DR. GANLEY: If you just wait one second.

DR. SULEIMAN: I guess with regard to what Dr. Avigan was talking about phenytoin interaction what we know is based on limited numbers of subjects and based on, I believe about three studies that were conducted. The studies showed mainly an increase in plasma levels of phenytoin by about 15 to 20 percent.

There was one study, of course, in epileptic patients which did not show any significant pharmacodynamic adverse events associated with that increase in plasma levels which was conducted by the sponsor. Those are the only available data that we have at this moment.

DR. CANTILENA: Okay. Are there any other questions specifically about the pharacokinetic data that we saw? Dr. Davidoff.

DR. DAVIDOFF: I had a question about some pharmacokinetic data that we didn't see and that had to do with digitalis drugs because the therapeutic margin -- of course if their dig is relatively narrow. The patients taking it are often quite fragile and are electrically unstable. I just wondered if there are already data that would help us decide about if we should be thinking about that for the label or not.

DR. CANTILENA: Is the sponsor aware of

any interactions with dig?

DR. TRIEBWASSER: Can I introduce Dr. Tommy Andersson? He's our pharmacology expert on omeprazole.

DR. ANDERSSON: I'm sorry. Can you repeat the question?

DR. DAVIDOFF: Yes. The question is about interactions with digitalis derivatives specifically because the therapeutic margin is so much smaller for dig than many other drugs.

DR. ANDERSSON: That is not an interaction on the metabolism level as was suggested in the presentation before. That's an absorption interaction. I mean, digoxin are degraded in the stomach before it's being absorbed by some bacteria degradation.

By increasing the pH that degradation prior to absorption does not happen. That's what we see here as an increased AUC or some 10 percent as an average value in the study we did. It's nothing to do with metabolism.

DR. DAVIDOFF: The mechanism isn't so important as the end result. If there really is a 10 percent increase, that could be quite substantial for some substantial number of patients. I wonder if that

should be considered as a conservative thing to do to put that on the label?

DR. ANDERSSON: That's more of a clinical judgement, I guess.

DR. CANTILENA: Yes, Dr. Houn.

DR. HOUN: I'm just wondering if the company could comment on other drug interactions with diazepam

and clarithormycin.

DR. TRIEBWASSER: I was still under digoxin and I found a study.

DR. CANTILENA: Okay. I'll take notes of the other ones and we'll remind you.

DR. GANLEY: Could I just intercede with just a clinical point as you're looking just to raise this issue that patients with renal failure, for example, were not tested and, again, some patients were on digoxin and have other reasons to have reduced clearance of the drug which in combination with such a challenge might have a more exaggerated blood level response.

For drugs where there is a narrow therapeutic index, those are the kinds of issues that, again, I don't believe have really been directly tested. Those kinds of patients have not been

stressed.

DR. TRIEBWASSER: Regarding clarithromycin there have been three studies that have been done. One study showed a positive interaction with a 15 percent change in clari levels and no changes in the others.

I would like to address part of the rationale with regard to which drugs perhaps should go onto the label had to do with worse case scenario what would be a clinically significant effect. Our feeling was that, first of all, for clari this would not be clinically significant.

Whereas with warfarin and phenytoin although we regard the risk as exceptionally low, the risks of extended prothrombin times of any cause obviously have fairly significant medical consequences. That was the rationale for choice.

I forgot the other drug in addition to clarithromycin.

DR. CANTILENA: Diazepam, digoxin.

DR. TRIEBWASSER: We have -- we're relying on our own data and other drug interaction studies where with diazepam one can see what would appear to be significant changes in clearance of the drug between 25 and 54 percent.

We referred in our submission to another drug interaction study that was done between diazepam and cimetadine which showed a similar level of interaction but no clinically significant effects with regard to CNS status. Again, based on the clinical effect study we do not regard the interaction as clinically significant.

DR. HOUN: That is a decrease in clearance. Correct?

DR. TRIEBWASSER: Yes. Let me show slide 53 just so there is clarity on this. I would ask you to look at the bottom two curves where we are looking at the usual extensive catalyzers, and you can see the difference. The bottom of this curve is when omeprazole is coadministered with diazepam.

Then the second curve up is with placebos. You are seeing a bit of a washout following the start of treatment. This is intravenous infused on diazepam.

There was a question on digoxin. I can show this slide rather than waste time but we do have evidence of a study where in a crossover study with placebo or omeprazole there is actually no difference seen in digoxin levels in that one study. It involved 22 subjects.

DR. CANTILENA: If you have that data, that would be good.

DR. TRIEBWASSER: I can -- could I have slide 64. I apologize. This may be difficult to see. It's the top most bar, digoxin. Elderly patients and of 22, baseline and concomitant treatment so there is a crossover study using digoxin doses of 0.125 to .25 milligrams daily. Omeprazole was administered 20 milligrams daily for 10 days and there was no affect seen on the serum digoxin levels.

DR. CANTILENA: You mean no affect as in statistically significant or whether outliers?

DR. TRIEBWASSER: We would have to dig that data up.

DR. CANTILENA: Yeah. I think that addresses some of the issues as best we can in the setting.

What I would like to do now is actually move to Dr. Katz to charge the committee and I think sort of begin to focus our discussions on the issues at hand. Then you will all have time to ask questions and to share your comments about sort of everything that has been discussed.

If I can now ask Dr. Katz to charge the committee.

DR. KATZ: Good afternoon. I feel like you've already been charged with the issues and this discussion has gone full speed ahead. But I'll take you back again a little bit and kind of go through some of the issues that we would like to -- that we talked about earlier and we would like to have you think about and focus on as you go through your deliberations for the rest of the afternoon.

What I would also like to do is to highlight a little bit about some of the products and where we are in the current armamentarium of OTC heartburn products. A little bit about the prescription to OTC switch process. Then finally touch on the issues that you will discuss this afternoon.

In the interest of time I will skip around a little bit from some of the slides since you do have all of the slides available to you. Let's kind of begin now with currently where we are in terms of the OTC marketplace.

As we've heard, there are currently two classes of products that are available OTC. The first ones that have been out there the longest are the antacids that are approved for the relief of heartburn, that are actually indicated for the relief

of heartburn only.

The H_2-receptor antagonists, also known as the acid reducers, are approved for relief of heartburn and prevention of heartburn as related to a meal at different specified times depending on the nature of the product.

As we have also heard today, Prilosec 1 is not looking for these two indications but are looking for the indication as a prevention of frequent heartburn, frequent heartburn described as greater than two episodes per week for a 24-hour period of time.

When considering whether or not a product should go from the prescription to the OTC arena, there are a variety of different places where we stop to look in the decision making process.

We look for the benefit-risk. The consumer's ability to self-diagnose and self-treat the condition. The consumer's ability to understand labeling instructions including monitoring, follow-up care, and treatment.

The ability of the consumer to understand what the goal is that they should reach from the treatment and if they've attained it. And the ability to recognize any toxicity and, again, to understand

what to do about it if toxicity does occur.

This is an old slide and I'll just kind of run through it very simply again to compare and to contrast the prescription versus the OTC marketplace. When we have prescription drugs what we think about are patients.

Patients have a disease or a condition that requires monitoring and requires perhaps prescription medication which the healthcare practitioner is the one who prescribes what is appropriate and follows the patient to make sure that no adverse effects occur.

On the other hand, we have the OTC drugs. In the OTC drugs the patient actually is the consumer and they are seeking to relieve some kind of symptoms when they go to purchase a product. No prescription is needed and the consumer may or may not have the benefit of somebody to give them advice at the point of purchase depending upon whether or not they buy the product.

So clearly the labeling must be understandable enough for a consumer to understand which product they might want to buy or choose to get the maximum benefit that they may achieve which would be the relief of their symptoms for very little cost

which would be an adverse event.

We have also heard earlier today descriptions about the actual use and label comprehension trials. These are conducted on most products that originally switch from the prescription to the OTC world to be able to understand a little bit about consumers behavior for using these products.

These studies are aimed at looking at the consumer's ability to self-select, ability to use the correct dosage for the specified time on the label, the ability to identify when to see a physician, the ability to identify serious as well as any adverse events, and the ability to avoid any interacting drugs.

With that, I would now like to turn slightly to the issue -- to change gears a little bit and just try and talk a little bit about the issues for the discussion before you.

As you'll see, this is a brief summary of the questions that you have in your package. But these are some of the salient points again that we want you to focus on.

The first would be as the sponsor identified an appropriate target population? When answering this question, we would like you to think

about the symptomatic overlap with GERD. What happens to consumers who have less than two episodes a week of heartburn use the product. The issue of relative contraindications.

The issue of recurrence of symptoms after discontinuing therapy. The issue of chronicity of therapy; that is, repeat dosings since the label indicates that the treatment is only for 14 days and symptoms may recur and consumers may need further advice or may choose to use the product again.

And what to do about the acute symptoms since people may again have acute pain that they want to have relieved.

Further, other issues that you will be asked to address would be has the sponsor demonstrated that the consumer can adequately self-select to use the product. Did consumers with recurrence understand how to use the product. And has the sponsor proposed an acceptable duration of therapy for OTC use remembering that the OTC proposed label is for 14 days and the currently proposed -- the currently approved prescription labeling is for 28 for treatment of GERD.

Also for issue is part of the discussion would be the short-term versus chronic intermittent use of the product. The issues which we discussed

earlier about delayed diagnosis of a potential serious condition and concerns about rebound or recurrence after discontinuing treatment.

Finally, we will ask you to address the approvability. Has the sponsor provided sufficient information to support the approval of OTC Prilosec 1 for the treatment of frequent heartburn.

In answering this last question, if your answer is yes, we would also like you to address the possibility of if there is any additional information that you might feel might be needed to give that answer such as additional information from the sponsor, a Phase IV commitment, further labeling, modifications that would help you to arrive at that decision.

If the answer is no, we would also like you to give very succinct reasoning as to why and what kinds of things the sponsor might do to be able to eventually combat or to be able to further deliberate on this issue.

With that, I would like to turn the meeting now back over to Dr. Cantilena to begin the afternoon's discussion.

DR. CANTILENA: Okay. Thank you, Dr. Katz for that excellent summary and I think sort of the

beginning to help us focus on our discussion.

What I would like to do now is open the sort of general discussion of the issues and we'll try it just going in an open fashion. If it looks like we're not getting anywhere, then we'll sort of go issue by issue using Dr. Katz' handout. I would elect not to do that to potentially inhibit individuals if we just start that way.

I would like to hear, for example, from some of the GI members about the issues that Dr. Katz has just talked about, but there are other important issues that can also be discussed. At this point let's just open it for general discussion. Would anyone like to start?

Are we ready to answer the questions? Just kidding. Dr. Johnson.

DR. JOHNSON: As a non-gastroenterologist I would like to hear what the definition or the difference is between frequent heartburn and GERD.

DR. CANTILENA: Are you a gastroenterologist, Dr. Brass?

DR. BRASS: Yes. No, but I thought about this question for two years in the context -- nonstop -- in the context of this particular switch and have concluded that Dr. Johnson's question is theologic and

that there is, in fact, no meaningful answer, differentiation, and that focusing on the question becomes a distraction.

Clearly while our evolution in the past 15 years of understanding about upper GI pathology has led to both changes in our labeling of individual patients and our management of individual patients. From the patient's perspective nothing has changed.

They have this symptom of chronic heartburn and they frankly don't care what you call it. Also there is no doubt in my mind that patients who are in this cohort that we are talking about now, however, we label them, are currently being treated with OTC medications. We are not, in my opinion, opening up a vast new population.

We are shifting a population that is currently being treated with OTC and considering an option of another OTC paradigm for that same population whatever you label them. I don't think it matters. Nor do I think it matters to a primary care physician who has a patient come in with these sets of complaints. Again, they will treat that without differentiation.

DR. CANTILENA: Comments from other members of the committee? Dr. Cryer?

DR. CRYER: I take a slightly different view to the answer to that question. I think it is a matter that is something more than theologic. I think it is, in fact, a very practical issue. I think it is actually, in fact, the crux of the issue being discussed.

That is if you look at the currently recommended treatment guidelines for the management of the symptom of heartburn versus the treatment of a chronic disease such as GERD it is critical what we are actually -- how we are actually categorizing what's being described as frequent heartburn.

So it is an issue really in my mind of semantics but looking at the actual data, and this gets to the crux of the question that I asked earlier, what is the actual distribution of frequency of heartburn that was experienced in the patients who were evaluated in the trial.

We were provided data here. I guess this was in Dr. Shetty's discussion. In this patient population it looks like to me that 50 percent of the patient population or greater was experiencing heartburn four times per week or greater. In fact, 40 percent of the people have heartburn six or seven days a week. As a gastroenterologist I would call that

GERD.

I think if you look at the current management guidelines as suggested, for example, by professional associations such as the ACG, that dictates a specific treatment course that is not one that is episodic or that is associated with short-term treatment.

DR. CANTILENA: Bryron, I think sort of the issue of duration of therapy is something that we are asked to comment on specifically. I'm sure that will be something that is very important.

Other comments? Yes, Dr. LaMont.

DR. LaMONT: I'm a gastroenterologist and I would like to side with the first speaker. I'm sorry, I can't read your name from this distance.

DR. BRASS: Since you agree I will identify myself as Eric Brass.

DR. LaMONT: Excuse me, Eric. I would like to quote from the previous meeting that was held here. Dr. Sid Cohen was a member of the group that deliberated on this. Perhaps that is where the idea about religion came in. He said, "Are you trying to make a distinction between GERD and heartburn?" I don't see how you can do it. I don't know a difference.

I think if you filled the room with a group of Talmudic scholars, they couldn't tell you either. There is no difference. I agree. I don't think we should spend a lot of time trying to tease this out because I don't think it's relevant to the discussion.

DR. CANTILENA: As you see it, is it sort of just a question of severity in terms of the number of episodes a week?

DR. LaMONT: It's likely that the vast majority, greater than 90 percent of patients that have the symptom of heartburn, have reflux. Then I guess we're going to argue about the word "disease." Is it a disease? Do they have end organ histologic changes in the esophagus?

I don't think it matters because whether or not they have erosions or not, or Barrett's or not, or whatever it is, relies on control of acid and that is precisely what the medication does. I don't see it as relevant.

DR. CANTILENA: Okay.

DR. CRYER: If I may have a rebuttal to my colleague's opinion. I agree that the definition, the semantics, really are not relevant. I guess what my position is is that the course of treatment really is

dictated by the severity or the frequency of whatever it is that we're describing.

For individuals who have more frequent disease, that would likely require either more potent, more aggressive therapy or longer duration is essentially the point that I think we actually agree on.

DR. CANTILENA: Dr. Fogel.

DR. FOGEL: I think I agree with Dr. LaMont, although after the comment comes out you may think that I disagree with him.

The majority of patients who have reflux symptoms who have heartburn have what is called nonerosive reflux disease where there is no structural damage to the esophagus. Our professional society says that it is okay to treat people with symptoms actually for four to six weeks without doing any investigation. The concept of treating someone for two weeks, or even four weeks with an over-the-counter medication certainly is within the range of what is acceptable.

The concern that I have is that the use of this drug may remove the physicians from the care of patients with esophageal reflux. If you have a treatment that is available over the counter that

removes your symptoms, there is no need to see a doctor. What we know is that a percentage of these people will have Barrett's Esophagus.

A percentage of these people will have erosive esophagitis which requires more aggressive treatment. We won't be able to identify and treat them appropriately because of the fact that their symptoms will be controlled with this over-the-counter medication.

The greater concern to me is not the two weeks of treatment which the sponsor has suggested but what happens to the people who take the medication more than twice. From the use data and the comprehension data, it appears that is a significant risk.

DR. CANTILENA: I have just a quick question for the GI doctors. A comment was made at the beginning of the sponsor talk about when you normally start someone on a PPI you go through some screening questions.

I guess my question to you as some specialist is will that interaction, will sort of the information that you gain in that sort of history, can that be substituted by the label? Are you comfortable with that substitution, the interaction that you have

version on the box on the shelf?

DR. FOGEL: Most of the patients who come to the people in our practice, and I guess for most gastroenterology practices, are already on PPI. They are already receiving medication. These are drugs that are prescribed by the primary care physicians. I guess the question is whether the primary care doctors ask those questions.

DR. CANTILENA: Any other comments from GI? Then we'll go to primary care.

Go ahead, Ed.

DR. GILLIAM: My question goes to the actual use trial. It's at the three-month follow-up more than 58 percent had their heartburn return but only 20 percent went to their healthcare provider. My question to our GI folks is how much does that concern them and do we need to have stronger labeling for follow-up if your heartburn returns.

DR. CANTILENA: Dr. LaMont.

DR. LaMONT: Yeah, I can start. We have already discovered in discussions during the break that there is a big range in how frequently or how soon we decide to endoscope patients and look for disease.

There's one group that would say you don't

have to start looking for Barrett's until you've had heartburn for 10 years which is what a lot of gastroenterologists do. That leaves a lot of time for starting and stopping medications.

Others feel, for example, Peter Karilosys, a noted esophagologist, he says any patient who requires continuous maintenance medical therapy should undergo endoscopy to rule our Barrett's Esophagus. You have a huge range here. I think the incidence of Barrett's is low.

The number of patients with Barrett's who get cancer is very low indeed. It only comprises a tiny wedge of the entire pie of adenocarcinomas of the esophagus. I think the danger could be easily overstated of delaying workup, if that's what your question is.

DR. GILLIAM: So then you wouldn't have a problem with these people who have heartburn that --

DR. LaMONT: Don't get studied?

DR. GILLIAM: -- don't get followed up and don't see their primary care provider, whoever that is.

DR. LaMONT: Unless they had some of the danger signals that are listed on the label.

DR. CANTILENA: Dr. Goldstein and Dr.

Brass.

DR. GANLEY: It occurs to me in listening to this discussion that just as easily one could interpret the 14 days of therapy or even, let's say, in a certain percentage of instances a second course of therapy as a filter as those who are relieved, well, of course, by definition get relieved. Those who are not clearly will be directed -- apropos Dr. Fogel's earlier comment, will be directed not away from the medical establishment but into it truly needing it.

DR. CANTILENA: Dr. Brass.

DR. BRASS: Yeah. Again, I think it helped me to crystalize this problem in terms of putting it into another context. That is, I truly do wish everybody who had chronic uncontrolled symptoms or minimally controlled or required chronic therapy would, in fact, go see a healthcare professional for advice.

All the data continues to say those patients are already out there not getting advice. Look at the entry cohort. The entry cohort into the actual use study and other cohorts we've seen presented here and a number of other studies. There is no doubt in my mind these patients are out here.

To say that just because they happen to use this OTC product versus another, there is a different expectation. I don't think it's realistic. The fact that we are directing a portion of the cohort, though not as large a cohort, might be interpreted as some positive impact. I think again in my thinking the fact that these patients are out there right now self-treating is really critical to providing a context for what the impact is going to be.

DR. CANTILENA: Dr. Camilleri.

DR. CAMILLERI: Just to expand on that point but to give it a slightly different twist, I believe marketing studies have been done with regard to the prescription practices for PPIs. It certainly appears that at least 50 percent from my recollection -- and the sponsor's may have a more accurate assessment -- at least 50 percent of prescribed PPIs is still for the symptoms of heartburn and GERD.

To dismiss this as a nondoctor oriented issue that is dealt with entirely in the community with over-the-counter preparations I think would also be an error.

DR. CANTILENA: That's a very good point.

Other general comments or specific

comments? Yes.

DR. NEILL: Richard Neill. I'm a family doctor at the University of Pennsylvania. I sat through the meeting two years ago when we were presented data about the 10 and 20 milligram dose and I appreciate the work that the sponsor has done to address some of the concerns that were raised then.

My remembrance is not as clear as the transcript in our book, but to summarize my memory this combined group felt that the 20 milligram dose was safe and effective, the patients could self-select. We asked for an indication that would fit.

It seems like you have come up with that in this frequent or recurrent heartburn. I think it's appropriate if we discuss some of the concerns about whether or not allowing a medication like this over-the-counter is going to result in patients who never come in to see the physician or a healthcare provider, and yet it's clear those patients are already there.

They are already taking other medicines. There are also obviously other contributors to Barrett's Esophagus and morbidities that face those patients which have never been discussed by the group and probably aren't the proper topic for us, but which, I think, put the risk of Prilosec in tiny, tiny

perspective given the risks that they bring to the table.

I guess what I'm doing is building up to an overall conclusion of the things that I've heard. It certainly seems to me like something that ought to be approvable. I guess I would like to get on to answering the specific questions about the advice that FDA staff is looking at since much of the discussion that we're having now seems to remind me of what we talked about two years ago.

I don't think we're talking about safety and efficacy today. We did that two years ago. I think we're talking about patient selection for this indication and labeling and label comprehension for this indication.

DR. CANTILENA: I think that is exactly what we're talking about. We have to make sure that everyone is on the same page and everyone is comfortable with having an understanding so we can go forward.

Any other general comments before we start to address the questions? One more. Dr. Cryer.

DR. CRYER: Actually I'll follow-up on a point actually that was raised by both Dr. Goldstein and Dr. Brass. I guess it's the issue of how we see,

or how maybe we might discuss the differences between kind of the acid reduction therapies, the currently available H_2-blockers and how would that differ with respect to OTC use and kind of my view on it.

I agree entirely with you. We're talking about a very safe and effective class of medication, specifically the PPIs. I think the major difference with respect to the consumer and OTC use is selecting out severity of symptoms or selecting out severity of disease, however we call it.

With the H_2-blockers clearly there is going to be a population of individuals who are not effectively treated by H_2-blockers. In many instances that would likely drive them to further evaluation.

In contrast with a proton pump inhibitor, for example, providing free access, open access to a consumer, there would likely be a greater population of individuals who would be more effectively treated and, therefore, we are selecting out more severe disease that might have otherwise have gone on for medical attention.

I guess one discussion point, at least for consideration, is what would be the consequence of having selected out that more severe disease population by having treated them with the proton pump

inhibitor in an OTC fashion and are those consequences significant clinically with respect to other down-the-road consequences of not having involved a healthcare provider for more severe disease.

DR. CANTILENA: I think that is a very good point. Also the fact that these individuals will probably recurrently treat themselves inadequately possibly and what are the consequences of that which hasn't been studied obviously. We have to sort of estimate that with our expertise.

Dr. Brass and then Dr. Geller.

DR. BRASS: Yes. I think the proposition posed is a very fair one. I think it is part of the crux of the issue. Again, having thought about it, where I came out is that to some degree it's the ability of the individual consumer to replicate the empiric therapy that would be done as a first round therapy for a healthcare provider setting.

Though the duration might be different in a healthcare provider recommendation, that an empiric treatment with PPI would be done and if symptomatic benefit was taken over a period of time people would be happy and no further evaluation would be done. If that empiric therapy was ineffective, further evaluation would be done and that is certainly the

intent of the labeling. Form a first-round decision I'm very comfortable.

The concern is whether or not the warning will be completely ignored and you'll get large percentages simply going on continuous OTC therapy and missing a cohort of unknown size both in terms of what percentage of patients will do that and what percentage of the cohort is at risk if they do that and what your judgement is on that relative size. I guess my bias is currently that is not a large product if you look at the two different groups.

DR. CANTILENA: We have Dr. Geller and then Dr. Levine.

DR. GELLER: A second concern aside from the continuous administration that I have is how to write the label clearly for distinguishing between relief and prevention. I don't think that the company has succeeded in that and I don't know how to do it.

DR. CANTILENA: Dr. Levine and then Dr. LaMont.

DR. LEVINE: I'd like to make the point that in my experience I have a lot of confidence in patients with chronic heartburn. They know their disease. They can almost tease out and tell the physician when they come in, "I tried H_2s. I tried one

and I tried two pills, etc., of the pill you gave me."

One of the interesting things is the day-con score or the daily average consumption scores that people who take Prilosec for chronic disease. Some 27 million Americans have nocturnal classical reflux. Of that group a large proportion have classical GERD. Maybe erosive or nonerosive gastritis.

The average score was 1.6 for PPI so they are actually taking more than one a day. I do suspect realistically patients will decide if they have more severe symptoms they will try to relieve it with more than one pill a day necessarily.

I think we ought to give a little more confidence to the people out there with chronic heartburn because they do know their disease. Most of them -- many of them have been to doctors before.

I agree entirely with Dr. LaMont. I think the physician has to get into the loop but I'm not sure the physician has to get into the loop soon and with the advice and counsel of the patient we can probably do a pretty good job.

DR. CANTILENA: Thank you.

Dr. LaMont.

DR. LaMONT: I would just like to extend that a little bit. In fact, there is some data from

the Bardhan study that was reviewed this morning that about half of the patients would have some kind of recurrence so it's a big number.

What happens when patients recur if they go to a healthcare provider be it a primary care physician or a specialist they would probably be put on omeprazole. In fact, the people that I would worry more about are those that don't respond. Maybe they have something else.

Maybe it's really gallstone disease or angipectis or something else. I don't think a lot is going to be lost by patients continuing this medication for a period of time because it's precisely what we're going to do anyway in the vast majority without a big workup.

DR. CANTILENA: Okay. I would like to move -- if there are no strenuous objections I would like to move to the questions. We will not read the big preamble under background and we'll jump to subject area No. 1 which is population.

The first question is, "Is it acceptable that some patients with GERD plus or minus erosive esophagitis self-treat with OTC medication?" What I would like to do is first get a show of hands and then we'll go around and have you explain the circumstances

that it's either acceptable or not acceptable depending on your vote.

Let's say all in favor -- all in agreement that it is acceptable to self-treat with Prilosec -- excuse me, with an OTC medication for this problem raise your hand. All in favor? All opposed? Any abstentions?

Okay. The vote was 16 to 2 with the negative votes coming from Dr. Cryer and Ms. Cohen. If I can actually ask Dr. Cryer to comment on why he said no and then we'll ask everyone else.

DR. CRYER: There are two principle concerns. I guess part of it has to do with the duration of the therapy that is required for, and the question is specific, GERD plus or minus erosive esophagitis.

We've seen that and we know from experience that while the PPIs are very effective, the duration of therapy that would be required in an OTC setting is likely to be more than 14 days, particularly for someone who has erosive esophagitis.

Once these individuals come off of this therapy, the efficacy studies indicate that there will be a 75 percent recurrence of symptoms of frequent heartburn within three days after cessation of

therapy.

So it's not so much the initiation of therapy but the expectation that there will be a durable response with only short-term, and the continued requirement for prolonged therapy.

Look at the population overall of the mean results than some aspects of the presentations today depending on whose presentation you listen to, either the FDA's or the sponsor's. For the group overall it looks like many people are able -- not all are able to self-medicate. That definitely changes in 10 percent of the population that was low literacy.

The thing that just sticks out in my mind is that there was a 50 percent response rate in terms of the label comprehension for individuals who fell into that category. I think from a public health perspective and a public health concern, I'm just not so sure that even though we are potentially providing greater access for them, that that would be the appropriate thing to do for that specific subsection of the population.

DR. CANTILENA: I agree with you on that and we will have an opportunity further down the questions to talk about that. I think that is a very important point and I agree with you in that regard.

Ms. Cohen, can I call on you to ask why you voted no?

MS. COHEN: Dr. Cryer is very eloquent and I have a feeling you're talking about people. We get a little esoteric and we talk about all the people seeing physicians. I would like to talk about all the people who are not, the 44 million who don't have health insurance.

I'm concerned about relief versus prevention. I'm concerned that people have serious problems and these might take care temporarily for 14 days, but they can't afford to go see a physician. I am concerned about direct advertising to consumers. What's going to be said to them? How much information is going to be given to them? How much are they going to know about relief or its periodic? I just feel that the labeling is inadequate. I'm just worried that we have to think about the consumers out there.

Dr. Cryer, I have a feeling you deal with people and I work in some areas in the community. It's not esoteric. It's really people just being able to manage and can't afford a lot of things. I want to make sure that people can take less expensive products that will take care of the problem.

I'm concerned about those who have serious

problems. Not everybody knows what angina is or a lot of things. I don't think there's enough information to help our consumers.

I repeat again I am very concerned about direct advertising to consumers. We have to educate consumers about diet and prevention and maybe some of that will take care of needing to take any medication.

DR. CANTILENA: Okay. Thank you very much. Thank you for your comments.

The next question that we're asked to deal with is in the category of self-selection. The question is, "Has the sponsor demonstrated that consumers with heartburn can adequately self-select use of Prilosec 1?" I think with this question we'll also do similar style of voting. We'll vote by a show of hands and then we'll go around to get individual opinions if needed.

Let me call for the vote. The vote is all who agree that the sponsor has demonstrated that consumers can adequately self-select for the use of this product, please raise your hand.

All who feel that the sponsors have not adequately demonstrated that consumers with heartburn can adequately self-select for the use of the product, please raise your hand.

Okay. Any abstentions? Anyone abstain?

Dr. Fogel, I think we missed your hand.

DR. FOGEL: I thought that they had shown.

DR. CANTILENA: Okay. So he was a yes. So the final vote was three yes, 15 no. I think in this case maybe if we go around the table and just ask for individual opinions.

DR. TITUS: I want to enter into the record the three yes votes were Drs. Brass, Levine, and Fogel. The remaining votes are obvious from the record then.

DR. CANTILENA: Okay. Thank you. Why don't we start on this side of the table with Dr. Davidoff. If you could, explain your answer or your vote, please.

DR. DAVIDOFF: There are a couple of levels. One is that the actual use study was based on people who had actually read the label. But we also know from a number of pieces of information, some of which you've gotten today, that a very sizable proportion of people don't even read the label to start with which changes the denominator very substantially.

On top of which, although there is some argument about interpreting the data, it does look

like a very substantial proportion of people select themselves inappropriately no matter how you look at the actual data of people who have read the label.

DR. CANTILENA: Dr. LaMont.

DR. LaMONT: Yes. My concern is about how many times they might use it in a year and it may not be appropriate for this particular question of self-selection. My concern is how many times it can be used over a period of time. I don't think the label tells us about that.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: Yes. My understanding is that 24 percent of the self-selection population incorrectly self-selected themselves. To me that's a high percentage, unacceptably high.

DR. CANTILENA: Thank you.

Dr. Lam.

DR. LAM: I have the same concern as Dr. Patten that some of the data provided did not actually provide sufficient evidence that the consumer can adequately self-select the product.

DR. CANTILENA: Thank you.

Dr. Levine.

DR. LEVINE: My concern is that a lot of patients will not look at that label and we all

recognize that whatever the label shows. The other day I looked at the Pepcid AC label just because I haven't seen an OTC label and I was very impressed with bold print, red strips. I think that is very important when you get into labeling.

I do think my vote was yes with the provisal and thought that there would have to be some type of educational campaign at the level of the pharmacist, etc. I gave credit to the fact that there is a group that won't even look at it but that we absolutely need some type of educational campaign.

DR. CANTILENA: Thank you.

Dr. Gilliam.

DR. GILLIAM: My comments reflect Dr. Davidoff. I do want to commend the sponsor on especially the packaging which I think is actually pretty good. It's just that we know that most people don't read the package inserts or, again, the cartons.

If we can do, again, more education to get people to actually read these and follow the directions on the label, then I would be in favor of it.

DR. CANTILENA: Ms. Cohen.

MS. COHEN: If I may read, please. This is on page 3. "Thirty-three percent took the drug for

less than 14 days. Only 48 percent of them had spoken with their physician within the last year. Thirty-five percent had not spoken to a healthcare provider at all."

DR. CANTILENA: Dr. Neill.

DR. NEILL: I actually had a hard time voting no because while I agree that the data suggest from the actual use study that patients can't self-select, of those that selected inappropriately, the majority of those seemed to be patients who had heartburn less than once per week and simply are taking a very effective medicine for their not as severe condition.

The remainder that fall into that group, the majority of those appear to have conditions for which the consequences of incorrectly self-selecting are meaningless. While I voted no, that they can't self-select, it doesn't seem to matter much.

None of the things that I've heard so far are different for this product and this labeling than what I've heard related to other OTC products that require patient self-diagnosis of a condition that may mask or represent other important problems. This is a long way of saying while patients may not be able to self-select perfectly, it's acceptable to me.

DR. CANTILENA: Okay. Dr. Clapp.

DR. CLAPP: I find the package labeling ambiguous and a little confusing. I can see room for lots of error. First of all, notifying your doctor if you've had heartburn for three months or longer without talking to your doctor seems a little sequitis. I'm sure that's an area that can leave lots of question in terms of interpretation.

One of my other problems is I don't see a clearly stated relative contraindication of saying -- not contraindication but saying that there is no acute symptomatic relief with this medication.

Thirdly, I think that it should be stated on the panel that there is no expectation that the drug will work for you sooner than two or three days. With those things in mind, I don't think it helps the population adequately select for this drug.

DR. CANTILENA: Dr. Geller.

DR. GELLER: I thought that there were two issues that weren't addressed by the sponsors. One of them is repeat use because their study is only about using the drugs for 14 days. The other is whether patients expected relief -- immediate relief rather than just prevention. These were not addressed.

DR. CANTILENA: Dr. Uden.

DR. UDEN: I basically voted no on the principle that the sponsor doesn't go into doing their -- we haven't asked you do so that's why it's on principle -- go into their label comprehension studies with a benchmark that they are going to try to achieve in all the populations that they are studying.

I'm still concerned about the low literacy group in terms of their understanding the present label at 50 percent. My final concern, and Dr. Clapp touched on this, is that I think if we are concerned about the individuals who have episodic heartburn less than two episodes per week, that there has to be somewhere in the label some expectations for efficacy of the product, that it's not going to work for a day or two or three.

DR. CANTILENA: Dr. Williams.

DR. WILLIAMS: My vote no was purely on the basis that we know that people can identify heartburn but specifically for Prilosec 1 there is an indication for the prevention of heartburn. I think too many people will look at the box and miss their diagnosis of prevention. I think that the sponsor should provide a little bit more caution as to it's use, especially for prevention as its main focus.

DR. CANTILENA: Dr. Fogel.

DR. FOGEL: I voted yes for the same reasons that Dr. Neill voted no. Of the 290 people, I think it was 169 were taking the drug because they had heartburn less than one day a week. They were just wasting their money.

Among those who had contraindicated symptoms and contraindicated medications it's not really clear what the actual medical risk is. I agree with the other comments made around the table that the labeling could be substantially improved but I think that the sponsor is moving in the right direction.

DR. CANTILENA: Dr. Camilleri.

DR. CAMILLERI: Two points. One has already been made. One in four patients got it wrong in the self-selection process. The second is I still think that the deselection study is an important one in terms of risk management.

I think that the sample size was insufficient. Even probably the study setting in a kiosk in a mall probably didn't really address the question in the right study population.

I don't think that this is a show-stopper. This is the sort of study that can be done in the future in terms of making sure that risk can be managed because it is a very small quantitative risk.

DR. CANTILENA: Dr. Brass.

DR. BRASS: I voted yes. I was so impressed by the use of the word sepisodically that I just had to vote yes.

DR. CANTILENA: Thank you, Dr. Brass.

DR. BRASS: We were forced to vote black and white on a gray question. Clearly my yes vote does not reflect my opinion that the label is perfect and there are not things that can be done to improve it.

Key to my vote was the word "adequately." The implications of that word in terms of the decision making in this cohort. I think that we have to be very careful about our expectations about actual use studies and label comprehension studies.

Those of you who have not looked at lots of these studies and understand the kind of protocols and the mechanisms and the all-comers type of data, I mean, to pretend that these numbers have absolute significance, I think, is really overextrapolating.

My standard is always intimately related to an understanding of the consequences of getting it wrong. And as has been pointed out by several of my colleagues, that in terms of the self-selection criteria the errors would be of no clinical

significance and would be auto-correcting in terms of subsequent decisions based on the experience of the incorrect selection and represent, therefore, no incremental risk from a public health or an individual subject perspective. Therefore, I voted yes.

DR. CANTILENA: You are sort of rolling question five into question two basically.

DR. BRASS: Everybody else was rolling the label into it and redosing.

DR. CANTILENA: That's all right. You don't have to apologize.

Dr. Cryer.

DR. CRYER: The reasons in support of my vote no have already been stated.

DR. CANTILENA: Dr. Johnson.

DR. JOHNSON: I voted no but it was, again, sort of a difficult no vote on a gray question. I felt that strictly speaking they hadn't adequately shown, but I agree with Dr. Neill and others that those who selected incorrectly is probably clinically irrelevant.

DR. CANTILENA: Comments from Dr. Alfano and Dr. Goldstein.

DR. ALFANO: I would have voted yes on the basis that people are already self-selecting products

over the counter to manage this condition de facto. I thought there was a reasonable job done to achieve better education with the label. I do believe, though, as has been stated several times, the label could be improved.

DR. GOLDSTEIN: I would have voted as well yes, but I would like to make an observation to address directly something that Dr. Levine said and indirectly other members of the panel and which the sponsor cannot make.

It is widely acknowledged within our industry that they are probably the best at addressing the consumer. They have had long experience in a variety of fields. And I think in terms of education the concern of Dr. Levine and, indeed, of all of us I think they will develop the programs and are certainly able to and have done so in the past to address that particular issue.

DR. CANTILENA: Thank you. We are on to subject area number three.

DR. PEURA: (Inaudible.)

DR. CANTILENA: I'm sorry? Is there a comment you want to make?

DR. PEURA: A couple of comments that I have heard repeatedly around the table that I really

would like to just respond to. One is the comment about 50 percent self-selection within the low-literate population in the label comprehension study.

DR. HOUN: I just want to make sure from the Advisory Committee rules is this okay to have an open discussion now? Is it going to influence further questions? I just don't want to have --

DR. CANTILENA: I understand. In fact, why don't we just say if you have a specific comment that would correct something that has been stated incorrectly, that would be good. Other than that, we have to go on with the questions. If there was something that was assumed that is not factually correct that you have data for, sure, that's fine. If we are going off --

DR. PEURA: Well, the statement that I was going to address is that the 50 percent comprehensional low-lit in the label comprehension is factually correct. I think we lose cite that in the actual use study the low-lit numbers were considerably higher than that.

Also the question of whether it's effective on the first day or not. The drug does begin to become effective on the first day. The first day is statistically significant. It's not like it

doesn't work then.

DR. CANTILENA: Okay. The point is that the actual use data is a little bit different than the comprehension study.

DR. UDEN: I absolutely understand that it starts working the first day. When do they appreciate their symptom resolution, though? That was my concern.

DR. PEURA: We have data on symptom resolution on day one. They do appreciate it.

DR. CANTILENA: Okay. Thank you. Let's go ahead and get back to subject area three, actual use. The specific question is, "Did consumers who had a recurrence of heartburn symptoms respond appropriately?"

They want you to specifically comment on the likelihood that consumers will seek advice from a healthcare professional or the likelihood of the consumer using the product again without the advice of a healthcare professional.

DR. GELLER: Could I address the quality of the question?

DR. CANTILENA: Actually --

DR. GELLER: I don't think the studies were designed to answer this question.

DR. CANTILENA: I think here they are actually asking for advice based on your experience, your specialty and expertise. The questions have been revised, edited, thought about, and we are just going to try to answer the questions as written.

In the comments that I will solicit from everyone, you are certainly free to say, "If you had asked me X, I would have said Y." I think for the purposes of the committee, why don't we just stick with the program as they say.

DR. LEVINE: Mr. Chairman.

DR. CANTILENA: Who is talking?

DR. LEVINE: Dr. Levine here.

DR. CANTILENA: Okay.

DR. LEVINE: Could you possibly since this leads into number four, I think, directly, could you combine three and four? Some of our answers would complete be dependent on the duration of therapy.

DR. CANTILENA: I understand that but there is a specific reason why they want to separate these out internally with the divisions. We've had this conversation. That was my first suggestion as well and then the explanation, I think, was satisfactory. It will take a little bit more time but we are significantly ahead of schedule.

DR. FOGEL: Mr. Chairman, I also have a question. There is a great variation in treatment of people who have recurrent symptoms. What exactly is the appropriate treatment that they should have done?

DR. CANTILENA: I actually think that would be in your mind what you think they should have done. We would ask you to explain that as we go around the table because you are exactly right. Really sort of depending on your specific views, that certainly can change. There is no gold standard that is accepted.

I agree it's a difficult question but there are a lot of reasons why we will answer the question so we will answer the question.

Okay. So as you are thinking about this, have in mind sort of the specific data that you are referring to. Let me pose the question to the committee. All those who believe that the consumers did respond appropriately when they had a recurrence of heartburn symptoms, please indicate in the affirmative by raising your hand.

All those who feel that consumers did not respond appropriately, please raise your hand and kept them up for a minute. Sandy is straining.

Okay. Can we have the nos vote again,

please. All those who feel the consumers did not, please raise your hand.

DR. GELLER: I'm having a little trouble finding exactly the data that I'm looking for here.

DR. CANTILENA: Okay. The recurrence data in the actual use study.

DR. PEURA: Dr. Cantilena, would you like the slide?

DR. CANTILENA: Actually, I think we have your slides. Correct?

DR. PEURA: Yes. Slide 45.

DR. CANTILENA: Slide 45.

DR. GELLER: That really doesn't tell us what they did.

DR. CANTILENA: What about the FDA slide?

DR. GELLER: Then there is --

DR. CANTILENA: 27 on Shetty's slide.

DR. GELLER: Thank you.

DR. CANTILENA: Our numbers did not add up so what we'll do is we'll revote here in just one minute. Slide No. 27 of Dr. Shetty's presentation. It lists exactly what people did when they had their heartburn return by percentage.

The question to the committee is, "In your opinion is that an appropriate response based on that

study?" What we'll do is Dr. Titus will read the no votes and see if we missed anybody.

DR. TITUS: The nos are Dr. Camilleri, Dr. Cryer, Dr. Clapp, Davidoff, and Ms. Cohen.

Dr. Uden, are you a no?

DR. UDEN: I'm a yes.

DR. TITUS: Okay. So there are five nos. That means everybody else voted yes.

DR. CANTILENA: Hold it. There's -- okay. There's one abstention.

What's the final?

DR. HOUN: Sandy, you should just do this again. Yes, no, abstentions.

DR. CANTILENA: Start from the top. Take it from the top. All who believe that the consumers acted appropriately with a recurrence of their heartburn symptoms, please raise your hand indicating yes, that they acted appropriately. Keep your hands up, please.

Okay. All you feel that the consumers did not respond appropriately, please raise your hand and keep them up. Okay. All who have abstained. Okay. So we have 12 yes, five no.

DR. TITUS: The record needs to show that Dr. Geller was an abstention. The remaining 12

members on the committee voted yes.

DR. CANTILENA: Okay. Now what we would like to do is to go around the table and this time we'll start on this side. We'll start with the voting members and then we'll come back to Dr. Alfano and Dr. Goldstein after we complete the circle.

Dr. Johnson, if you could tell the FDA why you voted the way you did.

DR. JOHNSON: I voted yes. There are several reasons for that. One, I think that the responses of individuals probably wasn't perfect and didn't follow necessarily the package instructions because only 20 percent consulted a healthcare professional.

The majority did something. Most of them sought other therapy, in some cases prescription therapy. My sense is that many of them if this product was available OTC would seek another course of this therapy. I guess I'm not terribly concerned about that because my impression is if they saw a physician, the physician would probably give them a course of this therapy.

DR. CANTILENA: Dr. Cryer.

DR. CRYER: I voted no. I agree with several of the comments that Dr. Johnson made. The

perspective I come from is I see the entire goal of this is if the patients, the consumers are not responsive to therapy, it's to get them to a healthcare provider. That's been a recurring theme in our discussion today.

Looking specifically at the proposed label, it states, "Do not continue beyond 14 days unless directed by your doctor. If you frequent heartburn continues or returns, it could be a sign of a more serious condition."

It's the specific statement with specific instructions to the consumer that recurrence could indicate a serious condition but, nevertheless, only 20 percent of those individuals went to a healthcare provider. I think, in my opinion, that constitutes a no.

DR. CANTILENA: Thank you.

Dr. Brass.

DR. BRASS: I voted yes because I rewrote the question in my own mind and I posed it to myself as if the results of the actual use study were replicated in the general population would you care? No, would you mind so I could vote yes. I won't mind. The point is, I don't care. It's fine.

DR. CANTILENA: What did you vote anyway?

I forget now.

DR. BRASS: Because this profile if it occurred in the general population would be okay with me. That apropos of Dr. Cryer's point, I would have been very interested in the breakdown of a follow-up based on symptomatic relief during the primary treatment course.

In other words, did those 30 percent who didn't respond, were they more likely to have sought medical attention whether or not they recurred quickly after. In other words, how did the clinical response predict the segregation in terms of behaviors afterwards, I think, would have been interesting data to help address that point.

DR. CANTILENA: Dr. Camilleri.

DR. CAMILLERI: I voted no because I looked at the actual use study as a trial run of what would happen if and when this medication was approved for the OTC market. The answer to me is unequivocally that people did not respond appropriately in the context of the study and the question that was being asked.

The question that was being asked was, "You go and see a doctor if you don't respond at the end of these two weeks." That is the standard that we

will need to maintain in the label in order to make sure that this can be used safely in the OTC situation. I voted no for that reason.

DR. CANTILENA: Thank you.

Dr. Fogel.

DR. FOGEL: I voted yes. I think that for people who have a mindset of self-medication, these people did the right thing. It would be nice to have a little bit more patient information but the study wasn't designed that way to tell us what was going on, severity of symptoms, so on and so forth.

To my way of thinking, it would be nice if these people came to doctors but a lot of people don't come to the doctor for these symptoms. The way they treated themselves is appropriate.

It's an unrealistic expectation to expect an over-the-counter drug to alter how people think about healthcare. You can't expect people to go to the doctor just because the over-the-counter medication caused them to have a recurrent -- because they had a recurrence of their symptoms when the drug effect disappeared.

DR. CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: I voted yes with the

understanding that at least 20 percent of the individuals that received the product did come to the doctors and 20 percent that would have never gone. I'm more optimistic about what I'm seeing than what is negative.

DR. CANTILENA: Dr. Uden.

DR. UDEN: I voted yes because those who didn't respond treated themselves. I wish I could have seen more diet and exercise but this is America and that's not going to happen. End of statement.

DR. CANTILENA: Thank you, Dr. Uden. Dr. Geller.

DR. GELLER: I think I should probably change my vote to no because I just realized that the abstention is totally wasted so I think I'll change my vote to no. I do that because 20 percent said they consulted a healthcare provider but that number probably has a bit of an overestimate because if they did read the label, then they would have known that was what they were supposed to do but they may not have done it and just said they did it.

I guess some of the other issues raised about questions not answered are very disturbing to me. In particular, at the three-month follow-up period there was no opportunity to go and get your

Prilosec 1 again over the counter so I would like to know if patients would have gone back to have a second trial of Prilosec 1. I guess I'm distressed that none of the studies the sponsor provides answers the question about compliance in that regard.

DR. BRASS: No, the actual use study did include the opportunity to go back and buy more.

DR. GELLER: But actually the period of time is too short because over that three-month period people are coming in.

DR. BRASS: I'm just correcting the statement that you said they didn't look at it.

DR. GELLER: That was inadequate because people coming in uniformly over the period.

DR. CANTILENA: Thank you.

Dr. Clapp, please.

DR. CLAPP: As the question is posed, I have to vote no because clearly 37 percent did not respond as the package label panel instructed them to, and that is to seek medical advice if the treatment time of 14 days was not sufficient.

DR. CANTILENA: Dr. Neill.

DR. NEILL: I voted yes looking at slide 27 from Dr. Shetty's presentation and considering the fact that we still haven't settled what is

appropriate. Given that you are asking us to make a decision about whether consumers are doing the appropriate thing and none of us up here have reached any consensus on what is appropriate, I trust that staff is taking all of these comments with a large grain of salt.

Having said that, of the things that they did in the actual use study, all of those things strike me as being appropriate. I've got to tell you I can't get 10 percent of my patients to change their lifestyle related to anything.

The question and the one concern that I've heard seems to be that not enough of these patients have chosen to go back and see a healthcare provider who in many instances is simply going to tell them to do one of the things that they have already done here.

One of the choices that a consumer does not have but which may be appropriate given the large number that had heartburn for more than five years is doing an endoscopy.

Maybe that will be a meeting sometime in the future when we have endoscopy suites in the mall and patients can take a kit home and they will check their cholesterol on the way home and endoscope themself with a little virtual endoscopy device or

something.

DR. CANTILENA: You'll probably be off the committee by then though.

DR. NEILL: Gladly.

DR. CANTILENA: Ms. Cohen, please.

MS. COHEN: Dr. Neill, will you take the endoscopy for me? I would like to quote again because it's the best way I can do it, the responses to the follow-up question here, three months after the study showed that 58 percent of the consumers available for the follow-up had their heartburn return.

Forty-six took an antacid heartburn medication. Twenty-seven took a prescription heartburn medication. It's here, 21 took an OTC acid reducer and 20 of those contacted their healthcare provider. There's more.

What was the final result? They did it but what was the final result? Did they go to a physician? Did they find that they had something serious? I feel it's inadequate information. It starts out and gives it but you don't know the end results. Pardon my Boston accent. I can't do any better.

DR. CANTILENA: Thank you.

Dr. Gilliam.

DR. GILLIAM: I voted yes mostly for the reasons Dr. Neill stated. Also the comments that he and Dr. Brass made on the previous question. I really changed by vote to the previous question in the way I vote this time.

DR. CANTILENA: Dr. Levine.

DR. LEVINE: I voted yes mainly for the reasons Dr. Johnson and Fogel pointed out and for my hope and confidence that with the next question when we change it, possibly the duration of treatment that 57 percent figure will plummet to 25 or 30 percent.

DR. CANTILENA: Dr. Lam.

DR. LAM: I think the question can go either way actually but I voted yes because, in my opinion, the patient did act appropriately by opting for alternative treatment.

DR. CANTILENA: Dr. Patten.

DR. PATTEN: I voted yes based on the information in Dr. Shetty's slide No. 27. As I take a look at that, of the 57 percent who had a recurrence, 27 percent took a prescription medication which says to me they are already under the care of a physician. Then an additional 20 percent consulted a healthcare professional.

DR. CAMILLERI: Excuse me. It's not

additional.

DR. PATTEN: Pardon?

DR. CAMILLERI: Nowhere does it say that it is additional.

MS. PECK: Oh, I see. Okay.

DR. CANTILENA: It could be the same person.

MS. PECK: I see. Thank you for correcting me. At any rate, I would concur with Dr. Neill that to have 20 percent of a population opt to see a healthcare provider is rather impressive.

I would like to have seen a longer period of follow-up. I'm not sure when within that three month window the recurrence occurred so I don't know how close in time the recurrence was to a decision to change lifestyles, see a healthcare professional, and so on. It's clear to me that people are doing something.

DR. CANTILENA: Dr. LaMont.

DR. LaMONT: Yes. I agree. In fact, I was going to make the same point that possibly more than 20 percent consulted a physician. I would also like to clarify that we don't do endoscopy on patients who when they stop their PPI get heartburn. What we do is put them back on the PPI. We're not looking to

scope a whole bunch of patients and look for cancer that have this complaint. This would be, in my view, inappropriate use of a resource so I voted yes because I think these behaviors are safe and appropriate.

DR. CANTILENA: Thank you.

Dr. Davidoff.

DR. DAVIDOFF: I voted no because I also focused primarily on the issue of whether people went to see a healthcare provider. My concerns there were two. One is the number of 20 percent which I think is a pretty squishy number for two reasons. One is there was no conformation that they did as has been mentioned.

The other is that there is no confidence interval so we don't have any idea what the behavior might be if this kind of behavior were generalized to the general population. This is in one small study.

But then the related question -- important question is does it matter whether they saw a healthcare provider. I agree that very likely many times healthcare providers would have done many of the same things that are on this list. But the healthcare providers might actually have taken a good history.

DR. CANTILENA: Comments from Dr. Goldstein and then Dr. Alfano and then, I think, Dr.

Johnson had her hand up.

DR. GOLDSTEIN: The word "appropriate" gave me pause. It depends on how you want to interpret the word "appropriate." Appropriate for whom? For traditional medical orthodoxy or -- and I'm a physician -- or for themselves? Was the patient acting in their own best interest? If it's medical orthodoxy, then perhaps by our standards they did not react appropriately, but if it's for themselves, then it's my feeling that they acted very appropriately and very normally.

I should also point out and reinforce the fact that as Dr. Williams and others have pointed out, the fact that 75 more people were some how persuaded to see their physician who had not is a good on the whole public health outcome. I would have voted certainly yes under those circumstances.

DR. CANTILENA: Thank you.

Dr. Alfano.

DR. ALFANO: I, too, thought it was a good outcome because it was a better outcome than they had before they entered the study in the sense that they saw a healthcare provider or they consulted a healthcare provider at twice the rate that they did in the prior year. Then it does look like there was a

modicum of lifestyle changes that occurred.

DR. CANTILENA: Thank you.

Dr. Johnson, did you have an additional comment?

DR. JOHNSON: One additional comment I wanted to make that I guess makes me optimistic is that I think there is a potential in the real world situation for this to be better. While I share many of Ms. Cohen's concerns about direct-to-consumer marketing, I think it can either be used sort of inappropriately or it can be used in a very educational way.

I think if the DTC marketing focuses on reenforcing the importance of follow-up, particularly television advertising where there is a verbal message, follow-up with their physician, I think there is the potential that there may be many, many more patients who eventually have care by their physician than do at present.

DR. CANTILENA: Yes, Dr. Fogel. You have an additional comment?

DR. FOGEL: Actually, can I ask a question to the sponsor about the data?

DR. CANTILENA: About the data, yes, please.

DR. FOGEL: Of the 57 percent that had return of their heartburn, what was the -- do you have any data about the response to these various treatments? Were they still symptomatic or did their symptoms go away with antacids, change in lifestyle, etc.?

DR. PEURA: We did not ask that question. We only asked if it returned and what they were doing about it.

DR. CANTILENA: Okay. Thank you. Let us now turn to the issue of the duration of therapy and repeat use. The next question is, "Given that the treatment for GERD with erosive esophagitis is a minimum of 28 days, is the proposed 14-day duration of therapy acceptable for this population?"

Then I guess if you answer no, we'll ask you in the comment period should the treatment be longer. Does everyone understand the question?

Dr. Johnson.

DR. JOHNSON: Would it be possible for us to have some discussion on this? I frankly am not comfortable voting on this without some discussion and hearing from the gastroenterologists, their feelings on this point.

DR. CANTILENA: Sure. If you would like

to open the discussion, go ahead and then we can ask for their input.

DR. JOHNSON: Okay. I would like to hear the opinions of the gastroenterologists. And Dr. Brass, of course.

DR. CANTILENA: Are you going to set the board exam soon?

DR. BRASS: I think, again, in my mind here is how I thought about this. I have no doubt from reading the literature as well as sponsor's data that if you treat these patients for a 14-day course of treatment with omeprazole at 20 milligrams per day, a percentage of that cohort will be symptom free for some follow-up period afterwards. And that if you did endoscopy there would be endoscopic improvement in a subset of that population. Those would both be significantly different than placebo.

I also have no doubt that if you treated for four weeks those numbers would both be higher. If you did it for eight weeks, they would be higher still. I have no doubt that at two weeks there is benefit in terms of both a period of complete symptom relief and endoscopic healing.

At the same time, I am also aware of this being a philosophical shift in trying to get consumers

to use an OTC product for a daily basis during which they are not symptomatic but need to complete the period to get benefit. We have all raised concerns about masking symptoms, appropriate compliance, patient's decision making.

That is only with a two-week course. It is unclear in the absence of data whether going behind two weeks would, in fact, be associated with the kind of improvement that has been observed in clinical trials and whether that would be offset by further deterioration in parameters that the committee has already expressed concerns about with respect to compliance, etc.

DR. CANTILENA: I just have one comment in that regard, and that is really you have to balance sort of that issue with the fact that you would be approving and basically endorsing substandard therapy. If the standard therapy is 28 days for this indication, then you are saying it's okay to treat half as long knowing that the failure rate will be higher.

DR. BRASS: We are dealing with a different cohort. Again, remember the cohort we recruited in those studies all had endoscopic inclusion criteria, or at least many of the studies

had endoscopic inclusion criteria so the cohorts are not identical so that whether it's substandard care or whether a different care option for a population that selects it is open on the risk to benefit. I'll leave it at that.

DR. CANTILENA: Just one more point and then I'm just going to ask Dr. Ganley one question. If you look at the actual use and you have really more than half the people with recurrent symptoms, my question is what would that have been if we treated for 28 days? That is sort of the first issue in the back of my mind.

Then the question for Dr. Ganley's group is what are the data? Is the Rx label for GERD 28 days? That is the first question. If so, are there data where they looked at shorter courses for efficacy?

DR. GANLEY: The Rx labelling for GERD without erosive esophagitis indicates that -- recommends a dose of 20 milligrams up to four weeks of therapy. For erosive esophagitis the recommended duration of therapy is four to eight weeks.

DR. CANTILENA: Okay. And is there any information if you treat for shorter periods of time?

DR. GANLEY: Well, I believe the sponsor

may have a comment. I'm going to -- I'm sorry. Repeat the question, please.

DR. CANTILENA: Yeah. I was just asking if you have any efficacy data and if the treatment period is half of that time for 14 days other than the actual use study here where we have 57 percent recurrence.

DR. RACZKOWSKI: We have seen that data but also with the original approval of the product there was some more data, yes.

DR. PEURA: Dr. Cantilena.

DR. CANTILENA: Yes.

DR. PEURA: I believe we do have data that speaks to shorter duration, two weeks.

DR. CANTILENA: I've seen the efficacy but are there larger studies, I guess, is the question. Are there larger studies that would add our confidence or increase our confidence?

DR. PEURA: Yes, there's the databases published by Bardhan that talks about period of time. There's the Castell study, 14 versus 28.

DR. CANTILENA: So if you treat for 28 is the recurrence rate significantly lower.

DR. ZORICH: I believe I can address that. May I use this? Thank you very much. I would like

to specifically address this because the Bardhan study really adds some interesting perspective to this because when you look at the clinical trial data, of course, and even as I showed as healing, and Dr. Brass mentioned going longer is always better.

With the question relative to what actually you need for consumers who are electing to use this product, what the bardhan study actually showed was that the strongest indicator of a good outcome was symptom control at two weeks. In fact, that was more important interestingly enough that negrade of esophagitis at entry, duration of symptoms, body mass index, gender, or age.

So what Bardhan allowed to do, and I didn't really spend a lot of time during my presentation, but for those people who did not respond at 14 days, they immediately were given another 14 days. In that group of individuals, all it really pointed was that you have identified a group of people who will go on to need more chronic therapy. That is the enriched population who ends up being dosed on a more maintenance basis.

It does not, in fact, stopping at 14 days you do not, in fact, have a lesser affect in the majority of the people. In fact, what you're doing by

letting those people go for another 14 days is just identifying the people who would be better served we think being directed to their physician after 14 days.

DR. PEURA: Dr. Cantilena, the other point here I think just to be very clear on this from the sponsor's point of view is that the indication that we are seeking to switch is for prevention of frequent heartburn. Although we understand there may be some GERD people within that population, we're not asking for that indication to be switched.

The second point I would make is that when you look at symptomatic relief 14 days is essentially as good as 28 days for symptomatic relief in this population. You get 90 percent of the symptom relief in 14 days so you don't need to keep going any longer than that.

The other thing I think I would say is that in moving this product into the OTC setting, one of the reasons that we looked at a 14-day label instead of the 28-day Rx label is that we think it's actually more prudent in moving this product into the OTC setting to give people instructions for shorter duration of therapy because we think overall that is a better course of therapy for the overall target population as opposed to trying to seek to treat some

subset of that population just to be clear.

DR. CANTILENA: Okay. Thank you.

Dr. Geller.

DR. GELLER: I just wanted to say that I would hope the committee would not vote to change the number of days to 28 because we haven't seen any data in this population and it would be, I think, very unfortunate if we would make a decision based on what we surmise to be the case.

I think we have seen plenty of data on 14 days and I think there would have to be many additional studies in this population if they wanted to go to 28 days.

DR. CANTILENA: Dr. Neill.

DR. NEILL: I still haven't heard any of the gastroenterologists on the panel speak and I would like to.

DR. CANTILENA: Dr. Levine, Dr. LaMont, and then Dr. Cryer, and Dr. Fogel.

DR. LEVINE: A comment by the sponsor left me a little fuzzy because our organizations clearly show, as shown right up there, that 28 days of treatment be it intermittent versus maintenance.

Twenty-eight days of treatment with a PPI will markedly increase the healing of a subpopulation

who will be taking this drug because of frequent heartburn. That is the group with GERD and that is particularly the group with either nonerosive or erosive esophagitis, etc.

If you, in fact, take this drug for 28 days, the population that will be effectively treated, the percentages will go down significantly. Perhaps 20, 25 percent. At that point if these patients do not have relief, it is much more significant -- albeit there are some exceptions -- it's much more significant to have a referral and subsequent follow-up by the individual physician, general physician, or specialized physician.

To me to negate the 20 percent, 25 percent patients who could use this drug makes no sense. I think it's so hard with symptoms to tell this heterogenous population that we have to treat all the patients with frequent heartburn. That is why I think 28 days is preferable and almost mandatory than 14 days.

DR. CANTILENA: Yes. There's a comment from the FDA first.

DR. RACZKOWSKI: I would like to give Dr. Hugo Gallo Torrez, who is our medical team leader in the Gastrointestinal Division an opportunity to

address some of his issues. Thank you.

DR. GALLO TORREZ: This is a quick comment in support of 28 days and in support of what Dr. Levine has specifically just mentioned. According to the labeling erosive esophagitis is healing.

The healing at four weeks with 20 milligrams is 39 percent only, I should add. At two weeks it has to be in the late 20s, early 30s. There will be significant improvement in the healing if one administers the medication for 28 days rather than 14 days.

The early data from the labeling from Prilosec will be 74 percent healing in eight weeks. This is from the labeling.

MS. COHEN: For how long? How far has that been carried out to see how long that lasts, the efficacy?

DR. GALLO TORREZ: Oh, eight weeks treatment 74 percent. Four week treatment, 39 percent.

MS. COHEN: But were those people followed afterwards? It was 74 percent at that time but did that continue?

DR. GALLO TORREZ: After the eight weeks?

MS. COHEN: Yes.

DR. GALLO TORREZ: I don't know.

DR. CANTILENA: She's asking about the recurrence rate of symptoms.

MS. COHEN: Thank you.

DR. CANTILENA: Dr. LaMont, you had a question?

DR. LaMONT: Just a comment about in response to the request for GI input. I think 14 days is the right duration of treatment because it strikes a balance between what the ideal treatment would be at the hands of a gastroenterologist which might be six weeks or even longer and what we could expect with over-the-counter self-treatment. These are patients that are self-treating.

The goal here isn't to heal esophagitis because we don't know whether they have esophagitis or not. It's to heal a simple symptom of heartburn. It seems like if after 14 days that hasn't healed, then these other things would happen.

Notice that in this table on Dr. Shetty's data on slide 27 only six percent of the people that had frequent heartburn return did nothing. That means all the rest did something. They either took more medicine, which would help healing, or they went to a doctor or both.

I think 14 days is right because if we are worried about masking symptoms, and I've heard a lot of that, masking other diseases with this treatment, then this would be a good balance between efficacy for a simple symptom and avoidance of masking.

DR. CANTILENA: Dr. Cryer and then Dr. Fogel.

DR. CRYER: So I agree with Dr. LaMont's comments. It's clearly -- if we are speaking about GERD and erosive esophagitis, the data are very, very clear that 14 days would be inadequate for the treatment of GERD and erosive esophagitis. Thinking about applying that patient population to this potential OTC setting, my overriding goal is to get these people to a doctor for the ones that have severe disease.

So if it is an accurate statement, and it is definitely an accurate statement, that erosive esophagitis will clearly take 28 days of treatment, and the proposed duration is only for 14, what we are doing then is kind of selecting out the people who will have severe symptoms and get then potentially to a healthcare provider earlier even though it may only be 20 percent of those.

Also another comment I would like to make

kind of in defense of a previous comment that Dr. comment that Dr. Triebwasser made is that I don't know that this is the appropriate question to ask of comparing this patient population of what we are considering to be frequent heartburn to those who have erosive esophagitis because the population under question is not necessarily -- will not 100 percent have erosive esophagitis.

I have kind of come around a little bit on this. I was looking at the actual use population. Looking at the data from two of the efficacy trials, after 14 days here, if I'm reading it correctly, 75 percent had recurrence of their symptoms within five days. Clearly for 75 percent of the people 14 days of therapy was inadequate. That would likely be the people hopefully who would be pushing to the healthcare provider for 25 percent it was adequate.

DR. CANTILENA: Thank you.

Dr. Fogel.

DR. FOGEL: The Bardhan data and a comment made by Dr. Goldstein previously used the term that this is a filter. A subset of people with heartburn will get better with a 14-day course of treatment. I think that we should accept that. We are not looking to treat reflux disease or chronic heartburn or

erosive esophagitis. We just want to treat the symptom.

For those people who remain symptomatic since the drug is going to be over the counter, they may choose on their own to take a second two-week course or they may choose to see a doctor. They have a choice as to what they want to do. They can use other over-the-counter medications.

I think if we go towards a 28-day treatment regimen, I believe Dr. Geller's comments are correct that we have no data about it. We are going to change the locus of care from the physician to the patient with all the risks that are associated with that.

DR. CANTILENA: Dr. Camilleri.

DR. CAMILLERI: Well, you asked the question, Mr. Chairman. If you extend this to four weeks of treatment, what would be the recurrence rate? I would venture to suggest from clinical experience that if you take people with an average of five days of heartburn a week and you treat them for four weeks, you will keep them in remission a little longer but ultimately all will recur within 12 months.

DR. CANTILENA: Okay. Thank you.

Dr. Johnson, have you had enough input

from the gastroenterologists? Okay. Very good. We will proceed to question area four. The question will be answered as follows:

All those who believe that a 14-day duration of therapy is acceptable for this population, please raise your hand. All those who feel it is not acceptable, please raise your hand.

DR. TITUS: I want to enter into the record that, if I watched hands correctly, there was one no which was by Dr. Levine. Everyone else voted yes. That means there were 17 yeses and one no.

DR. CANTILENA: Dr. Levine, would you like to add anything to the comments that you have already made on this?

DR. LEVINE: Yes. My point was I think at 28 days you would also have the same recurrence rate that you would have at 14 days. I think the window of getting the patient to somebody is very important for the alarm symptoms.

I think the alarm symptoms of dysphasia and weight loss, etc., are very important to be explained to the patient in anyway that we can educationally. I don't think significant changes in the long-term outcome will change from 14 to 28 days if the alarm symptoms would be lesser or greater by

just making that one change.

DR. CANTILENA: Okay. Thank you. Would anyone else like to comment? I'm not going to go around the table unless we have a burning desire. Not heartburn but a burning desire.

Okay. Let's get onto the ultimate question, question five, in the subject area of approvability. Has the sponsor provided sufficient information to support the approval of Prilosec 1 for the prevention of frequent heartburn? Any discussion required?

DR. BRASS: Clarification.

DR. CANTILENA: Yes.

DR. BRASS: If we feel that the label isn't yet perfect but we thought it was probably doable, how would you like us to vote?

DR. CANTILENA: I would prefer that in that case you vote in the affirmative because underneath that we are going to ask you about specific things that you want.

DR. BRASS: Thank you.

DR. CANTILENA: Dr. Ganley, is that correct? Okay. Any other clarifications?

DR. GELLER: Even if you think that there should be another -- that the label should be

significantly rewritten and there should be an additional comprehension study with the new label, then you still should vote yes?

DR. CANTILENA: I think so. If you think the condition is something that can be treated that the consumers can adequately self-select ultimately but it needs more work, you'll have the opportunity to specify what that work is. Is that on track with the FDA?

DR. GANLEY: The third bullet under that where it says, "Are there any additional labeling or marketing suggestions." We are trying to make it really clear cut.

DR. HOUN: I think if the panelists feel strongly that something should be done premarket, that should be stated clearly. If you think it could be done postmarket, that should be stated clearly.

DR. GELLER: To clarify, if you think something should be done premarket, should you still vote? And you think it can be done.

DR. HOUN: If you think ultimately it can be approved but you want something done premarket, you can vote that it ultimately can be approved. It is approvable but you would like to see X, Y, or Z premarket. If you think that it should not be

approved now at all, then you would be voting no. If you think it can be approved but some of the studies can be done after market, you could state that.

DR. CANTILENA: So really the question is approvability and on your judgement considering really all the data that you've seen and all the discussions that have taken place.

Let me pose the question to the committee. All those who feel that the sponsor has provided sufficient information to support the approval as recently now clarified as an approvable condition and proposal, please raise your hand in the affirmative. Keep your hands up, please.

All those who feel like it's not approvable, raise your hand. Ms. Cohen and Dr. Davidoff negative. Any abstentions?

Did the math check out?

Okay. For this part what I would like to do is as we go around the table, for those of you who recommended approval, we'll ask you to comment on each one of the areas that are listed under the section if the committee recommends approval so that we capture your comments right here and now.

For those two who recommended that it should not be approved, please specify in your

comments what additional information should be provided to ultimately support the approval.

We are due to start over on this slide with Dr. Davidoff. You were in the negative so if you can start, please.

DR. DAVIDOFF: Yeah. This is a really difficult vote for me to decide on because I realize that there are potentially some very substantial potential benefits. They are, however, in my view moderate. The number needed to treat in terms of efficacy is in the range of five to 15 which is pretty good but not fantastic.

The gain would be if people actually read and followed the label, the availability of a single course of 14 days of treatment before they went to see a physician and dealt with the issue in another way. This would get more people to physicians, I agree.

On the other hand, the risks, it seem to me, would be a sudden major increase in essentially unsupervised exposure to a drug for which there are, in my view, a number of very major unanswered questions.

The one that concerns me particularly for which I feel there is not evidence that at least I have seen or that I have not seen as being convincing

is the issue of potential oncotgenecity. We are not talking about exposure of small numbers of people. We are talking about the exposure of millions of people over long periods of time potentially.

I feel, therefore, it's premature to approve this for over-the-counter use when, in fact, patients can continue to get the drug by going to see their doctor but they are doing it under a somewhat more supervised, followed, and monitored kind of situation.

Finally, I agree there are some labeling issues. I think those probably can be dealt with but they are substantial.

DR. CANTILENA: Thank you.

Dr. LaMont.

DR. LaMONT: Yes. I think the repeatability is the issue that I am most concerned about regarding the labeling. I would suggest that wording to the effect that if the symptoms of heartburn recur within four months of finishing the course of Prilosec 1 or however it's going to be identified, that you should contact your physician.

That would allow them by strict definition a person could take this two or three times a year which I think would be safe. That is, could take 14

days of this medication two or three times a year.

DR. CANTILENA: Okay. So the number of courses then should really be no more than three per year and you are comfortable with the 14 days. Are there specific issues with the label other than for the number of courses that you would like addressed?

DR. LaMONT: No.

DR. CANTILENA: Okay. Dr. Patten. I'm sorry, Dr. Katz had a question.

DR. KATZ: Yes. When people are giving their answers, can you also ask if the answers are things that need to be done prior to or after so where it would lie in terms of additional information requests.

DR. CANTILENA: Thank you.

Dr. LaMont, would you like to go back over that?

DR. LaMONT: This would be a labeling thing so it should be done pre.

DR. CANTILENA: So everything that Dr. LaMont had said would be prior to marketing.

Dr. Patten.

DR. PATTEN: Yes. I have a question regarding the third bulleted point here, "Are there any additional labeling or marketing suggestions?"

Does that translate into requirement?

DR. CANTILENA: Yes.

DR. PATTEN: Suggestion is a requirement?

DR. CANTILENA: Yes.

DR. PATTEN: Okay. I'll revisit this.

DR. CANTILENA: So you would like us to come back to you after we go through? Okay. You'll have, I think, probably plenty of time by the time we get around the table.

I'm going to just go out of order here very briefly to Dr. Camilleri who has to leave early so we're just going to skip over here to Dr. Camilleri and then we'll go back.

DR. CAMILLERI: Thank you very much, Mr. Chairman. I completely agree with Dr. LaMont that the issue of repeatability is of paramount importance in my mind. I had actually come to the same conclusions that about once every four months and two to three courses of 14 days each per year would be appropriate. Therefore, under bullet three the unsupervised use of this medication would be two to three courses per year in my mind.

Under bullet four in Phase IV commitments I still think that the deselect study in patients with alarm symptoms, perhaps in a clinic, would be quite

important to do just to make sure that the comprehension is also at a very high level for the package insert, for the labeling in the context of a high risk group. Thank you very much.

DR. CANTILENA: That would be something that you would want after approval obviously, Phase IV.

DR. CAMILLERI: Yes. Thank you.

All right. Let's go back here to Dr. Lam.

DR. LAM: On the second bullet I actually put down the limit on the number of calls to about two so basically that is in agreement with two of the GI specialists. As far as the time period, it will be up to about four months or so.

I think actually there are a lot of labeling that need to be worked on in terms of instruction and making it clear to the consumer such as prevention with relief of symptoms and some of the information on the drug interaction. Do not use with the other acid reducer that we have actually have visited before.

Rather than saying that it had to require faithful commitment, I'm thinking in terms of if we do revise the label significantly, that the sponsor should actually do a new label comprehension study

before we actually approve it.

DR. CANTILENA: Right. So your specific comments are that we need to improve the labeling on those areas that you mentioned. That should be done prior to approval. I'm sorry. What did you say for the number of courses?

DR. LAM: Two.

DR. CANTILENA: Two courses per year?

DR. LAM: Yes.

DR. CANTILENA: Per year. Okay. Very good.

Dr. Levine.

DR. LEVINE: I'm more concerned about alarm symptoms more than anything else. I think even more than Barrett's in the long run. I think somehow the expertise of the OTC committee and those who have had experience with it to make it headlines, bold, red type, etc., I think that would be the most reassuring thing that I would recommend.

The other thing I would recommend is, again, with techniques like communication techniques, educationally-wise or on the print, that the healthcare provider be contacted. I concur with two or three recurrent episodes.

DR. CANTILENA: Thank you.

Dr. Gilliam.

DR. GILLIAM: I would agree with the alert symptoms. It would be nice if they could -- on the package insert they have, "Keep your doctor in the loop," and if they could somehow bring that out on the carton I think would be good.

Then also bring out more of the tips for managing the heartburn, the lifestyle modification which we know patients have trouble doing. It would be good if that would be brought out more. I would agree with the two to three courses per year.

DR. CANTILENA: Thank you.

Ms. Cohen.

MS. COHEN: I have a question for the FDA. If the advisory committee feels that further work needs to be done in terms of labeling, is there a requirement that they have to do it within a specific period of time?

DR. GANLEY: It depends on whether we think it's a prerequisite for them to get the drug approved. They could get an approvable letter that states that they have to fix the labeling and they have to do a label comprehension study.

MS. COHEN: Within a certain period of time.

DR. GANLEY: Well, no. If they get an approvable letter, they can't mark it until they do the study so I'm sure they would do it rather quickly. The other option is that we would suggest labeling changes and then as a Phase IV commitment. Now Phase IV commitment has a timeframe in it of when they have to have that study completed and submitted to the agency. In previous years that was not the case but now that is a requirement so they have to do that.

MS. COHEN: You can tell I come from a consumer protection background. I feel the follow-up studies are not complete by any means. I think it's premature. I don't know about repeatability I think that the labeling is totally inadequate. I am very concerned about consumer advertising on television.

I think it has moderate efficacy and there might be other things out in the market that will work just as well for consumers. I certainly think we need to give consumers a lot more consumer education and I'm concerned that people will not see a physician.

DR. CANTILENA: Thank you.

Dr. Neill.

DR. NEILL: I agree with Dr. Gilliam that on the package insert it would be nice to put, "Keep the doctor in the loop" on the outside. However, I'm

anxious to know what physician you've ever been involved with that allows you to say it never hurts to make a phone call to the doctor. It hasn't been my office. Don't answer that question.

The other comment that I wanted to direct to staff related to the package insert has to do with the graph that is on the top that very clearly to me implies that the advantage of this class of medicine -- this particular medicine is going to be that it begins to work and lasts for 24 hours and that you ought to take this, not the other two.

It doesn't adequately convey that this medicine works differently than the other two. I would hate to see direct consumer advertising that used that same type of representation because I think that it's misleading.

It's not that it's a bad medicine. It's a different medicine which in some respects is better for what it carries an indication for. That's the only thing I would add there. I don't have any other useful comments.

DR. CANTILENA: Thank you, Dr. Neill.

Dr. Clapp.

DR. CLAPP: I concur with Dr. Lam on his opinions on the duration of treatment and frequency of

four months and two courses per year, as well as the concerns that he expressed about labeling.

I really would like the labeling to address in a very clearly stated manner that this is not for acute relief of symptoms. I think that is an important use of disclaimer to have on the label packet. Also I think it would be useful to guide consumers as to when to expect maximum relief of symptoms.

I think there is some ambiguity with saying that it's the prevention of the symptoms of frequent heartburn for 24 hours which then implies that if you use it, within 24 hours you will have relief of symptoms. As I am guided by the pharmacologists, it seems as if that is not the case.

DR. CANTILENA: So just to clarify then, you would want the changes in the label and then another comprehension test or just the changes in the label?

DR. CLAPP: I think the comprehension test is essential. I do have very great concern for low literacy. I see that their studies imply that they were not as competent at self-selection but they were more attentive to taking the medication properly so then we have a group of people who will be then

victims of circumstance because they don't understand the use. They will be more likely to purchase and then use unnecessarily.

DR. CANTILENA: Thank you.

Dr. Geller.

DR. GELLER: I agree in large part with what Dr. Lam and Dr. Clapp have said. I am very concerned about the label as written. I think it's written in poor English and it's redundant and needs to be redone. It needs to be written more on a level comprehensible by a population that doesn't read quite so well. That includes use of the phrase "acid reducers." I'm not so sure about wheezing. The sentence, "Notify your doctor if you have had heartburn for three months or longer without talking to your doctor." This is gobblety gook. "For prevention of the symptoms of frequent heartburn for 24 hours." This, too, needs to be rewritten so that a normal person, or even one who is educated can understand it. So the use of the word "frequent" in the label is not good because it means different things to different people. "Not to expect a response in a day," and "Not to use it for symptom relief," are not clear.

I think that once the new label is written

there should be a comprehension study prior to marketing this drug OTC. One thing the company should do is have benchmarks for what is acceptable levels of comprehension, preset levels.

As far as a limit on the number of courses a consumer should take over a period of time, I think it should say that we don't have -- data was not given for taking it on more than one occasion of a 14-day period in this population. Rather than extrapolate from other populations, I think it should be -- we should base our information on what has been shown to us.

I guess regarding the Phase IV commitments, I guess some of the phrases used which are informal phrases, "Keep your doctor in the loop," I would like to see an educational campaign that assures that people are more aware that this condition may not be just a passing thing.

DR. CANTILENA: Dr. Geller, can you just clarify on your comment about the number of courses that you can take? Are you saying that it should just be one course without submission of new data?

DR. GELLER: Well, I'm saying that there hasn't been any other data shown. Anything else is extrapolation.

DR. CANTILENA: Okay.

Dr. Uden.

DR. CRYER: I was wondering if I just might make a comment in response to Dr. Geller's concerns. I was wondering whether or not the Bardhan data might actually help you in that assessment. That was a 12-month evaluation. In that evaluation 68 percent of the individuals requested three or fewer recurrent treatment regimens with Prilosec. Courses I should say.

DR. GELLER: I actually wouldn't feel comfortable using that as evidence without reading the study. I was a little bit concerned about again this slippage in the denominator somehow. I noticed that in the presentation but it wasn't anything to ask about. I'm just not familiar enough with that study. I would need to be more familiar with it to be able to use that as evidence.

DR. CANTILENA: Dr. Uden.

DR. UDEN: I'm a recommender of two treatments within two months because if they need two treatments within two months, they should see a physician. I'm a little different in that aspect for others.

Looking at the label I do like -- even

though Dr. Zorich apologized for putting in, "Ask your doctor if you have frequent chest pain," etc., I do like that section of the label. I think it is mandatory that it be kept.

I do believe that there have been many suggestions for improving the label and again including the one I would like to see that, "The symptoms will last for 24 hours. You may not see symptom relief for six to eight," or whatever number you want to use that will be supported by literature should be in there as an educational piece.

I do believe, Dr. Brass, that the rigor of these studies can be designed and evaluated better than, I think, what they are. Sometimes I think the information is presented to us not necessarily by this sponsor but by sponsors that we will give them something and they will approve it anyway. I don't like to be in that position.

Lastly, I would like to offer to the sponsors the Mall of America in Minneapolis is a great mall to do your next label comprehension study. Thank you.

DR. CANTILENA: Dr. Uden, are you conflictive with the Mall of America?

Dr. Williams.

DR. WILLIAMS: I endorse the Mall of America. I've been there. It's a great place. My concern on voting yes is two fold. I think that the repetition of two cycles is adequate. No more than three in a year.

The other concern that I have that's not really been talked about is the delay in the onset of action. I hear two things. One was that the product should be taken before breakfast on an empty stomach with a glass of water or any other beverage. I don't know if that's been clarified.

The second thing is that the product has a time delay of about one hour before it's useful. I'm concerned that those two things be evaluated as we go to the marketing of this product and that the labeling that we talked about certainly be put in place.

DR. CANTILENA: And then should that label be tested prior to approval for marketing?

DR. WILLIAMS: Yes, I agree. Prior to marketing.

DR. CANTILENA: Okay. Dr. Fogel.

DR. FOGEL: I voted yes with regard to subsequent courses of medication. The literature indicates that 80 percent of people will have recurrence of either erosive esophagitis or symptoms

within a number of months.

I agree with the suggestion of two, three courses a year. I think that is fine but I think there has to be an emphasis in the information that goes with this drug that if symptoms are not better after two courses of if you require more than three courses of the drug in a year you should see a physician.

The other specific point I want to make is that on the label where it says ask a doctor before use if you have any of the following and it talks about chest pain, wheezing, etc., that's really not strong enough. The labeling needs to say that, "The following symptoms may be indicative of series diseases other than heartburn. If you have the following symptoms, see your doctor. I think that needs to be made much strong. I think in general the labeling needs to be improved substantially and I think it should be retested before the drug is released,.

The final point I wanted to make is I think that the direct-to-consumer advertising that goes with this drug needs to be scrutinized carefully. This is a major change in how we treat people with esophageal reflux. I think close supervision of the

information that is disseminated is very important.

DR. CANTILENA: I would certainly agree with that. I just have one sort of follow-up question for Dr. Ganley regarding chest pain warnings. Is that on the other heartburn drugs that are out there now? Why not?

DR. GANLEY: Did you want class labeling then for them?

DR. CANTILENA: Well, I mean, I think if we are treating the same symptom we have the same concerns. It should be on the other products. Otherwise, it's illogical.

DR. GANLEY: I think the -- you know, I wasn't around when the other ones came over and some of the folks here, Eric, I think, were. I don't know if that was discussed then.

I think this is sort of a different situation where I don't think they envisioned the use that would be occurring with these products that occurs now which some people just take them all the time. Clearly if that is the situation, it may be something to consider. I know Eric may be able to add some historical --

DR. BRASS: Well, I won't rehash or even attempt to rehash. I think it's fair to say we are

learning all the time and we are learning more about the population that use it.

It think early on one of the concerns were whether these messages could be effectively communicated to a degree that would justify taking valuable label space. Again, every square centimeter on a label is very, very valuable and you prioritize. I think at that time there was concern about the effectiveness of communicating those messages and what the benefit would be.

DR. CANTILENA: Okay. I think it's your turn, Dr. Brass.

DR. BRASS: All my comments are related to the label and it would be my preference if they were addressed premarketing to the agency's satisfaction, whatever that took whether that was another study or your own wisdom.

I have a minor point that actually starts at the very beginning. Under uses it reads, "For prevention of the symptoms of frequent heartburn for 24 hours." I found the phrase "for 24 hours" dangling at the end of that to be very confusing how that would be interpreted.

I would put that under the paradigm of communicating the expectations about when benefit

would occur more clearly that you are really taking a two-week course and how that overall message gets communicated.

As was mentioned, I agree that a whole lot of more appropriate bolding and coloring and highlighting for the more significant messages would be important.

I already alluded to that I'm not sure the message under warnings, "Notify your doctor if you've had heartburn for three months or longer without talking to your doctor," has any added benefit against this whole matrix.

I agree completely with the intent of that message and if it's felt to contribute to patients contacting their doctor, that's fine, but we've actually not seen the impact of that statement evaluated and, again, it takes up a lot of space.

"Do not use with other acid reducers." Again, the complete rationale for that wasn't entirely whether it was because they were concerned it would interfere with efficacy or that you would be using redundant medications. If so, whether or not you need to name more specifically what medications.

Under the drug interactions, I would be in favor of leaving warfarin even though there is not

much data only because I believe any patients on warfarin should talk to their doctor before they take anything as a general rule. If putting a brand name next to that improved that, I would be in favor of that.

In contrast, I'm not sure if phenytoin has an adequate basis and would lean towards removing that. The differentiation between ketoconazole and itraconazole I confess to have been totally confused by the rationale, why one was on the Rx and the other was on the OTC.

Perhaps in that class whether some phraseology like a prescription medicine to treat a fungal infection or something like that might communicate that whole group more efficiently and more effectively than the generic names which might not be recognized.

Under, "Stop. Use a doctor if..." it says, "Heartburn continues or returns after using this product everyday for 14 days." That means you could have continued pain for the entire 14 days before you would call somebody.

I'm not sure if the curve of benefit suggest that is the optimal time point if you are still having symptoms to call or whether an earlier

time point might be better.

I agree that the label should contain something about repeat courses but I actually don't know how to do that. I think a number like three is right but I don't think we have very much experience in communicating. That is a relatively abstract concept at the time of purchase to communicate to a consumer.

I'm not sure we have any experience in communicating a message like that. That would be an example where if that was felt to be important for the safe use of this drug over-the-counter some serious thought about what syntax would effectively communicate that concept would be required.

I also agree with the comments about strengthening the "don't use" under various circumstances should be more dogmatically "don't use" as opposed to down at the bottom, "Notify your doctor," or "Ask a doctor before use." To my perspective, and this is a general issue we've talked about before in the labeling, "ask a doctor before you use" as opposed to "don't use."

Same with the pregnancy warning. It implies that it's probably going to be okay but just check as opposed to "you should not do this unless

instructed by." And whether the strengths or the warnings for the warning symptoms and the pregnancy can be made more definitive with stronger language would be another concern I would have. Thank you.

DR. CANTILENA: Thank you, Dr. Brass.

Dr. Cryer.

DR. CRYER: Sir, my principal two issues with regard to OTC usage as well as labeling are comprehension and getting the consumer to the physician early in the event of inadequate symptom relief. Given that, I would agree with all of the comments that have been stated that the label needs to be rewritten in a way that is more comprehensible at a lower grade level along the lines of some of the specifics that have been discussed.

It's my understanding that the label in its current format actually has not been tested. Given that it was likely to be rewritten, I think it would be very important to test comprehension of the rewritten label prior to actual introduction to the market.

With regard to getting people to the doctor earlier, we have here a comment that says, "Stop use and ask a doctor if your heartburn returns after 14 days of this product," which I think is

appropriate. I think you might want to consider also including that specifically under the directions.

It doesn't specifically state in the directions box that you might want to see your doctor if the heartburn returns after 14 days. You might want to either move it to that box or state it in two places.

Then with regard to this issue of these drug-drug interactions, I actually agree with the comments that Dr. Brass made. The impressive data that I saw was that the comprehension with respect to the drug-drug interaction significantly increased from 50 percent to 80 percent when comparing a generic -- when specifically listing the generic versus the trade name.

This may be one instance in which you may want to break your precedent with regard to the inclusion of trade names, specifically with respect to this drug-drug interaction. I think that is actually a public health benefit.

DR. CANTILENA: Thank you very much, Dr. Cryer.

Dr. Johnson.

DR. JOHNSON: I probably won't say much that hasn't already been said but with the thought

that repeated messages give strength, then I'll repeat them.

I think two to three courses per year is reasonable. In terms of labeling, again, I think there are a lot of changes needed. I find the "uses for prevention" statement confusing as many others have. I find the "notify your doctor" statement very confusing.

Under, "Do not use with acid reducers," I'm not sure that if you ask a lot of health professionals what exactly is an acid reducer -- that's not what we call them. I think there needs to be some way to make that message clearer to patients what that actually means.

I agree that the doctor statements are important and probably should be strengthened. As sort of a sidebar in terms of class labeling, I think one could make an argument that kind of labeling for antacids and H_2-RAs is even more important than it is for this product because those products are used for treatment of acute symptoms.

If you consider that the thing that we are probably most concerned about being confused is acute MI and you look at the data on acute MI and how many patients have taken an antacid prior to coming to the

ER, I think the evidence is even more compelling that it should be on those products. That is sort of a sidebar.

In terms of the drug interactions, I really think it's critical that brand names are on there. I'm not sure why the policy is such that it precludes that. I concur with Dr. Brass that warfarin probably is justified to stay on and phenytoin may not be. I think there is no logic to having ketoconazole but not itraconazole.

I think the message needs to be strengthened that this product is not for immediate relief of symptoms and is not for episodic use. I think that's about it for the labeling.

In terms of Phase IV, in terms of an assessment I'm not sure I have a recommendation but I feel very strongly about the direct-to-consumer marketing and feel that there really should be some mandatory aspects in their direct-to-consumer marketing.

I think it needs to encourage lifestyle changes that would increase the response or decrease the need for drugs. There needs to be a strong message in that marketing about referral to physicians or when they need to see their physician.

I think it may be also very important to clarify in that message that they are different than other heartburn medications. I guess that could be a selling point but specifically that they are not for acute symptoms so there is not confusion about use of this product compared to the other heartburn products.

DR. CANTILENA: Thank you, Dr. Johnson.

Dr. Alfano.

DR. ALFANO: Yes. I also agree two to three times a year is appropriate. I think it should be two to three because I think we all agree that it is an empirical decision as opposed to fixing a number as what's appropriate.

I've already commented that I think there should be some label changes along the lines of what everyone has suggested here and I won't repeat that other than to make a comment that I thought Dr. Johnson had a particularly cogent point about the number of people who get an MI and will take an antacid. The fact those other products are not labeled is actually a little disconcerting.

Also, I don't see a need for Phase IV trial but would agree with some of the other panelist that suggest that the FDA ought to be able to make a determination as to how the labeling should be

modified and whether or not it should be studied again and how.

DR. CANTILENA: Dr. Goldstein. I believe labeling always needs to be internally consistent and memorable where possible. In this case the caution, warnings I should say, about if you've had heartburn for three months or longer might well be linked to no more than two courses in a three-month period or three courses in a year, three being the link.

The other thing is I've spent considerable time looking at that "notify your doctor if you had heartburn for three months or long without talking to your doctor," and wondering how you notify your doctor without talking to him.

Of course, there are intermediaries. Nonetheless, I truly believe that the sponsor and the agency together will be able to with their resources and their viewpoints work out appropriate labeling that will make these committees and all of us satisfied.

As for Phase IV requirements, perhaps the sponsor may have more to say on that. I'll leave that to them.

DR. CANTILENA: Okay. Thank you. My comment is not to restate what has already been stated

but just in general to the agency that approval of this would be significant new ground for the agency. I think that you've all heard fairly consistency that the label needs a lot of help and revision and validation.

I think all that needs to be done prior to approval. We want to get this as close to right as possible. Then I think it would be helpful for a limited focused Phase IV study to test the effectiveness of the label. It's sort of the ultimate test but we have a lot of work to do on it for all the reasons that have been mentioned. I see it as an approvable proposition for the reasons stated.

Dr. Davidoff. I'm sorry, Dr. Bull.

DR. BULL: One clarification on your comments. Do you see the labeling comprehension as needing to be done before the drug is put on the market?

DR. CANTILENA: Oh, absolutely.

DR. BULL: Okay. That would not be Phase IV.

DR. CANTILENA: Absolutely. The label as presented is in great need. Significant changes have to be made. Then it has to be validated with a comprehensive study. All the comments about

subpopulations that need to be tested, I think, are important.

I'm sorry, Dr. Patten. I told you it would be a while but it was so long I actually forgot. My apologies.

DR. PATTEN: That's fine. Many of the things that I had in mind about label suggestions have already been made but there are a couple of additional points that I would like to make. It's very clear that this will be marketed as a preventive. I think people will be looking for something that they might do in addition to prevention to give them very quick relief.

It's noted here that it is not to be used with other acid reducers. I wonder if it might be wise to tell people what they can use for symptom relief. If it can be used with an antacid, for example, perhaps that should be stated.

I think the matter of comprehensibility when you are letting people know how many repetitions they can do in a year is going to be a very serious issue to be tested. I think that will be very challenging and very different than saying you can take eight tablets in a 24-hour period. I think that has to be attended to very carefully.

I think that something should be said about the relationship of the morning dose to food intake. Is there an optimal lapse of time between taking the tablet and eating your breakfast, for example. I think people should be given some guidelines if that is at all possible.

Then finally just a very picky point under "other information." Maybe this is even a theological issue. Is this a carton or is this a package? We are told, "Keep the carton and the package insert."

I gather that both of these terms refer to the box that this is going to come in. Just to be consistent with the terminology, I think it would be useful and would improve comprehensibility to a broader spectrum of the population. That's it. Thank you.

DR. CANTILENA: Thank you for those comments.

Are there any other issues? Dr. Davidoff and then for the FDA.

DR. DAVIDOFF: Yes. Since I voted no, I realized that I didn't meet my obligation to say anything about this question for those who did not recommend approval, namely what additional information needs to be provided.

Actually, since it looks like the recommendation is for approval, I should convert that into what should the agency require as any Phase IV commitments because essentially I think what I have in mind is the same thing. The drug, as I understand it, has been on the market as a prescription drug for 13 years.

That's a pretty long time, but it may not be long enough to detect some of the longer-term effects that I raise as concerns. It might take 15 or 18 or 20 or 25 years for substantial population-wide effects both in terms of masking of neoplastic disease or potentially induction to appear.

I would, therefore, strongly encourage that particularly if the drug is approved for over the counter some form of continuing monitoring, very close looks at the data from a sophisticated epidemiological point of view. I mean, it's one thing to hear about -- it's important to hear about the experience of individual practices, but I don't think that answers the question. I would strongly encourage that that happen.

On the issue of -- I also didn't comment on the label and I won't repeat what other people have said but there are a couple of things that I thought

might be useful to add.

One was that in terms of wording that might help understand what the purpose of this drug is, prevention of the return of symptoms strikes me as a kind of wording that might actually be more helpful than prevention for 24 hours.

When you think about it, that is really what it's aimed to do. It's not to prevent -- it's not to relieve what's happening now. It's to prevent it from coming back. The word return or recurrence or something might be useful.

My final comment on the label has to do with this issue of digoxin because that keeps slipping off the table. I can't understand why because we've heard two things about it. One is that it's a very small study, 22 patients with no confidence intervals presented showed no difference. We have no idea how negative that study was because we didn't see the confidence intervals.

We also heard there was a 10 percent increase in levels. Digitalis is a dangerous toxic drug and I would suggest either that there be more data collected -- that's what ideally I would like to have happen -- before a decision is made about labeling on digoxin. Or, pending that, that the

conservative thing would be to put some kind of wording that does at least make a caution about people on digoxin, particularly if they are in renal failure.

DR. CANTILENA: I think that is an excellent point. Just a short of word for future sponsors is that it's very helpful to the committee to see individual data and/or confidence intervals as opposed to just an average without anything. That's not very helpful and it probably does more harm than good.

Comments from the FDA? Dr. Houn.

DR. HOUN: I just want to summarize a lot of you gave labelling suggestions. Some of them very extensive dealing with the indications, the warnings, new information such as limited course two or three times a year and no more than maybe every four months or so, new messages.

Most of you except for, I guess, Dr. Brass as voting members are wanting to see them tested out in terms of their level of comprehension by a naturalistic public setting prior to approving the final label. Is that a correct summary?

DR. CANTILENA: I believe it is.

DR. HOUN: Then I also heard this new information about limiting frequency to two to three

courses in a year. Is that something you want tested to show that, in fact, people are not taking this continuously or are you saying this is nice to have on the label but you don't need to have the data to show that people are, in fact, complying with that aspect?

DR. CANTILENA: We didn't actually answer that. I guess -- well, I'm not sure. How many of the committee would want to see that specific statement actually tested as opposed to just being there? All in favor of seeing it actually tested?

DR. BRASS: Tested on a comprehension basis or a one-year longitudinal trial for use?

DR. CANTILENA: Tested in a comprehension. Is that what you're asking?

DR. HOUN: Well, I would ask both. I'm asking both.

DR. CANTILENA: Okay. How many would like to see the new label including that specific message tested in a one-year or longer actual use study? All in favor, raise your hand. One hand. I don't know if you're recording this.

DR. GELLER: Can I just justify that? I guess I don't like the idea of putting number of doses permitted or recommended on the label without any data. The alternative is to say that only one dose

was tested.

I mean, people -- it's obvious from what has been said here that we expect people to use it more than once. Perhaps some caution should be urged but to say two or three times is okay without data is, I think, really an extrapolation that we shouldn't be making.

DR. CANTILENA: Okay. I guess just to follow through, how many would like to see that message that you should not have more than two or three courses in a year tested in a label comprehension setting? Hands? Okay.

Sandy, do you have them all?

How many of you don't want to see that tested at all or don't think it's required? Don't think it's required.

DR. GOLDSTEIN: Mr. Chairman.

DR. CANTILENA: Yes, sir.

DR. GOLDSTEIN: If I may, all of this, two, three courses of presumably the original 14 days has been in the last few minutes talked about with the background of 28 days over and over again. A little while ago we heard that 28 days was more effective. To now limit it in this fashion may be not entirely appropriate.

DR. CANTILENA: I just think that we're asking if that message should be tested that we can effectively translate that or communicate that. I think that is all we are saying. I think the job of the Advisory Committee is to advise the FDA on whether or not there should be a limit and, if so, what it should be. A lot of what we do we don't have the specific study to answer the question. If that study existed, they probably wouldn't ask us the question because they would have the answer.

Are there other issues from the FDA that you would like addressed? Any issues -- I'm sorry. Dr. Clapp.

DR. CLAPP: I have concerns about the methodology of the testing. Of course, all testing has to be contrived to a degree, but in that the participants were given a diary and the diary was rather -- well, we didn't hear specifically what was requested of the diary but it seemed like a rather nebulous vehicle for putting your thoughts and impressions of the medication rather than asking specifics as to, "What did you take instead of the medicine when you missed it?"

My other concern is that there was a great deal of artificial incentive in that and writing in

the diary would make you more likely to take your medication just by the fact that you knew that was an obligation for which you had to resubmit your diary to get your 100 dollars and get the 20 dollars at the onset of the study. I would see that there could be other mechanisms by testing whether or not people were compliant that wouldn't involve such an inherent incentive.

Perhaps having a nurse go to the home at the end of the 14 days and see how many blister packs are left. There could be other methods that would increase the reliability of the data and not make it such an incentive driven solution.

DR. CANTILENA: Okay. Other questions or comments from FDA? Do you have one?

DR. HOUN: I hate to ask this. Are you interested in seeing this again?

DR. BRASS: No.

DR. CANTILENA: Does anyone else want to come back to Bethesda? I guess why don't we just vote on it for whoever is left.

DR. HOUN: Or you could just leave it to us.

DR. CANTILENA: Why don't we -- yeah. If it's an issue where it's a hard call, then it's

obviously something you should look at but I think all the issues are addressed. I think we've probably talked about it enough.

Are there any other issues from FDA? Any issues from the sponsor? Thank you for your patience in having us talk about your drug all day.

DR. PEURA: No, not at this time. I want to thank the committee very much.

DR. CANTILENA: Okay. There are just two announcements from Dr. Titus and then we will close.

DR. TITUS: Thank you all. There are taxis downstairs going to National for those that are leaving immediately. If you want your material returned to you, put your name tag on top of the material and we will mail it to you. Otherwise, we will take care of it here. Thank you.

DR. CANTILENA: Okay. Thank you, everyone. The meeting is adjourned.

(Whereupon, at 4:35 p.m. the meeting was adjourned.)