgery, where there's total abdominal hysterectomy, when we don't have data in that area shown in the presentation?

DR. BUCHMAN: Ms. Corkery-DeLuca, any comments?

MS. CORKERY-DeLUCA: I haven't heard enough negative to think --

DR. BUCHMAN: Use your microphone, please.

MS. CORKERY-DeLUCA: Pardon me. I haven't heard enough negative comments to say that it would not be.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: Richardson, Mayo. I have a comment, and perhaps Dr. Talamini and some of the other surgeons can answer this for