me. I know that at our institution, more and more bowel resections are being done laparoscopically, and that has shortened up the stay substantially. And I guess I'm wondering, if you're looking for this narrower indication, that is using this particular drug only in the situation of the open laparotomy, is this going to be relevant as practice evolves?

DR. BUCHMAN: Dr. Chang?

Dr. Talamini, go ahead.

DR. TALAMINI: Should I respond?

DR. BUCHMAN: Go ahead. But this is going to be your one time to respond, so make it a full one.

DR. TALAMINI: I think that the data's pretty clear that right now the majority are open surgery. I think over time, though, those numbers will shift and it's an unanswered question.

I would say in terms of my answering of Question No. 2, the endpoints that are key to me are GI-2 and Ready,

because GI-3, flatus, patients just can't explain most of the time, and discharge order depends on another human being in the chain. So those are the data points that are important. And I think that this is significant based on those endpoints.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: I would say I like what Dr. Krist said about the mean being 12 hours and at the 75th percentile, it's 24 hours. But I would go by GI-2 because it is objective. I don't feel like Ready or discharge orders -- that's more subjective and it's based on -- it could be variable. But obviously, the results support the GI-2 endpoint, so I definitely think this is efficacious.

DR. KRAMER: I'd like to say that I do think that it's efficacious for -- I agree that GI-2 makes sense, although it does bother me that it looks like it was a post hoc decision after the data was looked at, but it does make sense. But I think the statement must specify

that this is in the context of opioid PCA.

DR. BUCHMAN: I'd have to say who am I to question the surgeon's judgment when to send their patient home, although I don't infrequently do that.

If I was the patient at 4:00 a.m., and you're going to send me home, I'd beg you to not wake me up first, and secondly, to wait until 8:00 a.m. But given that there is a feeling around the table from our surgeons that 12 hours is clinically important for ready for discharge, then I would have to say I think that that is efficacious as well.

The problem with the written order for discharge is it suffers from exactly the same problems as actually going home, because it's a red flag for insurance companies. If I know a patient from out of state, for example, is ready to go home on Friday and they can't get picked up until Monday, I'm not going to write that order. So it suffers from exactly the same problems. So ready to

discharge is important. We're talking about a benign condition, but if we can get the patient out earlier and basically save money -- that's the only thing we're talking about here is potentially saving money -- then I'm going to concur with my surgical colleagues.

Dr. Hennessy?

MR. HENNESSY: Thanks. I would say that the endpoint is clinically meaningful, but only marginally so. It's right at the cusp.

DR. LINCOFF: As a non-GI specialist, I would say that I think this endpoint is very clinically meaningful from other conditions. A day in the hospital or a half a day in the hospital, I think is relevant, particularly a day or a half a day of having an unpleasant condition, like an NG tube or nausea. So from that standpoint, I think that even a half a day would be clinically relevant.

In terms of the endpoints, I think that the GI-2 is the hardest endpoint, in

that it's most linked to an objective finding. But I also believe that the DOW and Ready are very important as well, in particular because they're concordant with the more mechanistic endpoint, and because this is a blinded trial.

So for all the limitation -- these are blinded trials. So for all the limitations inherent in the physician's decision of when he's going to discharge and if he's got people wandering around at night ready to kick people out into the cars or not, but whatever these are, they apply to both groups, and they model clinical practice. So for the very question of relevance, where GI-2 is science, DOW and Ready are clinical relevance and relevance in medical practice. And so I think they're all meaningful. They all support each other.

And I think together it's a very -- as much as I hate to use this overused word -- robust findings, set of

findings, that there is efficacy for this drug.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: Yes, I agree with my colleagues so far. And even just modeling Dr. Talamini's hospital, the number of surgeries he does, if you apply some numbers to this, it's a very substantial clinical savings, cost savings, time savings, that would outweigh any cost of the medicine and its delivery.

DR. BUCHMAN: Dr. Talamini had his chance, but he begs me for one more. We have time, so go ahead, Dr. Talamini.

DR. TALAMINI: The only thing that I would add to the differentiation that you're bringing up, Dr. Buchman, is having personally had a PCA after a very painful operation, it is the Rolls Royce of pain control. And if this does ameliorate or make that easier to use, I think that's a consideration.

DR. BUCHMAN: We're actually now going to vote on this as a committee. And the way the

voting procedure is going to go is I'm going to read the question for the record, but then all committee members who are going to vote yes, I'm going to ask them to raise their hand. Now, unfortunately, you're going to need to keep your hand up in the air until Dr. Phan has recognized that she has recorded your vote.

Separately, we will then -- I will then ask for those that are voting no, and finally, those who abstain. And remember to keep your hand up until it's acknowledged. Not quite the secret ballot that we're used to.

So the question again is do you consider the efficacy results from the submitted POI studies to be clinically meaningful? All those that say yes, please -- I'm sorry, we have an interruption.

DR. KRAMER: Can I just ask a clarification?

DR. BUCHMAN: Yes.

DR. KRAMER: Can we specify that

this -- since all the studies require PCA, that this is the setting in which we're making the statement?

DR. BUCHMAN: Well, I think you can make a comment, but as far as voting goes, the question stands as is. You can certainly abstain if you feel that it's an incomplete question.

Any comments from the agency? Would they like to see that any differently?

DR. KORVICK: I agree with what you just said.

DR. BUCHMAN: So all of those that feel that the efficacy is clinically meaningful, please raise your hand. Oh, please -- now that you have your hand up, that was just an exercise. Now you have to actually state your name and say yes. And we're going to start with Dr. Talamini.

DR. TALAMINI: Talamini, yes.

DR. EPSTEIN: Epstein, yes.

DR. BUCHMAN: And you can put your

arms down. The war's over after you've voted.

DR. LINCOFF: Lincoff, yes.

MR. HENNESSY: Hennessy, yes.

DR. BUCHMAN: Buchman, yes.

DR. CHANG: Chang, yes.

DR. BUCHMAN: Losing hands over here. Put them down after you've been recorded.

MS. CORKERY-DeLUCA: DeLuca, yes.

DR. LEVINE: Levine, yes.

DR. PASRICHA: Pasricha, yes.

MR. PROSCHAN: Proschan, yes.

DR. KRAMER: Krist, yes.

DR. CULLEN: Cullen, yes.

DR. ROSING: Rosing, yes.

DR. BUCHMAN: All those that vote no, that the efficacy has not been shown, please raise your hand. All those who are abstaining? Please state your name.

DR. RICHARDSON: Richardson, abstention.

DR. KRAMER: Kramer, abstention.

DR. BUCHMAN: With that, we're going

to --

DR. PHAN: So we have 13 yes, no nos, and 2 abstains.

DR. BUCHMAN: Thank you, Dr. Phan. With that, we're going to move on to Question No. 3, which is a non-voting question. The question is: based on currently available data, do you have concern for the use of alvimopan 12-milligram capsules in the short term, that is seven days or 15 doses, for the patient following a partial large or small bowel resection with primary anastomosis with regard to the following: Cardiovascular events, neoplastic events, and/or bone fractures?

If you noticed I only call on anybody, put them in the hot seat if it's a voting question, so this is a free-for-all here.

If you have a comment, please make it. Dr. Hennessy?

MR. HENNESSY: So yes, I do have concerns with regard to cardiovascular events.

I think that a meaningful signal for cardiovascular events, and in particular MI, was raised for other studies. I think that the studies in postoperative ileus were too small to address that. I think there's a potential mechanism underlying the potential signal, and that is mu-opioid agonism can reduce arrhythmias, so blockage would reduce that reduction of arrhythmias. Given the number of patients that are likely to see this drug, I don't think that that safety signal has been adequately addressed.

DR. BUCHMAN: Dr. Proschan?

DR. PROSCHAN: Yes, I also had concerns. I was -- you know, for me, the two big questions are, is 014 really different than the others? And is the OBD different from POI? And when I look at -- I did my own statistical test to see if the results were different in 014 compared to the other trials, and I got something that was statistically significant, showing that there's a difference between 014

and the other OBD trials. Now, I don't know why that is, so it's hard for me to dismiss GSK014, because that's the one that had most of the MIs.

You're taking a trial that had more of the information and trying to dismiss that. I have a real problem with that. In particular, you're estimating the odds ratio better in that trial than you are in all of the other trials in terms of variability.

The other thing that bothered me was that it wasn't just MI. If you look in 014 in the briefing document, it looked like it was arrhythmias, it looked like it was other cardiac events. So that, to me, suggests that this is not really just a chance finding, those two factors.

As far as POI versus OBD, I did my own statistical test and I did not get a statistically significant difference in the odds ratios for those two classes of trials. And so that suggests that maybe the harm, if you believe that there's harm, in OBD might

also apply to POI, and we just don't have enough events to detect that. So I did have those concerns.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I would say that I have concerns. I don't have concerns regarding bone fractures. I don't think I have concerns about the neoplastic events, because looking at each individual case, they're all over the board, and many of them really just make no sense to me in terms of long-term use of the drug in that study.

I do have concerns about cardiovascular events, which I think are somewhat allayed by the comments here today that nobody can point to a short-term drug like this creating a longer-term cardiovascular event. So I have concerns, but I think they've largely been addressed.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I do have concerns, in particular about the cardiovascular events. And

it's not just short-term exposure causing long-term effects, but I would say that the follow-up in the short term was really inadequate. Granted, at the time these studies were done, it was not known that there was a signal -- a signal would later show up in this OBD population. But I think we have to keep in mind that this was passive adverse event reporting, and we know how doctors collect that information. It's not an active solicitation of cardiac events.

But furthermore, a very large percentage of these patients were not followed when they left the hospital, that there's -- if I read the slide correctly, I think it was 257 patients did not have any further information. And that is not even short-term follow-up. I mean, they could have had an event at 10 days or 2 weeks. And my understanding, even though the metabolite is less potent than the parent drug, that the metabolite would have been present past the

time these patients were observed, a large percentage of the patients were observed. So I don't think we have adequate information to say that there's even no relatively short-term problem in the POI population.

So I do have a concern, and I think that given that this benefit -- it's really striking. The FDA is not allowed to make decisions based on financial information or cost savings, but now our clinicians are making those decisions based on saving hospitals money.

But our patients are being asked to take this drug, I suspect without, as Dr. Krist said, I suspect without a lot of informed consent about what the potential downsides are. Everyone has acknowledged that it's really for those patients who are going to have a problem. But since we don't know who they are, all the patients have to take it. That's when you get into trouble later on, retrospectively, if you do discover

the signal is real, that you have mud on your face or egg on your face, however you want to say it. So I have a concern.

DR. BUCHMAN: I had some concern as well in terms of the long-term data. I don't think we can ignore the long-term data, because if we look at corticosteroids, for example, well, you say seven days' worth of corticosteroids, there's no increased risk of bone fractures, but with cumulative use, there certainly is. And it's the cumulative dose of corticosteroids that have the greatest effect on the risk of fracture.

So if we look at the long-term data, the cumulative dose that those patients have at a very small dose, but for a long period of time, is very similar to the much larger dose used for a very short period of time. And indeed, it may be -- we don't know this, but it may be the cumulative dose is what's most important. Because many of these patients that have an operation will be

re-operated on in the future, and do they get the medication again or are they allowed it once in a lifetime?

If we look at a Crohn's patient, for example, within five years of having a strictureplasty, they've got a 40 percent risk of being back in an operation again. Patients who -- an ideal obviously with IBD patients, but patients who have had an IPAA, within five years have a greater than 50 percent chance of being in an operation again because of a bowel obstruction from adhesions. And do they then get this medication again? Patients who have had 30 abdominal surgeries, they get 30 weeks of this medication, that may prove to be a significant risk. We don't have the information on that, obviously.

Dr. Pasricha?

DR. PASRICHA: I think everybody on this panel has some degree of concern about the cardiovascular risks. The question is what do

we do about them? And we have three options: We either don't let this drug come on the market or we do prospective trials, which you've already heard are going to require tens of thousands of patients and probably not answer the question; or we put in place a very strict risk management surveillance program, which are really the three options that we have here. I think a priori, we cannot necessarily come to any conclusion about how severe the risk is going to be based on the data we have.

DR. BUCHMAN: Dr. Rosing?

DR. ROSING: Yes. As a cardiologist, I would come at this with a little different approach.

First of all, I don't think there's any evidence in the short-term study that there was any cardiovascular risk at all. And even though there's a question -- Dr. Hennessy raised the question of arrhythmias, this was a blinded study and there were no arrhythmias. And just as

Dr. Lincoff couldn't think of any mechanisms to cause long-term myocardial infarction, I can't think of any reason once they're off the drug that these people should be having arrhythmias from a drug that's given over a very short period of time. So we're really talking about this concern about cardiovascular problems on the basis of this 014 study, which seems to me to have a lot of problems associated with it and doesn't make a whole lot of sense from a cardiology standpoint.

You raised the question, Dr. Buchman, of the cumulative effect, but even that breaks down, because once you get out beyond 60 or 70 days, there was no cumulative effect. That curve was perfectly flat. So it seems to be an isolated effect in a very brief period of time. There is probably -- and it doesn't even reach statistical significance apparently.

I think there's information we

don't have. I brought up the question of other drugs, but I didn't bring the question up a second time because I was convinced that the problem is not the seven or the nine events. The problem is the zero events, that if you take a patient population with these risk factors, including age, which the average age was in the sixties, you'd be very surprised over the course of a year, with an intervention such as surgery and other stresses, that you wouldn't come up with at least one or two or more events.

So as a cardiologist, I think I'd be less concerned and be willing to accept the short term use of this drug.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I still feel the same way I felt before when I had my little rant. And I disagree some, in the sense that, to me, what's different here is that it's not that it's questionable as to whether there's risks long term and beyond 14 days. I'll take it a step

further than what Dr. Kramer said. We need to look at it past 14 days. There's no systematic data collection beyond the short term use of the medicine.

And even building on some of what Jay said, I am concerned about, well, what would it take to evaluate this? But if you look at the Study 014, to at least see this blip, it didn't take that many people to see the blip. Now, it's not enough people to reach statistical significance, but it's enough to raise safety concerns, which I think is different than looking at an efficacy outcome.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: So I guess our role here is really to focus on the cardiovascular, "our" being the cardiologists. And I'm trying to put that in the context of what I would expect from other therapies and be concerned about.

I really do think there is a difference between long- and short-term

therapy. Cumulative effects have impact with some types of therapies, and corticosteroids are obviously an example of that, because the effect on bone may be cumulative.

But if we think about mechanisms of ischemic cardiovascular events, it's either progression of atherosclerosis, plaque instability, thrombosis, vasoconstriction. And it's hard to postulate how a short-term therapy would lead to a long-term risk.

Now, that only goes so far. Obviously, theory and pathophysiology are important up to a point, but in the end, you have to go by what your empiric data is. And so what we have here is empirically not a hint of any signal in short term, albeit with incomplete follow-up, but for what we have, no imbalance, virtually no events in this short-term follow-up.

And in long-term follow-up, in a study that was one-third of the total patients tested for this OBD indication,

albeit the longest study, one-third of the patients showing what appeared to be a numeric excess ended up being seven events.

Those events, that excess, if it existed -- because it didn't in the adjudicated, although that's with mixing of the MI being mixed with less severe unstable angina, et cetera. So if we just say we're going to talk about MI and we're not going to care about the others, even though they're mechanistically similar so you would have expected them all to trend in the same direction, but if you say we're just going to talk about MI, then what we're talking about is in the first three to four months of this large study, this study with one-third of all the patients in the OBD, you had these excess events.

In two-thirds of the patients in the other studies whose follow-up range from one to three months, that same period, that three to four months, you didn't see any

excess. In fact, there was almost a countervailing less -- numerically less than the active drug arm.

So it's not to say it isn't real. The reality is we don't know what we would see if we duplicated this 14. But it's not a strong signal. It's a signal that gives us a lot of question of stability with one or two events in either direction, with one or two extra events in the placebo group that one would have expected based upon the patient population. And so it's a very weak piece of evidence. And it's a piece of evidence that I'd have trouble hanging my hat on even for an approval of a long-term indication.

But certainly to then go back and say I've got a very short-term indication for which we have no signal at all and we can't mechanistically calculate -- or we can't mechanistically postulate why there should be, I have a lot of trouble.

So the long and short is, for the

short-term indication that we're talking about, even though the dose is much higher, of course, I don't have a concern for cardiovascular risk.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I'd like to shift the conversation to something that Dr. Pasricha raised, which is what are we to do about this? I mean, we can talk all afternoon, and part of the reason we're talking so much is because there's a lot of missing information, and you can only go so far with mechanistic discussions. But the question is what are our options?

I think there are a couple of options that maybe you didn't list that -- I didn't see in the plans outlined by the sponsor, if this drug were to be approved, any suggestion that there even be a registry of all patients that are taking this drug with follow-up, or that there be any observational studies in large health plan databases or any -- you know, as this drug is

on the market, if we just depend on passive reporting, we're going to be in the same situation we're in right now in the future, which is we will not have any information to add to the database. So I'm disappointed that there isn't some plan to actively solicit cardiovascular safety in the long term, and I'd like to see that laid out, I would suggest.

DR. BUCHMAN: Dr. Proschan, did you have a comment?

DR. PROSCHAN: I didn't have my hand up, but now that you called on me, I will say something.

DR. BUCHMAN: You stuck your light on.

DR. PROSCHAN: And that is that I think the argument that there are not enough placebo events, exactly the same argument was made in the cardiac arrhythmia suppression trial. It's not that these drugs are killing people. It's those -- you know, placebo patients aren't dying enough.

So I think that often happens in clinical trials, that the placebo event rate is lower than you thought it would be.

DR. BUCHMAN: I think that was worth including you.

We're going to move on. Oh, was there one other? Dr. Epstein?

DR. EPSTEIN: Yes, I just wanted to say that the three things that were asked, the cardiovascular events, I agree there was no signal in the short-term study. And to be able to do a follow-on study, that just statistically based on the numbers, even that you saw in the long-term OBDs, would be very impractical.

And I've often heard about these registries and things at various panel meetings, but that's a huge thing to require for something with a very small signal. So I don't necessarily follow along with that.

And again, the other thing we were asked is neoplastic. I agree with everyone else that there was a very scattered signal,

and again, not short term.

And the bone fractures, I don't know, was the floor more slippery in those -- no. But that didn't seem to have any real signal. So I don't see anything in the pooled data on the short-term studies that would indicate that there's any particular concern, particularly in regards to the cardiovascular.

DR. BUCHMAN: We're going to move on.

Dr. Pasricha, last point and then we're going to move on.

DR. PASRICHA: No, no, just for the record, I want to clarify. On the bone fractures thing, I think that was the only signal that was actually statistically significant, wasn't it? That is the only one with a 95 percent confidence interval that did not cross -- so actually, I think as far as the long-term data is concerned that is -- if I remember correctly, that is the most robust signal that we had amongst the three. I just

don't think it translates into a seven-day course of medication.

But I want to make sure that we have the record straight on that. Is that correct?

DR. KORVICK: Can you repeat your question?

DR. PASRICHA: The clarification was whether the fracture risk was statistically significant. If I recall from Dr. Dannis' presentation, it was. I just want to make sure we have that on the record.

DR. BUCHMAN: I think the lower was .99, which was still -- is my memory correct. that it actually kind of approached 0 as well?

MS. CASTILLO: This is Sonia Castillo, FDA. For Study 014, it was significant. For the non-cancer and cancer population combined, it was not. Let's see, for the combined cancer and non-cancer population, confidence interval, 95 percent, for the relative risk was .6 to 2.3. And for the Study 014, confidence interval was

1.1 to 10.4.

DR. BUCHMAN: Dr. Hennessy?

DR. HENNESSY: A very quick comment. I think that the way to address a safety signal is to do a study, even if it's difficult. Saying that we wouldn't require one because it's difficult essentially says that we're dismissing the safety concern. I'm uncomfortable doing that, particularly for a drug that is not life-saving, but is dollar-saving.

DR. BUCHMAN: We're going to move on to --

DR. KORVICK: We would be interested if the chair would be willing to ask the members to vote on the first bullet of whether or not they think that there is an issue for the short term use for cardiovascular.

DR. BUCHMAN: Absolutely. We can do that as an official vote. So let's do that now, and I'm going to read the question.

Based on currently available data, do you have concerns for the use of alvimopan

12-milligram capsules in the short term, that is seven days or 15 doses, for patients following partial large or small bowel resection surgery with primary anastomosis with regard to the cardiovascular events, neoplastic events, and/or bone fractures?

Just the cardiovascular?

DR. KORVICK: Please.

DR. BUCHMAN: Did you want three separate votes or no?

DR. KORVICK: I think we've got a lot of input on the other, but the first one seems to be an issue.

DR. BUCHMAN: So just for cardiovascular events. Can I have a show of hands for all those that do have concern with the cardiovascular risk profile?

Please keep your hands up and state your name and then you can put it down.

Dr. Krist, do you want to start?

DR. KRIST: Krist, yes.

DR. PROSCHAN: Proschan, yes.

DR. PASRICHA: Pasricha, yes.
DR. RICHARDSON: Richardson, yes.
DR. CHANG: Chang, yes.
DR. KRAMER: Kramer, yes.
DR. BUCHMAN: Buchman, yes.
DR. HENNESSY: Hennessy, yes.
DR. BUCHMAN: All those that vote no? Keep your hand up until you say your name and your vote's recorded.
We'll start over here, Dr. Talamini.
DR. TALAMINI: Talamini, no.
DR. EPSTEIN: Epstein, no.
DR. LINCOFF: Lincoff, no.
DR. LEVINE: Levine, no.
DR. CULLEN: Cullen, no.
DR. ROSING: Rosing, no.
DR. BUCHMAN: Any abstentions?
MS. CORKERY-DeLUCA: DeLuca, abstained.
DR. BUCHMAN: The state of Florida is calculating the vote.

DR. PHAN: We have eight yes, six no, and one abstain.

DR. BUCHMAN: We're going to move on to Question No. 4, which is a voting question.

Do we want to take a break? We need a potty break, I guess.

Okay, let's take a break. I forgot about that. I was so excited about how we were moving along here. So let's take a 15-minute break -- actually 13 minutes. If everybody could be back here at 3:15 sharp, we'll move on to Question No. 4.

(Recess)

DR. BUCHMAN: If I could have everybody's attention, please. There is one comment that I want to clarify for the press.

First off, I am going to give a brief chair summary of each of the questions at the end of today. But for those from the press that want to scram and not wait to see if I have a surprise up my sleeve, in regard to the vote that we had on Question No. 3, it

was not originally designed to be a voting question. We changed that. But what we voted on, as a committee, was only whether we had concern about the cardiovascular risk effects. We did not vote on whether we had concern about neoplastic events or bone fractures, although obviously those were discussed.

We're going to move on to Question No. 4, which is a voting question. Do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients with partial large or small bowel resections with primary anastomosis?

I'm going to start, actually, on this side with Dr. Talamini, what comments you have.

DR. TALAMINI: I want to just speak for a moment to the potential benefits of a strategy like this. Certainly the economic argument is there, and it's easiest to fall into

and look to the economic argument because it's easily quantified. But as a surgeon, I would also say that lying in a hospital bed for 12 or 24 additional hours with a bloated belly and not eating is not a healthy condition. It's much harder to quantify what is not healthy about that and measure it.

But I think most of us who take care of patients on a daily basis know empirically that that is not a healthy thing, and that if you reduce that by some percentage, you're improving the patient's overall care. So I just wanted to get away from this idea that the only thing sitting on the benefit side is economic. I don't believe that that's true.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: As a treating clinician who deals with a lot of patients with ileus, it is a very unpleasant condition. And if you can shorten that, I think, for the patient's benefit, you've really made a great improvement

in their overall outcome of health. And whether it's 12 hours or 24 hours, that's very significant.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I agree with that, and I want to emphasize that -- although we brought up the financial issues, I don't think that that's the key here at all. I mean, what we do in medicine is to make people live longer or to prevent unpleasant things in terms of make them feel better, and this is the latter, and I think it's very real.

DR. BUCHMAN: Dr. Hennessy?

MR. HENNESSY: While I'll agree that there is a clinical benefit to the patient rather than just to the hospital, and I'll admit that I don't see patients, it seems to me from looking at the numbers that the benefit can be characterized as modest or even marginal. And this is a drug that clearly doesn't save lives, and for which there's a significant signal of a cardiovascular risk from a randomized trial.

And in my mind, the benefit does not outweigh the risk while that concern has not been addressed.

DR. BUCHMAN: I would echo Dr. Hennessy's comments in that we're looking at a benign condition. And clearly, I think the drug, as we discussed earlier in this session, does have some efficacy and has physiologic effect. It's not very great, but it is statistically and perhaps marginally clinically significant.

We're asked to make a risk-benefit analysis here. We're dealing with a benign condition with fairly marginal but clinically significant effects of a drug. So therefore, it really can't tolerate any potential for significant side effects. And my concern is that the denominator, that is the risk potential, not necessarily the risk, but the risk potential, does at a minimum slightly outweigh the potential benefit for the patients.

Dr. Kramer?

DR. KRAMER: I would love to see a study that compared the effects of this drug in PCA-controlled analgesia after a bowel resection to an alternative pathway that was a postop pathway that involved opioid-sparing techniques, such as what occurred in the European study. I don't think we've demonstrated that this should be -- have a blanket indication for bowel resection surgery; I think it should -- as I've said many times before, bowel resection surgery in the setting of PCA. And I echo the comments of Dr. Buchman and Hennessy. I would not say yes to this question based on my concerns about risk, and the fact that it has been studied only in the setting of PCA.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: I think this is a really tough question, but when I brought the cost effective, that was just one example of measuring clinical meaningfulness. I mean, I take care of -- it's all about how they feel.

It's not really about that much more. But so I obviously think that's very important.

I think this is tough because I do have concerns, but I feel that the signal really is more in the long-term data, and it's a different patient population. So I would feel more comfortable if there was some monitoring of the patients that did get the drug. I feel very uncomfortable just giving it to anybody.

Just because you brought this up a couple times, Judith, is that there is a study on alvimopan in chronic constipation with no opioids and it didn't show efficacy, so I don't know how well it will help. And this is a different patient population, even if you didn't give opioids after a surgery, but I'm not sure how efficacious the drug would be if you're not on an opioid.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: I guess I'm troubled, as everyone else seems to be. Clearly, there

are some benefits to the various parties that are involved in this. The sponsor, obviously. The hospitals I think certainly can benefit from this. I think if you look at the patients, though, I think that benefit is much more difficult to describe.

I was quite taken by the effects of this with respect to use of PCA or not. I'm particularly interested in the effects of ketorolac in this group. Unfortunately, I don't see anybody who is a generic maker of ketorolac out there promoting that drug for this indication, so that I don't think we'll ever see that type of study find the light of day.

I'm also troubled by the fact that the number needed to treat -- if you combine the GI-2 and GI-3, which I think realistically, one probably should do because I don't see that there's a great deal of difference in those criteria, it seems to me that the number needed to treat is probably

around 10 patients to see one patient benefit. In medical oncology, at least, a 10 percent response rate would be regarded as a failure. And I don't see that the overall benefits are adequate for the patients.

I'm also troubled by the fact that the RiskMAP doesn't include any sort of input from the patients in this, but we'll wait until we get to that.

DR. BUCHMAN: Ms. Corkery-DeLuca?

MS. CORKERY-DELUCA: JoEllen DeLuca. As a patient that's had a lot of bowel surgery, I'll tell you, every day out of the hospital is a good day. And I protest mightily when I have to go in. And if I'm your patient and you're going to be doing an NG tube, you're going to be in for the fight of your life.

I didn't feel that the cardiovascular events -- to me, the GSK seemed to be more of a risk than the Entereg. The bone fractures, when you start picking up with age, when we start looking at people

being age 65 and up, that to me was what made me say I think I should abstain.

Because I am a patient, I don't know enough, but bone fractures are something that -- you're lying down, you're hitting 65, you're hitting 70, you're hitting 75, and I think that you're going to be much more likely to stand up and fall and injure yourself that way than perhaps even a cardiovascular event.

The overall benefits, even reading between the lines I think that some of the questions have been answered. And looking back towards an answer, at least in my mind, looking back toward how hospitals will handle this, I'm still not sure when gut surgery moves from doing one large bowel resection to another for another comorbidity factor, whether we're -- who's going to handle that.

But as a patient, I think sometimes we have to make strides when we can make strides. And the overall risk, to me, made

me say maybe this is a time when we should make a stride with a drug that is looking small and then -- even if we have to revisit it later. I mean, there is not anything else like this.

And I'm not just looking from my hospital's bottom line. They don't need another 12 hours. And I've been in the hospital for a weekend because the surgeon didn't make it. He had too many things to do and didn't make it on Friday before closing time and the nurses were gone, so I had to stay until Monday. So I think we can argue the 12 hours or the 24 hours, but the reality is, it's who -- which of the nurses got the paperwork ready or not. So I think the 12 hours or the 24 is sufficient for most general purposes. And my hospital is fairly large, so it's not a matter of just being a little community hospital.

So that's how I would feel. I think that the risk for a patient, that a lot

of us that have been in the hospital a lot for bowel resections, would say it's worth it.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: I'm more on the fence than ever, but I would say that, no question about it, as Dr. Hennessy and others point out, the hard data is marginal, modest, whatever you want to call it. It's not very, very significant. Again, I'm unimpressed, or relatively unimpressed, that there's a dose response data shown that's very significant between 6 milligrams and 12 milligrams.

On the other hand, there's no question, not only for the patient, but for the physician and everyone else, it is a big difference in seeing patients like this, if they can get that tube out in 12 hours or 24 hours. And the patients feel better, it's important, and I think we're going to have to have very strict risk management control here, but I definitely feel that probably the

patient outweighs it here than just the cost-effectiveness. And I think for the patient's sake, I would probably agree that the benefits marginally overcome the negatives.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I'd like to start by reinforcing the concept that while the discussion may have been a little heavy on the health care costs of this drug, I don't think that's what's driving the decision. I want to make sure that at least that's on the record.

Dr. Buchman, you mentioned that this is not a life-threatening condition, and that is true. But as somebody who's made a career of looking after patients who have chronic nausea, I can tell you next to dying, nausea is probably the most bothersome symptom that patients have. And if you can make a difference in that, it's a big advance.

So I would just like to say that,

and in that context, I actually was a little struck that the sponsor has not gone beyond some very simple measures and not, for instance, included any surrogate measures of quality of life or global sense of helping in their outcome. And I just -- maybe this is the time to ask them whether they have any data that actually looks beyond the objective points, such as we saw with GI-2. But also got a global sense from the patients if they had any questions that might actually reinforce what we're saying here.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I agree with the comments that this is -- as far as the potential harm, I mean, this is no slam dunk. I am persuaded that the signal is real for OBD. Even that's not a slam dunk, but I am persuaded that that's real. I don't see a reason to throw out 014. And so I'm more persuaded than not that that's real.

Now, the question then becomes is

POI -- is that similar? And the answer to that is I just don't know. And that's what bothers me is maybe that's right. Maybe you have to be on this drug long term to feel any harm, to have any problems. But I just don't know that and I don't have strong evidence that that's the case. I have some suggestion that that's the case, but I don't have strong evidence.

So for me, the benefit of reducing by one day versus the potential for an MI or something else is enough.

Maybe I'm just a 'fraidy cat, but that's enough to make me think, no, I wouldn't. I think the risks outweigh the benefit.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I'll echo what some of the others have said. And the way I think about it with this question, we're asked to do a benefit-to-risk analysis. And I think, if you look on one level, quality of life-type

measures, clearly having a postoperative ileus, having increased nausea and vomiting, having an NG tube, are significant things.

And I think we've seen relatively clear data suggesting that this medication reduces those risks.

And we do see decreased nausea and vomiting, in a sense, when you look at the adverse events. And people are more likely to stop placebo than the intervention drug because of nausea and vomiting. And then if you look at quality of life risks, like how people feel and those types of side effects, this medicine seems beneficial.

Where I get lost is looking at major morbidity and mortality. And as Dr. Hennessy has pointed out, in the studies, we don't see reduction in mortality from the medication. We don't see reduction of thromboembolic disease or nosocomial infection, and those significant things. It could happen from a reduced hospital stay,

and that's where I think there's benefit. But we don't see that in our studies. We don't even see a signal of that. And to me, the significant morbidity/mortality risks is a black box and we can't answer that. And because it's a black box, that makes me more afraid overall about the benefit-to-risk ratio.

DR. BUCHMAN: Dr. Cullen?

DR. CULLEN: As a surgeon, what a patient complains about, there's really basically three things postoperatively they complain about: pain, which you can take care with a PCA or something else; an NG tube, if they have one, which is a miserable experience, and their study shows that it reduces the incidence of reinsertion; and then the distention, they're not feeling very good because they're distended, nausea, and vomiting. And the study demonstrates that it's efficacious in that respect. So I think the benefits of the medication are there.

The stress of surgery is -- it's not like running a marathon, but it is a stressful situation on the cardiovascular system and the pulmonary system. So you're adding a medication to this already stressful system and you're not seeing an increased risk of cardiac events. So in the short term, I understand everybody's concerns, but I don't see the increased risk.

And then finally, my concern with this drug is if it was approved in a hospital, that my orthopedic surgery colleagues would use it and my vascular surgery colleagues would use it, and anybody who had anything done would use it, where it wasn't -- the studies didn't show an efficacy in those type of operations. And that's a concern I have in the back of my mind.

But those other two things I mentioned, unless you've been a patient sitting in a hospital with an NG tube, you don't know how miserable that is.

DR. BUCHMAN: So it looks like the surgeons and gastroenterologists are going to have to duke it out in the parking garage after the meeting.

Dr. Rosing, as a cardiologist, what are your feelings in terms of the risk-benefit analysis here?

DR. ROSING: I think the gastroenterologists are also going to have to battle the cardiologists, along with the surgeons. I've heard from the patient advocate, I've heard from some of the gastroenterologists, and certainly both of the surgeons. I've read the data and I think there is some benefit that arrives from this drug beyond the economic benefits. And I really don't see any risk from the short-term studies at all. I do respect some of my colleagues' concerns, though, and I think it would be reasonable to ask the sponsor to implement some form of long-term monitoring for this drug.

DR. BUCHMAN: I would just add one

last comment before we come to a vote. There was an interesting paper a couple of years ago that looked at all the drugs ever approved by the FDA. And as I recall, not the difference between the effect of placebo and study drug, but the benefit over placebo was actually only 20 percent. But if we look at NG tube reinsertion in this study, the difference was -- sure, the difference was 43 percent, but the real difference was 11 percent versus 6 percent.

Let's put it in perspective. We're looking at small numbers in terms of risk. We're looking at small numbers in terms of benefit.

So with that, I'm going to ask are there any other comments from the committee, any rebuttals or re-rebuttals?

Dr. Epstein?

DR. EPSTEIN: Just one comment. I'd like to point out we've heard about ketorolac as a opioid-sparing drug. And as a

gastroenterologist, if you want to talk about risk, start putting a lot of people on ketorolac and you'll see a lot of risk.

DR. BUCHMAN: Don't tell people that. That's how we make money.

DR. EPSTEIN: And the other thing is, just in terms of cardiac -- we've heard from Duke, we've heard the adjudicated data, we've heard from our cardiologists, we've seen no signal in any of the combined short-term studies. We're dealing with the fact that the placebo happened to have a zero number, and so we're dealing with a little bit of the tyranny of small numbers here. And I think it's a leap of faith to think that there's a big cardiac risk in the short term. That's just my opinion, based on the global cumulative data that we've heard today.

DR. BUCHMAN: I'm going to go ahead and read the question and then we're going to go for our vote.

The question again from the agency

is, do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients following small or large bowel resections with primary anastomosis?

All of those that feel that the benefit outweighs the risk, please raise your hand, and keep them up until you state your name.

Let's start over here with Dr. Rosing.

DR. ROSING: Rosing, yes.

DR. CULLEN: Cullen, yes.

DR. PASRICHA: Pasricha, yes.

DR. LEVINE: Levine, yes.

MS. CORKERY-DELUCA: DeLuca, yes.

DR. CHANG: Chang, yes.

DR. LINCOFF: Lincoff, yes.

DR. EPSTEIN: Epstein, yes.

DR. TALAMINI: Talamini, yes.

DR. BUCHMAN: All those that vote no, state your name.

MR. HENNESSY: Hennessy, no.

DR. BUCHMAN: Buchman, no.

DR. KRAMER: Kramer, no.

DR. RICHARDSON: Richardson, no.

MR. PROSCHAN: Proschan, no.

DR. KRIST: Krist, no.

MS. PHAN: We have nine yes and six no, no abstain.

DR. BUCHMAN: We're going to move on to Question No. 5, which is also a voting question. If alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks?

Explain what features of the proposal would be most desirable.

Dr. Rosing, let's start with you.

DR. ROSING: I think we can refocus on the questions that have been raised about the long-term effects, even though it's short term use of this drug. And I think that the features of the proposal that are not adequate would be

that I think there should be some form of long-term monitoring for the three signals that were identified in Study 014, namely cardiovascular complications, fractures, and neoplasia.

DR. BUCHMAN: Dr. Cullen?

DR. CULLEN: I agree with Dr. Rosing. I think specifically the cardiovascular effect should be monitored long term.

DR. BUCHMAN: And Dr. Proschan? All right, Dr. Krist, I'm sorry I forgot you.

DR. KRIST: I don't think that the risk management plan is adequate. We have a big black box on long-term safety, and the plan doesn't do anything to address that.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: I don't have a good sense of whether it would be adequate or not, so I really don't know.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I'd like to see a surveillance program for cardiovascular risk.

And secondly, I'd like to make sure that as far as possible, we've put restriction on off-label use for now. And that means perhaps more narrowly define the target population that this is really indicated.

DR. BUCHMAN: Dr. Levine?

DR. LEVINE: I definitely agree with the latter point. I also feel that there should be a much stricter approach in our past meetings with an already approved drug disparity. We noted that we used the touch phone. I think something in that line is really necessary for follow-up here. I think we have to be -- it would answer the question for short term and otherwise if we had a very strong type of risk management program, which we didn't hear from yet -- about from the sponsor.

DR. BUCHMAN: Ms. Corkery-DeLuca?

MS. CORKERY-DELUCA: I'm JoEllen DeLuca. For the long-term risk, I would like to see something more done about that. I think we owe it to the people who look for what the FDA

approves and not approves to say that there are risk factors. And for me, particularly, the cardio and the osteo.

And I didn't know, how can we monitor this? I don't know that. But that is a question for me. And the off-label use, it goes back again to my question about letting the horse out of the barn. If it goes then to bariatric or if it goes to then to another use entirely that we're not discussing today, who does that? Who is going to monitor that? I don't know.

DR. BUCHMAN: Dr. Richardson?

DR. RICHARDSON: I think we need to provide patients with a little more information on this. The RiskMAP talked about getting some sort of verbal consent from patients as they're being wheeled into the OR, and I don't think that's adequate. I think people have to have some written information that they can digest, say 24 hours before their procedure. I think the idea of having some health care provider

walk up to them when 10 other people are asking them to initial the site of their operation in the preop area and -- oh, by the way, we want to give you this drug. We're a little uncertain about the cardiac risks on this, but trust us and everything will be all right -- I don't think that's an adequate way of addressing that. I think patients have to have more information and some input into this decision.

DR. BUCHMAN: Dr. Chang?

DR. CHANG: There's parts of this that I like, that it is restricted to bowel resection and they're making sure it's only for hospitals. I think that they've put some things in here that are very good. I guess I'll have to think about the emergency surgeries. Sometimes you can't always give the patient all that information or they really don't care. But I do think that not only just looking at long-term monitoring, I think they should look at some predictors if someone comes in, like baseline characteristics of age or gender or

cardiovascular risk factors, and cancer or not cancer.

I think there are some things that may -- information they can get to figure out who may have the greater benefit over risk than others.

DR. BUCHMAN: Dr. Kramer?

DR. KRAMER: I think the proposed risk management program is predicated on process measures of assuring that it only be used in the inpatient setting and not outpatient. I agree with the comments that have been made that I think we need to go beyond that and look at clinical endpoints. As I've said many times, I believe the indication should be specified that it be given in the context of opioid PCA.

And I agree with the comments about trying to more carefully prevent off-label use. I'm concerned that once this is available, that anybody doing surgery where they think there's a chance of ileus might prescribe it, and therefore, increasing the

population potentially at risk.

I agree with the idea of trying to get consent. I realize this is challenging, but I think that patients should be informed. And I was concerned -- I heard a presentation recently within the last year by a wholesaler about what the impact of all these various risk management programs is having on their ability to function. They're an industry, I've learned from this presentation, that operates in a very slim margin of ability to manage, and really, the main brunt of this program is put on the wholesalers. So I agree with the FDA's comments that it really shouldn't be the wholesaler trying to sort out who gets this drug, and that the sponsor should take on some of that cost and responsibility.

DR. BUCHMAN: Quite frankly, I think that the RiskMAP proposed by the company was done haphazardly, and it looks like very little time was really put into it. It's very, very

short on specifics. Now, that can all easily be corrected, but I am quite surprised that we've come to the point of having a meeting here. You've had this drug under development for seven years. You've known about these risks, at least since last November, that you didn't come up with a more specific plan other than, well, wholesalers will going to control this. The Pittsburgh Pirates are not going to finish in last place next year because they're going to play better. You really need to have more specifics. You need to define things. "Acute care hospital" was mentioned only once. Otherwise, it's always "hospital." Hospital has various definitions, even including veterinary hospitals.

So I think you need to supply definitions. You need to have an algorithm, a framework of exactly how this is going to work, what are your check and balance systems? I mean, really, I mean, you guys can do a better job at this, putting this

together than we can as physicians, and I'm just disappointed in what I saw.

MR. HENNESSY: Sean Hennessy. I think that this drug needs additional study to characterize its cardiovascular risks. I'm not convinced that it needs a risk management action plan. Reading from Dr. Weaver's Slide 8, when should a RiskMAP be considered? When the risks are serious and preventable. When safe and effective use calls for specialized health care skills or settings. When a RiskMAP encourages appropriate use increase benefits relative to risks. Products in a class of product with similar risks that require a RiskMAP. I don't think any of those criteria apply to this drug.

The drug is going to be used in lots of patients, more so than can probably be accommodated by the more stringent risk management action plans that we've seen, like clozapine and patient registries to prevent pregnancies. So in my view, the risks need to be characterized in the context of one of

more epidemiologic studies, but they aren't typically part of risk management action plans. And I don't think that a risk management action plan will be effective for reducing the risks unless there are particular patient populations who can be identified who have better or worse risk-benefit balances. And in the absence of a benefit of the RiskMAP, then it's just added cost and added inconvenience.

DR. BUCHMAN: I just want to clarify my response. The RiskMAP here primarily, as I see it, is towards prevention of off-label use, because the concern here was in the long-term patients, again, the chronic opiate users. And there needs to be a clear way in which -- because it's very difficult to regulate off-label use for anything. And this is going to have to be a better attempt to keep it out of the hands of the narcotic addicts, those on methadone, patients in nursing homes, and all these sorts of thing. So I just wanted to

clarify my remark.

Dr. Lincoff?

DR. LINCOFF: I think we need to be realistic about the prospects of useful data from follow-up long-term epidemiologic studies. Such studies are notoriously limited in their ability to look at treatment effects, and we've got to be realistic. If we force a 10,000-patient registry of the next 10,000 patients on-label to get this drug, and we see and event rate, we're going to have an event rate. And we're going to have no idea if that event rate is higher than it would be if patients didn't get the drug.

And we're not going to be able to look at risk factors for treatment effect. We're going to be able to look at risk factors for cardiovascular events, but we've got better registries in existence right now to do that. So if there's really that much concern about what the long-term cardiovascular events are as a consequence of

giving these drugs, then the drug shouldn't be approved.

I personally don't believe that. But I also don't believe that the resources should be diverted toward elaborate registries and epidemiologic studies that aren't going to test causation. You can't test causation with observational studies, and that's really what we want to know. So I think efforts should be directed instead toward, as several people have said, trying to make this drug used only as the label does describe.

And I, too, am a physician, not a pharmacist or a manufacturer who can best design those systems, but I suspect they probably can be designed, especially since we are trying to make a wall between outpatient and inpatient, which seems to me to be a relatively discrete setting that's easier than some of the more difficult drugs.

As for consent, I think consent is

important up to a point, but realize, we use a lot of drugs without much in the way of consent that carry much more in the way of danger -- drugs for atrial fibrillation and some antibiotics, et cetera.

Hospitals institute programs with their pharmacies to require approval of specialists, et cetera, before it's given. But in reality, there are a lot of drugs that have much more evidence of danger that we use without elaborate methods of consent, et cetera. So I think the main issue should be to try to assure that these drugs are used within the label.

DR. BUCHMAN: Dr. Epstein?

DR. EPSTEIN: I basically second what Dr. Lincoff said. We have a very large number of trial patients in the pooled data set from the short term, and there was no increased cardiovascular signal, and that is the intended use. I think that the RiskMAP should include an order that states -- basically from the

physician that states simply, for use in a patient undergoing bowel resection, to limit it.

I think the biggest concern would be, as mentioned by Dr. Cullen, that the orthopedist or some other surgeons might want to use the drug off-label. So I think that's where we should focus the RiskMAP specifically.

DR. BUCHMAN: Dr. Talamini?

DR. TALAMINI: I would make a couple of points. I would say the risk management plan is not adequate because it's currently just an outline. And I would encourage the FDA to predicate approval on that being filled out to their satisfaction.

Having said that, I think the consent issue would be extremely difficult, for the same reasons that Dr. Lincoff already outlined. I've got a hunch that the preoperative antibiotics that we give are probably more dangerous than this drug, and we just don't have the means to ask consent

for every single drug that we give during surgery.

I also know that the story of post-approval studies is not an encouraging one. So my suggestion would be to be very focused there. And from a point of ignorance, I might suggest looking into the NSQIP database, which is becoming ever bigger and more robust, as a potential means to try to answer this question post-approval, if it's approved.

DR. BUCHMAN: Dr. Kramer, you wanted to clarify your comment?

DR. KRAMER: Dr. Hennessy's comments made me realize I did want to clarify what I was at least suggesting. I'm personally seeing the RiskMAP as a method of limiting the use until we have more information. And I would actually agree that post-approval epidemiologic studies, while not addressing causation, can identify safety signals. And I think that in an era where we're starting to put together distributed

safety networks, in the order of being able to accumulate 50 million patient lives to look at things, we have several pilot programs going on right now across multiple collaborative centers in this country, and I think we can get information with a control group to try to understand some of these safety signals. And I don't think we should be ostriches just because it's challenging. If there's any concern, we should look. And if it's no concern, then it's a waste of money, but --

DR. BUCHMAN: Okay, Dr. Korvick?

DR. KRIST: I just wanted to --

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I just wanted to quickly clarify my answer, too. That's the drawback of going very early on in this. I mean, I agree with both of these comments. I don't think a RiskMAP is going to address this and we need more research. I do worry -- and I wasn't going to say anything until you started talking, Dr. Kramer, I mean, I do worry about response

for follow-up for a short term use drug. I can see just methodologically that people are going to have low incentive to respond to having used the drug for five days. So I mean, it depends on the methodology used, if you use an existing database or something. But that's some of the fear that I have with some post-surveillance trying to figure this out -- or post-approval trying to figure it out.

DR. BUCHMAN: Dr. Korvick, with your permission, I'm going to split this into two different votes, with two different questions. The first question being, is a RiskMAP necessary? And the second question being, whether the RiskMAP proposed by the Adolor Corporation is adequate.

Is the agency in agreement with that, or would you just like the single vote as originally planned?

MR. PROSCHAN: Didn't we already vote?

DR. BUCHMAN: No, that was in another life.

DR. KORVICK: I think we'd prefer to go with the way that it's written.

DR. BUCHMAN: You heard the commander in chief. We're going to go with one single vote. And so that means that you're voting at the same time as to, A, if you think a risk management plan is necessary; and also whether you think the risk management plan as proposed is adequate.

So all those in favor that the risk management plan is necessary, and as proposed is adequate, please raise your hand.

DR. EPSTEIN: Point of order.

DR. BUCHMAN: Okay, go ahead.

DR. EPSTEIN: I'm sorry, Mr. Chairman, can you read the question as written? Because I'm confused about "is necessary" or "adequate."

DR. BUCHMAN: I'm going to reread the question then and just going to delete the last sentence. So if alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is

adequate to address the potential risk?

So we're not voting on whether you think they need to have a plan, you're voting on whether you think the plan that they have proposed is adequate, just so that everybody understands that. Okay?

DR. KORVICK: That's correct.

DR. BUCHMAN: So all those who think it's adequate, please raise your hand, for a yes vote.

All those that think it's inadequate, for a no vote, please raise your hands.

Please state your name.

Dr. Talamini, why don't you start?

DR. TALAMINI: Talamini, no.

DR. EPSTEIN: Epstein, no.

DR. LINCOFF: Lincoff, no.

MR. HENNESSY: Hennessy, no.

DR. BUCHMAN: Buchman, no.

DR. KRAMER: Kramer, no.

DR. CHANG: Chang, no.

DR. RICHARDSON: Richardson, no.
MS. CORKERY-DELUCA: DeLuca, no.
DR. LEVINE: Levine, no.
DR. PASRICHA: Pasricha, no.
DR. KRIST: Krist, no.
DR. CULLEN: Cullen, no.
DR. ROSING: Rosing, no.
DR. BUCHMAN: All those abstaining, please raise your hand. State your name.
MR. PROSCHAN: Proschan, abstain.
DR. BUCHMAN: Are we going to announce the vote here?
MS. PHAN: We have no yes, 14 no, and 1 abstain.
DR. BUCHMAN: We're going to move on to the final question of the day. This is a non-voting question. Based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short-term and long-term clinical trials with alvimopan?
Dr. Lincoff?

DR. LINCOFF: That's easy. This is the situation we all wish we were in, is knowing the risks prospectively beforehand. I mean, I think for short-term trials as well, for any trial it's fairly clear that we want to prospectively, not passively, but actively gather cardiovascular endpoints, and cancer and fractures, but particularly cardiovascular. By accepted definitions to do that, not by adverse event reporting, but by, at routine visits, a follow-up to explicitly ask patients, and then to fill in more detail as we typically do in cardiovascular trials if a positive response, or if there are triggers to suggest that there was an event.

And for short-term studies, that that follow-up be for at least 30 days after the last administration of drug. And for long-term studies, one could argue three to six months, depending upon how long term after the last administration of drug.

DR. BUCHMAN: Are you suggesting a

formal Phase IV trial?

DR. LINCOFF: To me, Phase IV -- the definition of Phase IV varies from person to person.

Some mean it to say drugs approved, and so any trial you do from that point on is Phase IV, even if it's randomized. And if that's the case, then, yes.

But if we're talking about, for example, another indication, the OBD indication, is that Phase IV or is that Phase III? Because it's a different indication. I don't know. But I'm talking about in a randomized trial format, any trial that is ever done from this point forward. And certainly none of us have seen the data for OBD, but if one were to want to come forward with an indication for the OBD, one would probably want better data than exists already, no matter how good the efficacy signal is.

DR. BUCHMAN: Dr. Pasricha?

DR. PASRICHA: I just wanted to clarify this because, I mean, are we talking about studies required for approval or post-approval studies? I'm not sure whether this is linked to the previous question.

DR. KORVICK: I think it's now after you've given your answers that you've given and where we find ourselves today. We've had a wide-ranging discussion on a lot of issues. So this is your opportunity for each one of you, if you feel, to register in what area you would like to see what works. So it could be short term, if you still think they need to do something. It could be longer term, as someone else said. So if you could just qualify what you mean, and we'd find any advice helpful.

DR. BUCHMAN: And Dr. Lincoff has suggested two very different mechanisms, one being a Phase IV study on this particular indication. Should this drug be approved in this particular population? And the second being, either in addition or instead of that,

for any future trials, Phase III or Phase II, in other potential indications.

Dr. Talamini, you had a question?

DR. TALAMINI: I completely agree with that. And I'm probably on thin ice here, but I think consideration is doing -- expanding the study to a group of patients that don't have bowel resective surgery, but do require high doses of narcotics postoperatively, and see what the benefits and potential cardiovascular risks might be in that population, where there may be equal or even greater potential benefit.

MR. HENNESSY: I would recommend a large randomized trial for cardiovascular safety endpoints. That would probably be best accomplished in a group at high risk for cardiovascular outcomes, since the problem of low numbers in the denominator won't be much of an issue. Given the size of the potential market, that should take relatively little time to accumulate the number of patients.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: I'd like to add to those last two comments because I think they're excellent for several reasons. First of all, these are groups which there still remains equipoise, because we don't have data. So the problem with doing pure Phase IV in the same populations, of course, everybody says, well, I already know it works, so how can I ethically randomize to a placebo? And you could say it's on the basis of safety, but it's much harder.

But if you expand the indications to other groups for whom there is logic that the high-dose narcotics would -- there would be a benefit, you then truly have equipoise and you could be focusing, for example, on vascular surgery or elderly patients undergoing orthopedic surgery. So that would be a very good trial from the standpoint of the science, the potential indication for the company, because of expanding it, and the opportunity to prospectively -- still in a short-term study, because I don't know if

you're ever going to pursue OBD -- but in the short-term study, gain much more data that can then be extrapolated backward in terms of cardiovascular safety.

DR. BUCHMAN: Dr. Levine? Okay, then just turn your mike off.

Ms. DeLuca?

MS. CORKERY-DELUCA: Are you saying, Dr. Lincoff, the 30-day trial that you had mentioned before, to follow up with the 30 days? What is your time limit?

DR. LINCOFF: Yeah, I was thinking 30 days after the last drug administration.

MS. CORKERY-DELUCA: Would this be paid from the cost of the drug as it enters the market? How is this going to be paid for?

DR. LINCOFF: These would be paid for by the sponsor, who stands to make a profit in the future.

MS. CORKERY-DELUCA: That's what I'm asking.

DR. BUCHMAN: Dr. Krist?

DR. KRIST: I was just saying, I'd be able to do the study you were talking about, randomizing people for the postoperative indication on the PCAs with equipoise. Because to me, there's still enough of a question that -- and I as a patient would be willing to be randomized for that. Because that's an important question that effects the overall risk-to-benefit ratio.

DR. BUCHMAN: Dr. Proschan?

MR. PROSCHAN: Proschan. Yeah, I think the problem with doing a trial in people who are at high cardiovascular risk is that if you show that there is a problem, then that doesn't answer the question for those who aren't at high cardiovascular risk. Now, I know Dr. Lincoff believes that it will not come out that way and that may very well be true, but I'm just saying if it does come out that way, then there's still an open question for people who aren't at high cardiovascular risk, is it fine?

DR. PASRICHA: And I'll have a very

hard time getting that study approved through an RB using a drug for which a stated contraindication is high-risk cardiac already for your first approval. So I think you're going to have to structure it in a way that gets around -- assuming this is a post-approval study.

DR. BUCHMAN: Dr. Lincoff?

DR. LINCOFF: First, I didn't know that we were going to suggest that the contraindication to the use of drug would be high cardiovascular risk, because I don't know that we've seen that. The cardiovascular risk was not a prerequisite, or did I miss it in the inclusion/exclusion criteria for entry into the trial?

But that aside, I would think that if you properly designed a trial with perhaps stratification according to whether or not a patient is at high risk and set a criteria, but enroll both high- and low-risk, again the issue is other surgeries. So there's the

payoff for the company and the motivation to do it, is to expand the indication. Because otherwise, there's no motivation. All they can do is downside. If a drug's approved and then they're going to do another study in the same indication, then all they can do is lose.

But if you have the potential for expanding an indication and you have both low- and high-risk patients, you get science, you get safety data, and they potentially get a reason to sponsor a study. So I think if you -- I mean, it's not straightforward, but if you think about it, you could probably satisfy all the criteria for a good design of another study and still get some information that we need.

DR. BUCHMAN: Dr. Hennessy?

MR. HENNESSY: The flipside of that is, if the drug is used extensively for off-label purposes, then the company gets its cake and eats it, too, because they don't have

to do the studies to show that it's safe and effective in the other groups, but they get the sales because of the off-label use, which, my prediction is likely to happen.

DR. BUCHMAN: It looks like we're going to finish early. So because we do have a few extra minutes here I want to see if anybody from the committee has any additional questions, either for the sponsor or for the FDA, or just some comments they want to make themselves.

If not, I'm going to give a brief chair summary of the six questions that we had.

The first question was a non-voting question. For the assessment of efficacy of clinical trials of postoperative ileus, GI-2 and GI-3 have been used to measure times for recovery of upper and lower GI function. What do you consider a minimum acceptable treatment difference, as measured by GI-2, GI-3, for alvimopan relative to placebo?

The committee felt that either a

12- or 24-hour difference was considered to have clinical efficacy, and that GI-2 and ready for discharge were the most important endpoints.

This also included Question No. 2, which was, do you consider the efficacy results from the submitted POI studies to be clinically meaningful?

So Question No. 3 was based on currently available data. Do you have concerns for the use of alvimopan 12-milligram capsules in the short term use, that is the seven days or 15 doses, for patients following partial large or small resection surgery with primary anastomosis with regard to the cardiovascular events, neoplasic events, and bone fractures?

The committee felt that there was some concern for the cardiovascular risks, although these risks were not adequately addressed. But certainly there was some potential concern. The major concern was

that follow-up was inadequate. Cumulative dose might be important, especially with repeated doses, but we have no data to either support or deny that.

Risk analysis for the most part was based on a single long-term study, and there appeared to be weak signals for these three problems. Nevertheless, the cardiovascular, neoplastic, and bone risks cannot be discounted. And that if the drug was approved, there was clear opinion on the committee that some sort of process would need to be put in effect to be able to monitor these specific potential side effects.

Question No. 4 was, do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short-term in-hospital use in patients following large or small bowel resections?

There was some concern with efficacy as demonstrated in the trial,

especially if the patients were not on opiate. Although the consensus of the committee was that there were benefits, even if these benefits were relatively marginal and mostly financial.

There is a potential for risk. There was some concern expressed in the committee that these risks might be real, although might not be applicable to short term use.

It was fairly unanimous that there was small benefit and small risk, although the risk was not zero.

Question No. 5, if alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks?

The unanimous decision of the panel was that the risk management plan was not adequate at all. However, it was also brought up as to whether a risk management

plan was even really necessary and whether, if the drug was approved, such a plan should be oriented towards more specific prevention of off-label use.

And finally, Question No. 6, based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short-term and long-term clinical studies of alvimopan?

It was the general consensus of the committee that prospective longer term safety monitoring studies for adverse events would be necessary. These could take the form of one of two mechanisms: either A, a Phase IV type trial to monitor the risk-benefit ratio -- or I should say, just the risks of these specific and perhaps other potential events in patients that end up receiving the drug; or to implement a more thorough and long-term follow-up in any future studies for potential future indications.

So with that, I'm going to adjourn

our meeting. Thanks for coming.

(Whereupon, at approximately 4:09 p.m., the MEETING was adjourned.)

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