DR. BRASS: I would like to begin -- actually, do you know the soccer score?

DR. CANTILENA: No.

DR. BRASS: Okay. Thank you. I would like to begin by asking for a clarification from the sponsor. You cited efficacy data from studies 171 and 183 as the basis for the efficacy conclusion. Could you just clarify whether the endpoint cited were the prospective primary endpoints of that study or were they secondary endpoints of that study?

DR. PEURA: The data that I presented on the screen showed both the primary and the secondary. The primary variable was complete prevention of heartburn on day one and our secondary variables were those across the 14 days.

DR. BRASS: Thank you. Second, I think it's extremely likely that if this drug is made available OTC there will be pregnancy exposures despite any warnings. Therefore, could you update us on your experience with pregnancy exposures from your safety database?

DR. TRIEBWASSER: Certainly. We are relying on the data that we have submitted to the FDA in which several large epidemiologic studies have failed to identify a signal among women who were

inadvertently exposed to the product during first trimester. This material is currently under FDA review and we've had discussions with FDA.

DR. BRASS: For the committee's benefit, could you give us an estimate of just the magnitude of that experience? How many exposures are you talking about to reach this safety conclusion?

DR. TRIEBWASSER: Sorry. We were able to accumulate data from three large epidemiologic studies where approximately 1,400 women were exposed to the drug and over 1,000 were exposed during the first trimester. It's on the basis of that data that we evaluated and failed to see any signal with regard to fetal risk.

DR. BRASS: Thank you. Then under your proposed labeling under warnings, you indicate that one should notify your doctor if you had heartburn for three months or longer without talking to your doctor. That would seem to capture 100 percent of the intended target population. I was wondering what your experience in the actual use study was compliance with that particular warning.

DR. PEURA: We found that approximately 65 percent of the people that had previous heartburn for greater than three months had seen their physician

previously.

DR. BRASS: About their heartburn?

DR. PEURA: About their heartburn specifically.

DR. BRASS: Thank you.

DR. CANTILENA: Dr. Camilleri, Dr. Fogel, Dr. Uden, and others.

DR. CAMILLERI: Thank you very much. I would like to ask for some further clarification regarding the effectiveness of this therapy for the proposed target population. I would like to refer you to figures 62 and 63 in your dossier and also slide 25 which was the day-by-day 14-day efficacy which you demonstrated.

On the one-day response you actually show in your dossier that less than 50 percent actually achieve the desired no heartburn over 24 hours. That is really quite acceptable because we know from the pharmacological action of this drug it is going to take three to five days to really kick in.

I think this slide in particular shows an important point which we should remember, and that that 30 percent or more of these patients do not achieve relief. I keep that in mind as I also note from the 171 and 183 studies that 57 percent of the

patients had frequent heartburn return at four weeks. In the Bardhan study 68 percent of patients required three or more courses a year of the omeprazole at the same dose of 20 milligrams.

The clarification I would like, if I may ask this, is is this truly a benefit for this particular population of patients who have what I would regard as a quite significant level of heartburn, more than twice a week occurring over a period of 30 days or more which I think was the conclusion criteria for your particular study.

What is the overall benefit for a patient to receive treatment for two weeks if the likelihood of needing yet another treatment two or three times in that next year is going to be at least 60 percent. Also bearing in mind that only 65 percent or so actually respond to the treatment. Thank you.

DR. BIERER: Well, first I would just like to say that for the people who are using OTC products to prevent frequent heartburn, this is a very considerable benefit to those people because they currently do not have products available to them in the OTC environment that can achieve this kind of symptom prevention. I think for those individuals it is clearly a benefit.

I think the question then of are there additional benefits for those people if they use the product over and over, certainly for those periods of time that they use them they will derive some dramatic benefit from those products.

DR. ZORICH: And I would just add that we do not consider people who are unresponsive to therapy after 14 days to actually be in the target audience and that is why I think a 14-day direction clearly advising them to seek additional physician interaction distinguishes them as what we consider to be the appropriate target audience.

DR. CANTILENA: Go on, Dr. Fogel.

DR. FOGEL: I have a question about potential unintended consequences on utilization of physicians if this drug is approved. We all know that over-the-counter H_2-receptor antagonists have limited efficacy in the treatment of reflux.

The cost of the over-the-counter H_2-receptor antagonists is somewhere between 20 and 30 cents a pill depending on what you buy and the quantity that you buy at any one time. These costs are not covered by insurers or managed care organizations.

The cost of omeprazole in the study that

you did I believe was $12 for 14 pills. If individuals have to pay for the medication out of pocket, the odds are after using it once or twice they will seek a doctor to try and reduce their expenses.

Do you have any insights or knowledge about whether insurers and managed care organizations will pay for an over-the-counter omeprazole? If they do, that would actually be a disincentive to see the doctor because the cost of care would be covered by your insurance and you would not have to have a co-pay. You would not have to go through the discomfort of seeing a physician. The question is is there any sense as to whether insurers will pay for an over-the-counter medication?

DR. ZORICH: I would say this is an area in terms of cost effectiveness in the general area of distribution of our healthcare dollars is constantly debated but at this time we don't have any -- we have had no indication if people will be picking this up, particularly when generics will be on board.

DR. CANTILENA: Okay. Dr. Uden. And then, just in general, usually cost of out of bounds for the Advisory Committee.

DR. UDEN: I have questions about the actual use studies and label comprehension studies.

It relates to industry established standards and how to interpret those. I saw information up there that the literacy people 49 percent understood the label or were able to self-select.

I think there was 70 -- understood the label and 70 percent were able to self-select. The general warning signs on the label were understood 81 percent of the time. I see numbers like 50 percent, 70 percent, 81 percent in terms of actual use and label understanding.

Has the industry established any standards which would give us some guidelines or use some guidelines as to what is reasonable for us to expect for understanding labels, being able to follow labels, or shall we just leave it to our imaginations?

DR. PEURA: I think as far as industry, there are no set standards for what is desired on label comprehension. I think it has to be determined on a case-by-case basis depending upon what the indication, the warning, and the statement is.

Certainly for some indications you would want a high level of comprehension. In other ones it may not make that much difference and I think we have to look at the risk for each one of those.

DR. UDEN: And where do you fall on

omeprazole then?

DR. PEURA: On omeprazole I would say that we have determined it is appropriate, that people do use it appropriately, even the low literate group. I would point out in the low literate group the number they showed of 49 percent, these people were low literate with frequent heartburn.

We presented this scenario to them or a hypothetical question that said, "Now, imagine yourself having infrequent heartburn and you woke up at 3:00 in the morning and you had eaten pizza but you hadn't taken the product for three days before that. What would you do in this situation?"

It's very hypothetical but we found out probably a truer reflection is when we look at the actual use study of people with low literacy that these people actually scored better and they had to meet all six self-selection criteria, not just the one I spoke earlier about infrequent heartburn. That's probably a more real world realistic situation.

DR. CANTILENA: Okay. We have Dr. Geller and other hands, Cohen, Levine. Dr. Geller first, please.

DR. GELLER: I just would like to point out how optimistic your reporting of the actual use

data is. I'm beginning with slide 41. 886 patients agreed to purchase the product. I imagine that means they did purchase the product. But then you report on only 758 of them because that is the number that returned the diary. To begin with, here you decrease your population to 87 percent of those who purchased the product.

Then if you take 87 percent of the next group of numbers, then the compliance goes down by about 10 or 12 percent. You have also here reported on the individual compliance, the three conditions. You have reported on only two of them and individually not together.

Then your definition of compliance on slide 43 is quite broad. Then you get an over estimate of the compliance because you define compliance broadly. That reduces the 79 percent to follow the labeling directions by about 10 percent.

Then if you look at slide 45 and talk about the return of frequent heartburn four weeks after the trial, well, now you are reporting on 83 percent of the 87 percent.

I guess it should be said that if you go back to slide 41 the 758 patients who used the product and returned the diary were more likely to be

compliant with dosing conditions than all of those others. Those 13 percent of patients that you lost are likely to be noncompliant with the dozing directions.

I think then you are reporting on 83 percent of the 87 percent and, therefore, the percents that have no frequent heartburn are just a misrepresentation of what actually happened from those who actually bought the product. I believe you are reporting very optimistically.

Last, you didn't ask if the patients who were in the actual use study used the product for relief instead of prevention. I don't know if you asked if they used antacids or other drugs to get relief.

I also have a question about the labeling. I would like to know the difference between prevention of the symptoms of frequent heartburn and prevention of frequent heartburn.

DR. PEURA: I think I heard six questions. Let me start with the first one from this graph. From the 866 we did not get diaries back from 96 people. We were actually looking at how did people actually use the product in this situation so that's where we came to the number of the 758. We assume

that those people since we didn't have a diary from them, you could assume that they --

DR. GELLER: I think you can assume we are noncompliant.

DR. PEURA: Well, we can't really assume that because I think we would -- I mean, you could make a case that they were noncompliant but I think I could also make a case that they could have been compliant with this. But we do know -- the best number that we do know is from the 758 where we actually do have diaries from those people.

If you can flip to the next slide. Next slide, please, 42 -- 43, the one with the description. This description gave us a range of 80 to 100 percent which I mentioned before is an epidemiologic standard that people use for compliance with an Rx dosing regimen.

The choosing between 11 to 14 doses for 11 to 17 days, well, that seems like a wide range. There is actually less than 1 percent of the people within that range. Less than 1 percent of the people who took 11 doses in 17 days.

Most of the people if they missed a dose took it on the 15th day, not on the -- they may have taken 14 consecutive. Some would have missed a dose.

If they missed one dose, they would have taken it on the 15 day so the range is very tight within that.

Onto the next slide, please, 44. In this you had mentioned that the range of -- if I can remember the question -- the range was 79 percent. You thought -- the position was there were three dosing instructions in that making sure they had the right number of tablets per dose, the right number of tablets per day.

As the FDA did, multiply that times the correction factor in this one. That would come out to pretty close to probably about 75 percent because those were in the 90s that were there.

Also, as I did report earlier, if you look at the people who took exactly 14 doses in 14 days, they did exactly what was on the protocol, the number is 63 percent. Not of the 79 but of the total pie.

There was one other question after that before we get to the labeling question.

DR. GELLER: There were three, I think.

DR. PEURA: Pardon? Okay.

DR. GELLER: It was on the percent with no frequent heartburn that now involved 83 percent of the 87 percent of those who purchased the product. That was the first one.

DR. PEURA: Okay. It's the same general theme. We are looking at people that we actually have data upon to make a judgement. I think the labeling question was in terms of between symptoms of frequent heartburn and why do we put the word symptoms of frequent heartburn on the label. That was really --

DR. GELLER: In fact, I did include the word prevention because I think that ends up -- when you say prevention of symptoms, it seems to me it kind of introduces the possibility of taking it for relief.

DR. PEURA: Okay. Let me come back to you asked about how do we know that the people took it for prevention. I believe that was one of the questions in there. The people that took it for the 14-day period, the 79 percent of the people were taking it over a regimen of therapy. They were maybe missing one day within that over the time.

These people were probably not taking it in response to a symptom because they would have to have it every day. They were most likely taking it for prevention since they were taking it on a regimen basis.

The reason that we included the words "prevention of the symptoms of frequent heartburn" is that we did not want to imply that we are preventing

frequent heartburn, preventing it was ever reoccurring whatsoever. It's not promising the cure. We're trying to define to the consumers the prevention of the symptoms which is more a consumer term.

DR. LEVINE: Symptoms is more OTC. Symptomatic relief or symptomatic prevention is what this is about.

DR. GELLER: I guess I just don't know what heartburn is if it's not a symptom.

DR. PEURA: It is. Perhaps we are being a bit redundant with it but we wanted to get the message across to the consumer that we are not preventing heartburn from ever reoccurring again. It is symptomatic treatment of heartburn. Prevention of symptomatic heartburn.

DR. GELLER: The two questions you missed were I asked if you asked in the actual use study if anybody used the -- if people used the product for relief. The other question was did you ask about concurrent use of other drugs for treating these symptoms.

DR. PEURA: Okay. Thank you for reminding me. If I could go back to the pie chart again. The pie chart before this, please. 44, please.

DR. GELLER: 45, I think, you want.

DR. PEURA: The full pie. Asked if anybody had used it for symptomatic relief. I think the best answer we can give you is that probably the people in this pie chart here between the 9 percent and the 9 percent looked as if they were using it not on a regimen basis.

Of that 3 percent of these people took only four doses of the product and then stopped. If we take those out, perhaps as much as 15 percent would be the max that probably we are using as a sporadically or for a PRN type basis. And accordingly --

DR. GELLER: Once again, that's of the 83 percent of the 87 percent.

DR. PEURA: Importantly they didn't use it beyond the 14 days. The last question was?

DR. GELLER: I see the data on -- oh, no. Did you ask if subjects also used other products at the same time?

DR. PEURA: We did collect it in the diary whether they used other antacids or H_2-RAs. Unfortunately the way the information was collected in the diary, if the person said they were on an H_2-RA, it was counted throughout the whole range. We didn't record on a day-by-day basis so we really

cannot answer that question.

DR. CANTILENA: Thank you. Ms. Cohen.

MS. COHEN: I have a lot of questions. We have 44 million Americans --

DR. CANTILENA: How about if I suggest that you ask them sort of one at a time.

MS. COHEN: All right. We have -- I will try the best I can because I suffer from GERDs and esophageal rings so I'm a good person to know about diet. The word diet has not been mentioned at all. Could we look at the label? The last time I asked for a copy of the label and the packaging. Did anyone think to bring one today? This is large. I'm sure this is much larger than is going to go on the box. Right?

DR. PEURA: Correct.

MS. COHEN: We really don't know the size of the print or if people can read it.

DR. PEURA: We do know that people can read the print since we did label comprehension studies and actual use studies and we used the actual box that we would market.

MS. COHEN: Thank you. When you look at the label it says "uses." It seems to me you could add, "Not for infrequent cases," like they say on page

21 in this report.

Dr. Bill mentioned three months along that some of these suffered from angina or something else. Three months is a long time to tell people not to see their doctor. "Do not use if heartburn continues after 14 days. See a physician," for those people that can afford to see a physician. Then we have 44 million Americans who can't.

I think it's very important that some foods can cause heartburn and you should check with a nutritionist or a physician or a library because a lot of foods can be eliminated that will stop people from getting heartburn which is a lot less expensive than having to buy drugs.

I don't see anywhere here the importance of diet like tomato sauce or red wine. A lot of foods cause heartburn and we can prevent that with people. I think the label, I would really like to see the size of the label how it is.

In reading the report that was put out, my question is it apparently says that a substantial portion of subjects experience no heartburn on day one or day 14 in the placebo group. Now, what was given to the placebo group?

DR. PEURA: Okay. Let me try and answer

your questions in order. The first one you asked about diet and diet restrictions. We do have a package insert with this product where we talk about tips for managing heartburn which includes diet, certain foods not to eat, elevating the bed, not eating dinner late at night and before lying down.

This is the label. Take the label off, please. Actually, we do contain that on the package insert. There is too much information that we cannot put on the back label of the package. We have discussed this with the agency. In the back it's called, "Tips for managing heartburn," down here which is what one would want to do. It's a primary one.

Second, you had said that some people may have chest pain or angina. We do clearly say in the label under "do not use" to ask a doctor before use if you have chest pain with shortness of breath, sweating, pain spreading to the arm, etc., things that could be confused with potential heart attack.

That we have included and believe it is important to include that on the label. In fact, it probably ought to be included on the label for all heartburn medications OTC.

The last one was -- I have forgotten your last question.

MS. COHEN: I was interested in the placebos. If people were give just over-the-counter antacids.

DR. PEURA: They were given the placebo called the matched placebo, everything that was in the active pill with the exception of the omeprazole, the active ingredient.

MS. COHEN: Well, they said that there was a 40 percent treatment failure rate after 14 days in subjects with high-frequency heartburn.

DR. LEVINE: Forty percent.

DR. PEURA: Right. For some people placebos do work well for heartburn. As Dr. Weintraub once told us, a glass of water works fairly well for some people. For this the failure rate in omeprazole does not work in every patient. There is a therapeutic range in which it works. The failure rate is the 30 percent of people at the top of that graph.

MS. COHEN: Your statistics all involve people in the study itself. That is already a special class of people and it's not the typical and average consumer who would use the product. These people are already more conscious. They are in a study and they should be doing things that are expected of them. How does that represent the average and typical consumer?

DR. PEURA: In our actual use study we actually ask people how they evaluated the product. We asked them in terms of their global understanding was this product good, very good, excellent, poor. We found that 90 percent of the people rated the product good, very good, or excellent.

MS. COHEN: And these are the people in the study?

DR. PEURA: They are people in the actual use study.

MS. COHEN: So this is not the person who would go in and buy it?

DR. PEURA: It is the person who would go buy it.

MS. COHEN: But these are the people that knew about it because of the study you were doing.

DR. PEURA: They were recruited from a low intercept and asked, "Do you get heartburn?" They were close to a purchase decision that people would want to make in a drug store or outlet store.

MS. COHEN: Thank you very much.

DR. CANTILENA: Dr. Levine.

DR. LEVINE: I'll ask one question. In reference to slide 77, you mentioned that the majority of consumers in slide 78 won't be using omeprazole

chronically. There is a subgroup, of course, who have chronic heartburn, mainly patients with gastrosophic geo-reflux disease.

In slide 77 you show Chiba's work. I believe that was with 20 milligrams but most of us recognize that it's at least 30 days or so where there is complete healing, much better healing, then what is shown in this particular slide at four weeks versus two weeks.

While we will discuss that later about the duration, as well as possibly dose of undertreatment populations, do you have any prospect of data in your studies that go longer than the 14 days to give us an idea, or other literature because the literature that I am familiar with clearly shows a better response rate between two and four weeks.

DR. ZORICH: Yes. I think that -- I don't mean in anyway to imply that this data should be taken very literally that there is a flattening here. I think it's more than fair to consider that if you smooth this line out that there is, indeed, a benefit.

But if you take into account the fact that there is also benefit that accrues with placebo, you can see that while there is a benefit, it is not as much of a benefit as you might anticipate.

But I think more importantly than simply t his data which is, as I said, a medianalysis of 43 studies, we could look at each one of the individual studies and each one would support that there is an incremental benefit as you go longer.

More importantly, we are not seeking to treat people with erosive esophagitis with this. We believe that those people should remain within the medical care system getting their medication from their physician. That is even more reason why people who are not responding to 14 days should be directed to their healthcare professional for evaluation.

I think 14 days in the OTC environment is a very logical place to say if you are not responding by 14 days, you may very well indeed have higher grades of erosive esophagitis best managed with the advice of your physician.

DR. LEVINE: Thank you. We'll discuss that later, I think.

DR. CANTILENA: Yes, we will.

Dr. Alfano and then Dr. Cryer.

DR. ALFANO: Yes. The reference is at slide 37. On slide 37 you list 385 people who elected not to participate. As I recall, you said some of them elected not to participate because they wanted to

check with their physician first. How many of the 385 wanted to check with their physician first?

DR. PEURA: About a third of these people.

DR. ALFANO: And yet that was excluded from your analysis. In other words, these are people who said the product was appropriate for them but selected out before they ever hit your database.

DR. PEURA: Correct. We excluded them from our analyses.

DR. ALFANO: The second question is slide 57. Dr. Levine states that the increased incidence of adenocarcinoma beginning in the '70s is not related to acid reducers. This is related to a question I had on something Dr. Wolfe showed us where he showed the epidemiological trend, which coincidentally ended, at least in his slide, before omeprazole was launched in this country.

My question is what is the basis, Dr. Levine, that you say that this change is not related to acid reducers?

DR. TRIEBWASSER: Actually, several lines of evidence. First, the superficial look at the time relationship to this cancer and use of products isn't sufficient to really draw any correlation. In fact, the rising incidents of this cancer predated the

introduction of the H_2 blockers. The H_2 blockers, as I'm sure you can appreciate, were introduced initially for treatment of peptic ulcer disease and GERD.

In addition, the initial introduction of omeprazole is the first PPI that was conservatively introduced for individuals with hypersecretory conditions like Zollander Allison syndrome and fully responsive in peptic ulcer disease. There was probably several years, in fact, of this rising incidence that bears no relationship from an epidemiologic perspective to the use of these drugs.

In addition, there have been careful epidemiologic studies that have, in fact, looked at the relationship of this type of cancer and acid reducers and the acid reducers basically seem to go along with the underlying condition which does increase the risk which is chronic persistent heartburn.

DR. ALFANO: Would it then also be true that these drugs bear no relationship to the decline in squama cell CA.

DR. TRIEBWASSER: I have no evidence to even suggest that, no.

DR. CRYER: I'd like to get back to a comment that Dr. Camilleri made a little earlier which

was that in his opinion that heartburn of frequency of greater than two times per week is considerable heartburn and I would agree. I guess one of the things that has really been ostensibly absent from this discussion is a description of frequent heartburn as being GERD, gastro esophageal reflux disease.

As a gastroenterologist I'm having a difficult time understanding the differentiation between frequent heartburn and what we really call the treatment of GERD.

The specific question is in your population of individuals who had frequent heartburn of more than twice a weekly, do we know how many, what was the distribution of those individuals with regard to their actual frequency? Specifically how many had it three times, four times, five times a week?

DR. ZORICH: I would say that within our actual use trial which observed people for a three-month window, what we found is that at the three-month contact that 43 percent of them said they were not having frequent heartburn. Here is a group of individuals who stated they weren't having frequent heartburn. The vast majority of them then took 14 days of omeprazole and when contacted at three months said they no longer had frequent heartburn.

Right there you see almost half of the population saying they are not having frequent heartburn. If you extrapolate that group, even if they were to then the next day after you called them have another bout of frequent heartburn and this went on, that would be perhaps four times a year.

That's why I thought it was very important to bring in data that is more specific to your question like the publication by Bardhan which looked specifically at people who had a diagnosis of GERD.

They did have screening endoscopy at the entrance to the study. Only Grade IV was excluded from participation on the grounds of ethical reasons that these people need healing, to your point, Dr. Levine. What you saw there was that 75 percent of the people actually did well using intermittent.

That brings us to the question that you asked first, are we making a distinction between frequent heartburn and GERD. I think importantly it undoubtedly reflects the same bias that limits our ability to look broadly in the data.

Most of the clinical trials have looked at maintenance of remission and really maintenance therapies dealing with erosive esophagitis. There's only a few trials like Bardhan -- and there's another

by Lindh -- that really allows people to elect to take treatment on the basis of symptom occurrence. The Lindh study is another one I didn't show but it shows very similar results.

What you see there is there are a population, and it turns out to be the majority of people, who have episodes -- well, that's not a good word in this setting because it means something else, but they have periods of time when their frequent heartburn is acting up and then is goes into a quiet phase and it may act up again in the future. Only about 25 percent of the people seem to be requiring more chronic therapy.

I think it's this 25 percent of the people who are those that end up in the clinical trials and the ones who are chronically seeking physician care for further intervention who have relapsing symptoms.

We're not targeting the therapy to them but it's a perfectly acceptable therapy for them if they are using it with their physician being knowledgeable about it.

DR. CRYER: Okay. So as you were responding, Dr. Camilleri actually pointed me, I guess, to the briefing document that was provided by the sponsor. From the efficacy trials the mean

reported baseline of heartburn frequency was five days per week. Would that be an accurate statement?

DR. PEURA: In our efficacy trials 171 and 183 the average days of heartburn was about 75 percent of the days which would be five out of seven days. The severity was mild to moderate on a three point scale.

You had also asked about the population in our actual use study as well as the people. Did you ask that question?

DR. CRYER: No, I didn't have the question but I would be happy to hear the answer.

DR. PEURA: It's similar population range within that. Less than 1 percent of the people actually had infrequent heartburn less than one day a week and about a third of the people had it two to three days a week. The other third had it five to seven days a week.

DR. CRYER: If I might, just to follow up on the population and the actual use study. I believe you said a little earlier that the population in your actual use study is as close as you can get to a population that would be making a purchase decision at a pharmacy or a drug outlet store.

Given that you actual use population is

fairly reflective of the actual population, I really want to get back to this issue of your low-literate population. Under low-literature population, if I understand it correctly, there was a 50 percent response rate in terms of label comprehension.

You've told us -- you've suggested that when the actual compliance over 14 days that their compliance was somewhat better. I think the description then was 50 percent but I never heard a quantification of how much better than 50 percent was their actual compliance over 14 days.

DR. PEURA: Over the 14 days the compliance was only 2 to 3 percent different than the "literate" population. This is in compliance for using the product appropriately, the one dose per day, one tablet per dose, and also over the 14-day dosing regimen period.

When we look at correct self-selection of those criteria, there was about a 10 percent difference. There was 70 percent for the low-literate group compared to 81 percent for the average group.

DR. CANTILENA: Okay. Thank you. I think we'll have some time as well this afternoon to ask more questions. I just have one which involves the actual use study. At what point in the study did you

obtain informed consent?

DR. PEURA: We obtained informed consent after the people made the purchase decision to buy the product.

DR. CANTILENA: Okay. I was wondering if you had a copy of the informed consent document with you?

DR. PEURA: We don't have it with us.

DR. CANTILENA: Okay.

DR. PEURA: We cam probably get you a copy if you would like to see it.

DR. CANTILENA: Okay. If you could have that for after lunch, that would be great. What I would like to do now is -- we are just a little bit over -- take a 20-minute break. Come back at just after 11:00 a.m.

(Whereupon, at 10:45 a.m. off the record until 11:06 p.m.)

DR. CANTILENA: While we're waiting for people to come back, the final score Germany 1, USA 0. But it was a great run.

Our first speaker for the FDA is Dr. Mark Avigan.

DR. AVIGAN: Thank you. I'm a board certified gastroenterologist. Before coming to the

FDA I served on the faculty at Georgetown University. There's been a longstanding interest by a number of sponsors to make treatments for the management of heartburn symptoms directly available to consumer in the OTC arena.

On the occasion of the first Joint Advisory Committee that discussed omeprazole magnesium on October 20, 2000, Dr. Larry Goldkind and I presented an overview of efficacy and safety issues related to the use of this product in an OTC setting.

At that time the sponsor was seeking approval for the following indications. First, the relief of heartburn, acid indigestion, sour stomach. Second, the prevention of these symptoms brought on by consuming food and beverages or other inciting events. Third, the prevention of symptoms for 24 hours.

Both FDA reviewers and a majority of the Advisory Committee attendees concluded that results of the studies performed by the sponsor did not demonstrate efficacy for the first two listed indications.

In the case of treatment of episodic heartburn as a symptom, neither multi-center placebo controlled trials 092 or 095 revealed superiority of a single 20 milligram dose of omeprazole magnesium over

placebo.

These studies contained over 600 subject with a history of heartburn occurring at least two days per week in each treatment arm. Although four hour prevention of meal-induced heartburn by single dose of omeprazole magnesium was demonstrated in a 1,200 subject multi-center double-blind placebo-controlled study. That study is 006.

This result was not replicated in a separate study, study 005, which was virtually identical in its design and execution. In contrast to the absence of efficacy in studies for the first two indications, results of studies 171 and 183 supported the third claim, the prevention of symptoms of 24 hours.

It is these two studies that the sponsor is now resubmitting for consideration of the newly proposed indication, the prevention of symptoms of frequent heartburn for 24 hours.

Results of clinical studies of omeprazole magnesium provided by the sponsor can be tied to the mechanism of action of all proton pump inhibitors including omeprazole. Normally omeprazole has a short half-life in the circulation; that is, between one and two hours, because the proton pump molecules, which

are irreversibly targeted by omeprazole, may not all be simultaneously accessible to binding by the drug.

The dosing interval with omeprazole is only once per 24 hours and the degree of acid suppression after a single dose is low. In fact, consecutive daily treatment for a few days is required to build up to a maximum PD response.

This characteristic can be contrasted with that of antacids and H_2-receptor antagonists which achieve identical pharmacodynamic effects after each dose including the first.

It is FDA's concern that omeprazole's buildup effect of acid suppression over consecutive daily doses may reinforce continuous unsupervised usage by consumers seeking optimal relief of chronic heartburn.

In the remaining time that I have I will touch on the following areas. First, the safety profile of omeprazole with regards to short-term and long-term drug exposure.

Second, findings of previously submitted studies which reflect on the potential for long-term usage of this product in an OTC setting without physician supervision. Third, the results of pivotal studies 171 and 183 measuring the effects of

omeprazole magnesium on symptoms.

Fourth, highlights of early symptom and drug usage patterns of the actual use study 007. Finally, some of the outstanding issues surrounding approval of the drug for OTC use that the advisory committee must address.

An analysis of the safety record of the drug is supplemented by an array of clinical studies in post-marketing surveillance data of the entire code of prescription formulation.

Short-term administration of omeprazole has been linked to a number of serious adverse events. Rarely these may be life threatening and include severe hypersensitivity reactions such as angioedema and anaphylaxis, toxic epidermal necrolysis, agranulocytosis, and clinically significant hepatic dysfunction.

Although the precise incidents of these adverse events cannot be determined from a voluntary post-marketing reporting system, it appears that they are quite rare and similar to serious adverse event rates associated with some other OTC approved products.

Omeprazole magnesium has also been associated with mechanisms that may lead to clinically

significant drug-drug interactions. Competitive inhibition of CYP 2C19 metabolism and gastric acid neutralization by the drug are each known to affect pharmacokinetic profiles of certain agents.

The potential for critical omeprazole induced increases in circulating levels of some drugs such as warfarin, phenytoin, diazepam, digoxin is small but it can be further minimized by appropriate consumer labeling. Similarly, the more likely disruption of effective levels of antifungal such as ketoconazole can be minimized by labeled instructions to consumers.

A separate series of safety concerns that were raised during the first Joint Advisory Committee meeting are relevant only to long-term continuous or intermittent self-administration of omeprazole without physician supervision. These were discussed because of the pharmacological properties and potential for such usage which I just mentioned.

Safety concerns tied to long-term usage include the following. First, there is a potential of the drug to mass symptoms associated with underlying medical conditions that warrant early diagnosis and adequate treatment.

These include severe forms of erosive

esophagitis, Barrett's, metaplasia and dysplasia, or cancer of the esophagus or stomach. In some individuals with these conditions, a significant delay and physician referral and patient evaluation may lead to worse outcomes.

A second safety issue related to long-term unsupervised administration of the drug is absence of prospective controlled trials to determine whether such exposure confers an increase in the absolute risk for the development of certain neoplasia in a large population of users.

All proton pump inhibitors induce increases in circulating gastrin concentrations which have trophic effects on some mucosal cells. In addition, these drugs may have genotoxic effects in a variety of cell types when in an activated form.

The concern about the potential for significant numbers of consumers to engage in long-term self-administration of omeprazole magnesium without physician supervision despite labeling for only short-term use was prompted because of the following points.

First, the drug is intended to prevent recurrent episodes of heartburn in individuals with frequent symptoms rather than effectively treat

episodic symptoms.

Both in the clinical efficacy studies and actual use studies based on clinical characteristics, it was not possible to assert that many of the enrolled individuals with frequent symptoms did not have gastro esophageal reflux disease referred to as GERD which is a chronic and often long-term condition.

As described by Dr. Castel at the first Advisory Committee meeting, individuals with long-standing heartburn and the spectrum of complications of erosive GERD and the severity of mucosal changes cannot be consistently correlated with symptom severity or frequency.

Second, the recurrence rates of heartburn in individuals with GERD are high within a short period of time after cessation of acid suppression treatment. Third, in a national usage study that was presented at the first Advisory Committee meeting more than 60 percent of individuals using omeprazole magnesium for the prevention of heartburn exceeded 10 consecutive days of treatment despite a labeled instruction not to treat beyond that point.

This is not surprising since large percentages of individuals who have self-selected for OTC treatment with omeprazole magnesium in those

actual use studies have had histories of long-standing heartburn that are consistent with the diagnosis of GERD.

It should be noted that at the first Advisory meeting the panel was split on the question of whether chronic heartburn or GERD is an acceptable OTC indication. The panel decided that sufficient evidence had not been provided to support either a favorable benefit risk assessment or approval for any of the three possible indications of acute symptomatic heartburn, prevention of episodic heartburn, or chronic heartburn.

In the current submission the sponsor has proposed an indication for prevention of symptoms of frequent heartburn for 24 hours and only for those who suffer heartburn two or more days a week.

Studies 171 and 183 were double-blind placebo-controlled two-week treatment studies which contained approximately 500 subjects in each treatment arm. Inclusion criteria included the presence of heartburn at least two days per week for one month prior to enrollment.

Although the primary efficacy variable was no heartburn over 24 hours between the first and second daily dose following randomization, heartburn

free 24-hour periods over each subsequent treatment day and during the single-blind placebo follow-up phase were also measured.

These studies were associated with the following findings. First, there was a substantial proportion of studied subjects who experienced no heartburn despite treating with placebo both on day one of treatment, 32 percent, and on day 14, 43 percent.

Second, although statistically significant, the therapeutic gain of omeprazole magnesium 20 milligrams versus placebo was only 16 percent on day one but increased to 29 percent on day four confirming that the maximal pharmacodynamic benefit of treatment relies in consecutive daily dosing.

Finally, even after 14 days of treatment with the 20 milligram doses, almost 30 percent of subjects experienced break-through heartburn.

It is significant that the frequency of heartburn symptoms prior to treatment had a substantial impact on the rates of response to omeprazole magnesium and placebo.

In subjects with pretreatment heartburn that occurred less than half the days, 50 percent of

the days, the difference between drug and placebo response rates referred to as the therapeutic gain was only 4 percent on day one of treatment.

This small difference was due to a placebo response rate that was over 65 percent. Even by day 14 of treatment the therapeutic gain in this group of subjects did not rise above 11 percent since the placebo response rate was over 70 percent.

In contrast, subjects with daily heartburn prior to treatment demonstrated more robust differences between drug and placebo in response rates. These differences reflected substantially lower response rates to placebo when compared to the group with less frequent heartburn. In the daily heartburn group on day one of treatment, the therapeutic gain was 18 percent and by day 14 it rose to 39 percent.

The conclusion that can be drawn are consistent with omeprazole's function as a potent inhibitor of gastric acid secretion and the important role that it can play in the management of severe forms of gastric esophageal reflux with associated frequent symptoms.

These conclusions can be summarized as follows: First, in subjects with low frequency

heartburn at baseline the therapeutic gain from drug was small because of a high placebo response rate. Second, the therapeutic gain was greatest in subjects with daily heartburn because only a small percent responded to placebo.

Nonetheless, despite the higher therapeutic gain in these subjects there was a 40 percent break-thru rate of heartburn on the last day of treatment with the drug.

The American College of Gastroenterology has issued published guidelines for the diagnosis and treatment of GERD. These include the following: GERD is characterized by chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. Furthermore, many, perhaps most patients, with GERD require long-term possibly life-long therapy.

Based on the distribution of frequency of heartburn prior to treatment in the sponsor studies, it is likely that many of the study subjects had GERD. Therefore, it is not surprising that in both studies after cessation of treatment with omeprazole magnesium the recurrence of heartburn was rapid. Within three days the apparent therapeutic gain compared to placebo disappeared and the daily percentage of subjects with

heartburn over 24 hours rose to approximately 55 percent.

In addition to three label comprehension studies, the actual usage studies 007 that measured characteristics of individuals who chose to purchase this product and their usage of the product of a duration of eight to 12 weeks has been provided.

Most patients who self-selected for OTC treatment in that study who had GERD is supported by the following observations. First, among the treated population more than 90 experienced heartburn for more than one year and almost 50 percent for longer than five years.

Second, 57 percent of these subjects experienced heartburn four or more days per week. Third, a substantial percentage of subjects used other products or prescription medications to relieve heartburn when symptoms recurred after completion of the 14-day course of treatment with omeprazole magnesium.

It should be emphasized that the actual use study did not measure the potential for long-term intermittent usage of the product. More details about results of study 007 will be described by Dr. daiva Shetty.

In summary, omeprazole magnesium will be used by substantial number of individuals with GERD. In the proposed labeling the consumers were warned to "notify your doctor if you have had heartburn for three months or longer without talking to your doctor," and instructed to "stop use and a doctor if heartburn continues or returns after using this product everyday for 14 days." The consumer is also instructed, "Do not continue beyond 14 days unless directed by a doctor."

The advisory committee must address the following issues. First, whether a single two-week treatment course of omeprazole magnesium in an OTC setting meets the short-term and long-term needs for acid suppression of individuals who purchase this product.

Second, whether occasional courses of treatment in an OTC setting without physician consultation are consistent with the sponsor's proposal. Finally, whether limitation of usage to a single 14-day treatment course is an important feature to protect the safety of consumers.

If so, it must then be determined whether the sponsor has provided adequate information about the potential for long-term continuous or intermittent

use of this product without physician supervision to ensure a favorable benefit risk assessment.

Thank you. Now I want to introduce Dr. Karen Lechter from CDER's FDA's Office of Drug Safety who will discuss label comprehension studies.

DR. LECHTER: I'm going to talk to you briefly about the purpose of label comprehension studies. I'll then discuss the two standard Prilosec label comprehension studies.

Excuse me. This mouse is not working. I'll have to use -- I'll just use the button. Thank you.

I'll focus primarily on the issues about which we have concerns where there is clear evidence of problems and where there is an adequate evidence to draw conclusions. I'll then discuss the implications of the results for the label.

The regulations state that OTC labels must be likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

As one way to satisfy this requirement sponsors conduct label comprehension studies to test how well their proposed label communicates. Sometimes

this i done as an iterative series of studies with the label changes being made after the study and then the label being retested.

In some cases this goes on for several rounds. For the Prilosec OTC product the sponsor conducted two standard label comprehension studies. The first was study 02255. There were 684 persons in this study, 43 percent male. There were five cohorts. 297 were in a general population.

Two cohorts were frequent heartburn sufferers. One was low literate which was 8th grade reading level or lower of which there were 162 members. Another was high literate and there were 155 in this group.

Frequent heartburn suffers were those who had heartburn two or more times a week or who were taking a prescription medicine for heartburn. The fourth cohort were 96 heartburn sufferers taking drugs listed on the label as requiring physician advice.

The fifth cohort was 42 pregnant or nursing heartburn suffers. These participants examined the label and answered questions about it with the label available for reference.

When asked about the product purpose, 39 percent of the general population were completely

correct. They said "prevent frequent heartburn." The two literacy groups had similar percentages of completely correct responses.

As this was an open-ended question, we're not as concerned about getting a complete response as we would be for other types of questions. However, these responses may reflect problems in understanding all the aspects of the indication and we need to look at questions in which the label information is applied to learn if there is a problem understanding the indication.

All of the hypothetical scenario questions about use for episodic relief or prevention should have been answered that the product is inappropriate. However, only about half of the responses were correct about episodic use. About half answered that the product could be used for prevention or relief of individual heartburn episodes.

For the three questions about episodic relief, the correct scores in the general population ranged from 48 percent to 55 percent. An example of these questions was, "You ate chili for lunch. The chili gave you heartburn. You have not had heartburn before. You want to take something now to get rid of this episode of heartburn. Based on the label, is

this product intended to be used for this situation of heartburn or not?"

For the two questions about episodic prevention in the general population, scores ranged from 54 percent to 61 percent. An example of this type of question is, "The food you brought for lunch today usually gives you heartburn. You would like to take something just for today before lunch so you don't get heartburn. Based on the label, is this product intended to be used for this situation of heartburn or not?"

Participants were asked if the product was intended for them personally to use. We call this the self-selection question. Frequent heartburn suffers with symptoms listed on the label as requiring physician consultation before using the product were correct only 41 percent of the time. Frequent heartburn suffers taking medications listed on the label as requiring physician consultation before use were correct only 50 percent of the time.

This rose to 82 percent after they were given a list of brand names that correspond to the generic names on the label. However, we believe that the 50 percent figure is more valid because consumers selecting OTC medicines in the store would not have a

list of brand names.

Overall 67 percent of those who should not use the product or should consult a doctor first were correct in the self-selection question. The cohorts of non-heartburn sufferers, infrequent sufferers, those allergic to the product, and pregnant or nursing heartburn sufferers responded correctly at the rate of '76 percent or greater.

However, we are concerned that the self-selection responses suggest there is a problem in applying the label to one's self when one has symptoms listed on the label or is taking medications listed on the label.

On the other hand, scenario responses based on hypothetical situations about use with listed medications or medical conditions suggest good understanding with correct responses generally in the 90s.

But the high positive results may be due to an artifact of the study in which almost all questions required a response that the product should not be used or a doctor should be consulted. This could have created a nay-saying basis in which responses are likely to be influenced by this artifact rather than by knowledge of the label.

In conclusion, in study 02255, the tested label failed to convey adequately that Prilosec 1 is not for periodic use, that it is not for acute symptoms or for prevention of meal-induced heartburn.

This conclusion is supported by data I presented earlier that only 48 to 55 percent correctly said the product could not be used for relief and only 54 to 61 percent correctly said it should not be used for episodic prevention.

Also it is not clear that people can apply the label well to their own situation if they take any of the medicines listed on the label or have any of the health conditions listed on the label as requiring physician consultation before using the product.

Further testing would help determine if the proposed label works better than the one tested in this study. However, the proposed label does not address the prevention and episodic issues any differently than the tested label. Improvement on these issues is not likely.

Study 12179 was designed to see if people who should not use the product without a physician's advice due to medical conditions would understand that fact and if they understood the indication and understood the label information well enough to apply

it to three hypothetical situations in which people should consult a doctor before use and in one situation which consultation is not necessary.

There were 145 study participants, 41 percent male. All had frequent heartburn. All had at least one condition mentioned on the label as requiring physician consultation. They were not taking medications listed on the label as needing physician consultation.

The label used was similar to the final proposed label but the tested label listed six medications requiring physician consultation rather than the three that were on the final proposed label.

We analyzed the results of this study differently than the sponsor did. We eliminated 40 of the 145 participants. There were two participants taking Prilosec but we were only to identify only one of those so the others still are in our analysis. We did remove the one that we could identify.

We removed those who should not have been in the study at all because they did not have a condition that required physician consultation before use according to the label. These included those with infrequent chest pain or infrequent wheezing. The label said those with frequent chest pain or wheezing

should consult a physician.

We analyzed the results for the 105 remaining who should not use the product without consulting a physician. All should have said they would consult a physician before using the product.

The sponsor scored anyone who had ever discussed their condition listed on the label with a healthcare professional as okay to use the product. These conditions included frequent chest pain, chest pain with other specified symptoms, trouble swallowing food, frequent wheezing, and wheezing with heartburn and unexplained weight loss.

Unlike the sponsor we did not believe that having ever discussed a nonheartburn medical condition with a healthcare professional is a surrogate for getting approval to use Prilosec 1. There is no evidence that these participants ever got or would have received approval to use Prilosec 1. All of the 105 in our analysis should have said they should not use a product or should consult a doctor first.

More than half of the participants in our analysis answered incorrectly about whether they could use the product based on the label. Forty-five percent answered correctly. Of these 26 percent said they would ask a doctor and 19 percent said they would

not use it.

When asked an open-ended question about the product purpose, about one-third of the participants gave the complete response "prevent frequent heartburn." A series of four questions asked about whether people with certain medical conditions could use the product, three of these conditions were listed on the label as requiring medical approval.

The other, headache, was not listed. Scores for these questions were in the 90s. however, one-third of participants said a doctor should be consulted if the person has headache. This suggest participants were very conservative in their responses and may not have been responding as they would in normal use. It suggests that the scores for the other conditions may have been inflated.

After these studies the label was not changed to improve communication about nonepisodic use and use only for prevention. However, the list of medications requiring a doctor's consultation was shortened in the proposed label from six to three.

The list of medical conditions in the proposed label is shorter and more bulletted than in the 02255 study and is the same as in the 12179 study. We do not have evidence that the proposed label

communicates the problem messages any better than the labels tested.

These studies suggest that participants understand Prilosec 1 is for frequent heartburn. Do not use Prilosec 1 if you do not have heartburn, have infrequent heartburn, are allergic, or are pregnant r nursing.

I mentioned in the beginning of my presentation I would focus on areas that concern us. Therefore, I did not mention that there was evidence of good understanding of some other aspects of the label information. This included that the product should not be used if you have trouble swallowing, chest pain with other symptoms, chronic cough, black tarry stools, unexplained weight loss, you are under age 18, or you have heartburn that has become worse with nausea and vomiting.

Despite some of these good results, these studies do show that consumers believe Prilosec 1 can be used episodically for relief of acute heartburn symptoms or to prevent meal-induced heartburn. Further, it is not clear if consumers with medical conditions listed on the label were taking medications listed on the label would understand they should seek medical advice before use or decline to use the

product.

The actual use study has similar results. Dr. Daiva Shetty from the OTC Division will now discuss the actual use study.

DR. SHETTY: My presentation briefly covers some highlights of the regulatory history of over-the-counter Prilosec program, the proposed label, target population, and the results of the actual use study 007.

As you have already heard Dr. Mark Avigan explain some aspects of the regulatory history of OTC omeprazole. I will summarize the differences between the original and the resubmitted NDA.

There were multiple changes made to the original NDA. The dose was increased from 10 to 20 milligrams. The target population from anybody above 12 years of age with heartburn symptoms was changed to 18 years and above with frequent heartburn symptoms two or more days a week.

The initial proposal had relief as well as prevention of heartburn claims. The current submission has only the prevention of frequent heartburn indication. The duration of treatment was extended from maximum of 10 days of intermittent use to 14 continuous days.

In support of the current submission, the sponsor has provided the results of one actual use study, three label comprehension studies, a new proposed label, and a safety update.

The study 17859 called deselection study was classified as label comprehension study. Actually it was a marketing study. Therefore, the data from the study will not be presented.

Now I'm going to talk about a proposed OTC label and the target population. The label used in the actual use study was very close to the label proposed for OTC marketing. The use section on the label states that Prilosec will prevent frequent heartburn for 24 hours in people who experience heartburn symptoms two or more days a week.

The directions also stated anyone who is 18 years or older should take this drug one tablet a day every day for 14 continuous days and directs to consult a doctor if symptoms return after this 14-day course of therapy.

There are multiple warnings listed on the proposed label. I would like to draw your attention to one of the warnings. It's called heartburn warning and it states, "Notify your doctor if you have heartburn symptoms for three months or longer without

talking to your doctor." I will refer to this warning once again when I discuss the findings of the actual use study.

Now I'm going to present the results of actual use study 007. There are certain actual use issues for OTC Prilosec. First of all, are consumers able to self-select and deselect appropriately? Do they understand what precludes them from the use of Prilosec? Are consumers able to treat themselves to follow label use directions for duration of use and do they follow directions when to seek advice from a healthcare provider?

The actual use for the 007 was a three-month duration multi-center open-label, all-comers with minimal inclusion and exclusion criteria. It was intended to assess how consumers would use omeprazole in naturalistic OTC conditions following proposed labeling instructions. It did not address all the issues that the agency is concerned about.

On the next few slides I will try to walk you through the disposition of the study subject. A total of 1,301 subjects participated in self-selection interview. After looking at the package the majority of them, 1,251, stated that Prilosec is appropriate for them to use.

The purposes of this presentation, subjects who self-selected that the product is appropriate for them to use will be called self-selection population. Unlike the sponsor, we believe that this population should have been the primary population for analysis of self-selection behavior.

I will later point out what the sponsor's definition of the self-selection population was. Of those who self-selected that the drug is appropriate for them to use, 683 chose to participate in the study by agreeing to sign some consent to buy the drug, to fill up a diary, and return for end of study follow-up visit. Three hundred and 84 subjects elected not to participate in the study.

The reasons why 384 subjects stated that it is an appropriate drug for their use but chose not to participate are listed on the slide. One-third of them stated that it is inconvenient for them to participate in the study. More than a quarter of them, 104 subjects, stated that they would not try new medicine without a physician's approval.

These groups actually could use the product if it were to become freely available over the counter. Of those 863 subjects who elected to participate, 854 purchased the drug and received one

or more diaries. Nine subjects did not meet inclusion criteria and were not allowed to enter the study. Four of those nine did not provide the consent, one was pregnant, and four previously participated in similar studies.

Seven hundred and 62 subjects completed the study by returning one or more diaries. Ninety-two subjects did not return diaries. Majority of them were lost to follow up. They were a minimum of five attempts by phone and at least one letter sent trying to locate these people.

Of the 762 subjects who returned diaries four returned blank diaries and 758 kept a record of the study drug use. Those who had the record of steady drug use will be called the treated population. I will focus on it talking about compliance with the label use directions.

Of the 758 treated subjects, 649 were available for a three-month follow-up. This final follow-up contact was done by phone and 109 subjects could not be reached.

If we are going into the results of self-selection behavior, I would like to show you the difference between our and the sponsor's primary population for self-selection objectives.

we believe that subjects who participated in the initial self-selection interview and stated that Prilosec is appropriate for their use, it's the actual over-the-counter population that would not be objected to further screening as it was done in the study.

In this presentation the sponsor called those subjects who decided to participate in the study as their self-selection population. However, in the background package to the agency, the sponsor's definition of self-selection population included treated subjects plus additional 12 subjects that were excluded from the study by the investigator.

These subjects not only selected a drug for their use but also had to sign a consent that they agreed to purchase the drug, fill up a diary, and return for a follow-up visit. Using sponsor's population for self-selection objectives have sufficiently increased correct self-selection rates.

Demographically the self-selection population was fairly representative of the overall U.S. population with 59 percent being female. The age of the participants range from 16 to 91 with a mean of 48 years. The majority were caucasian, 65 percent, and 18 percent were African American. Low-literacy

group consisted of almost 10 percent of the self-selection population.

Looking at the heartburn study for follow-up with the self-selection population, you can see that majority of them had long-standing heartburn. Over 90 percent of the self-selection population had heartburn symptoms for over a year and almost half, 45 percent, over five years.

Most of them had frequent heartburn as defined by the sponsor, two or more days a week. However, 14 percent of the self-selection population had heartburn symptoms one day or less a week and, therefore, failed correct self-selection.

Analyzing self-selection behavior and compliance with the label used directions the sponsor incorporated one variable, the consultation for heartburn that the healthcare provides them.

I would like to point out what the sponsor's definition of the consultation with the healthcare provider was. It included advice from a physician or any healthcare professional, or the use of any prescription heartburn medication anytime in the past.

This contact was not verified by the study personnel. Therefore, we don't know what particulars

were discussed or what advice was given by the healthcare provider.

As you recall, the label states to talk to your doctor if you have had heartburn symptoms for three months or longer. This pie chart shows that less than half of the self-selected population consulted healthcare provider for their heartburn within a year.

Additionally, 17 persons consulted a healthcare provider more than a year prior to the study. Thirty-seven percent did not speak to their healthcare provider about their heartburn at all. There was a similar ratio of these subgroups for the treated population, those who purchased and used the drug.

The correct subselection was based on the sponsor's predefined criteria. The subject had to be 18 years or older with heartburn symptoms at least two days a week, not pregnant, not allergic to omeprazole, not having certain contraindicated conditions, and not taking contraindicated drugs listed on the label.

The correct self-selection was 76 percent for the self-selection population which included, as I mentioned, subjects who stated that Prilosec is appropriate for them to use. Two hundred and 90

subjects failed correct self-selection for the following reason, 169 experienced heartburn one day or less a week.

There were certain relative contraindications listed on the label, yet some consumers with those conditions are taking the list of drug-selected Prilosec for their use.

One hundred and thirty-four were having certain contraindicated symptoms that were listed on the label. Fifteen were using contraindicated medications. Three were less than 18 years of age and one was pregnant.

Of those 854 subjects who purchased the product the majority purchased only one carton of 14 tablets. There were a few that purchased more than one carton. Even though the subjects were allowed to purchase up to four cartons, the limit of 14 tablets in the package have impacted their pattern of use.

Over all compliance with the label use directions was achieved by 63 percent of the treated population. Those were the subjects who purchased the drug and used the drug and returned diaries with the record of use.

Unlike the sponsor, we believe that compliance subjects had to follow all three label use

directions, take one table a dose, one dose a day for full course of therapy.

The compliance rate increased significantly from 63 to 79 percent when the sponsor changes the criteria for the compliance with 14-day regimen. The sponsor considered compliant dose who took 11 to 14 doses in an 11 to 17-day period. We believe that such an analysis increases the compliance rate.

The majority of noncompliant subjects took the drug less than 14 days. Nine percent took more than one dose per day. Four percent took more than one tablet per dose. three percent exceeded 14 consecutive days.

The response to the three-month follow-up questionnaire showed that more than half, 57 percent of the subjects available for follow-up, had their heartburn symptoms return. When these subjects were asked what they did after their heartburn returned, 20 percent stated that they talked to a healthcare provider or made an appointment to see one in the future.

Forty-six percent started using antacids, 27 percent switched to prescription heartburn medication, and 21 percent used over-the-counter acid

reducer. This suggest that subjects who used Prilosec already had access to over-the-counter as well as prescription heartburn medications.

The study had several limitations. It was a relatively short duration total of three months. It did not address a question if Prilosec is likely to be used intermittently, a few courses over a year, and what the consequences of such a use would be.

It did not address the concomitant use of other heartburn medications. The methodology of the study did not allow us to assess if consumers understand that this drug is for relief of acute -- is not for relief of acute heartburn symptoms and what consumers would do if Prilosec does not relieve their symptoms.

Overall conclusions that can be drawn from this study of who and how would use over-the-counter Prilosec would be summarized as follows:

Most of the consumers who self-selected to use Prilosec had a long history of frequent heartburn. Even though the label stated to see a healthcare provider prior to the use of Prilosec more than a third of those subjects did not do so.

More than half of the treated population available for follow-up had their heartburn symptoms

return. The majority of them switched to other prescription or over-the-counter heartburn medications. Twenty percent decided to seek advice from a healthcare provider.

It is unclear how the interaction with the healthcare provider prior to or after the use of Prilosec would have influenced consumer behavior. The study also showed that Prilosec is likely to be used by consumers with contraindicated symptoms and is likely to be used by consumers with infrequent heartburn.

This concludes my presentation and overall FDA presentations. Thank you.

DR. CANTILENA: Okay. Thank, Dr. Shetty. I would ask that Dr. Avigan and Dr. Lechter join Dr. Shetty for questions from the committee. We will now open the discussion, Brass, Johnson, and Goldstein to start.

DR. BRASS: I have three related questions. The first has to do with the issue of recognition of contraindicated medications on the label. This is certainly an issue the committee has struggled with time and time again. The issue of brand versus generic names is not unique to this particular NDA and is also an issue that has been

discussed.

But as was alluded to in discussion earlier today, the evaluation of these questions really has to be linked to the consequences of not accepting the information or not processing the information properly.

I would like kind of an integrated assessment from the review team as to whether concomitant use of omeprazole at this dose with any of the medications listed would pose a serious safety problem.

DR. ALFANO: Well, let me try to shed a more clinical perspective on that. There are two ways of looking at that problem. You can look at a whole population and ask what is the incidence of a bad untoward drug-drug interaction and find that it is a low number. Or you can ask who might be in the population susceptible to such an interaction. It really is the second type of approach where there are some concerns.

An example would be in the class of PPIs there's a known interaction as I alluded to with warfarin. Usually that is an interaction which is not clinically very important but there are already some known postmarketing reports for various members of the

class of individuals who might have developed increases in prothrombin time that have warranted reporting to the agency with the pages on chronic warfarin who then started a PPI.

In one or two cases, actually developed clinically significant bleeding. If you are asking a frequency question, the answer is generally these drug-drug interactions are not common for the group.

DR. BRASS: Yeah, but, again, has the clinical significance of the interaction between omeprazole 20 milligrams and warfarin been studied and what was the conclusion of such studies?

DR. ALFANO: It has been studied. Perhaps we might get some other comments on this but there have been studies in individuals where they have been challenged with single doses or who have been on one drug and then have been essentially tested with the other. Reassuringly in a small population of tested individuals there were no dramatic effects either on prothrombin time.

But the problem with that is the potential again in numbers of marketed -- if you market this to large number of people are the outliers and the confounding effects of new facts such as is the patient not only someone who is on these drugs but

perhaps has also a problem with metabolism because of something else, an isoform difference. I think this is where it is very challenging.

DR. BRASS: Okay. A similar theme question has to do with the contrasting of the two difference definitions of compliance in the actual use study, the rigorous everyday 14 versus the range.

My question is given what we know about the pharmacodynamics and the time course of action of this specific drug, do you believe those differences in definition would translate into meaningful differences in risk benefit assessment?

DR. SHETTY: Probably not. We just took the more conservative approach to see how people followed all three directions on the label.

DR. ALFANO: Again, just a clinical perspective. I think it was already noted by a member of the panel that one of the criteria for compliance that was not a criteria for compliance but is on the labeling is if you've had heartburn for three months go see your doctor first. That was excluded from the criteria.

DR. BRASS: Yeah, I asked that question before because I think that's an example, quite frankly, of a warning that is not very meaningful

because 100 percent of the population is going to qualify for it and already has not seen their doctor.

Finally, a question for Dr. Lechter. You identify quite appropriately a number of concerns and limitations in the label comprehension study.

My question to you is after seeing the actual use study and the difference in the results, and given all the methologic differences in those two trials whether you personally have any reassurance that your concerns from the label comprehension context are in anyway mitigated by the actual use context.

DR. LECHTER: I think in general we get better information from actual use studies but this study did have some limitations and we need to take that into account. We still have concerns about whether people understand the episodic use. Some things were not studied in this use study.

DR. CANTILENA: Okay. Dr. Johnson.

DR. JOHNSON: I have two questions that are directed towards Dr. Lechter.

You indicated that with respect to the contraindicated drugs that there was 50 percent comprehension with generics but it went to 82 percent when brand name was given. You suggested or implied

that the 50 percent is the meaningful number indicating that brand names can't be put on the label. I'm wondering if that's what you mean and, if that's the case, why? Why can we not put brand names on the label?

DR. LECHTER: I'm not sure. That may be an FDA policy which I can answer. I think typically we don't put brand names on OTC products but perhaps someone else could answer that.

DR. CANTILENA: Dr. Ganley, do you want to take a shot at that?

DR. GANLEY: Sure. In the OTC labeling rule -- it's not in regulation but in the preamble they had not wanted to put in brand names into the drug facts labeling. I don't think it really addressed the issue of contra indicated medications and putting actually the generic and brand name in.

I think Doug Bierer may have noted earlier that they wanted to have some discussions with us based on this results where there is a dramatic improvement in comprehension if you actually put in the brand name. From my viewpoint, I think that is something that could be a consideration. I don't think there is a regulation that says that we cannot do it.

DR. JOHNSON: I think those data are not at all surprising and frankly I am surprised that 50 percent recognize generic names. I would have thought it would have been lower than 50 percent.

My second question relates to the drugs that are on the list. I can't remember whose section of the FDA packet this was in but there were data on itraconazole which had significant interaction. Not quite as significant as ketoconazole but I'm wondering -- I wanted to ask this question of the sponsor and didn't get a chance -- why itraconazole isn't on the list or why you were not recommending itraconazole to be on the list.

DR. ALFANO: Right. I think there are two approaches again. One is to have a comprehensive list and fit it in, as we heard before, in a relatively small service area and add another word because in reality -- I think your point is well taken -- there is an effect where the gastric acid neutralization has an effect on all those related antifungal compounds. To be comprehensive and complete one would then -- if that was the attack that one was taking, one would have to have a complete -- write a complete list.

DR. HOUN: I think we can ask the sponsor your question relating to the itraconazole. We could

also ask them the other questions about the number of patients they formally studied on these various contraindicated drugs and the data they have on that. That would be important, too.

DR. CANTILENA: Yes. If you have that on a slide, that would be actually the most helpful.

DR. PEURA: Let me first address the itraconazole question. Itraconazole is listed as a drug-drug interaction in the Rx data package on that. However, for ketoconazole it is not listed on the Rx data package for that. We felt it was important to include ketoconazole in our labeling but not itraconazole.

DR. CANTILENA: Hold on just a second. Both drugs interact one slightly more positively than the other but now we're going to have on the Rx side one drug and on the OTC we're going to have another?

DR. ZORICH: It should be mentioned somewhere.

DR. CANTILENA: One or the other or both.

DR. ZORICH: Well, the important thing is communication to the patient. Since itraconazole does communicate it, they would be aware that they should not be taking omeprazole. When they were prescribed that, it is in that labeling. The question should be

whether ketoconazole does, too, but it does not. Since it does not, we felt an obligation to include it on our label.

DR. CANTILENA: As opposed to having itraconazole and ketoconazole on the OTC label?

DR. ZORICH: To ensure that somewhere there is appropriate communication to the person who might be using both.

DR. CANTILENA: But the OTC is sort of a stand-alone.

DR. ZORICH: Yes.

DR. CANTILENA: On the shelf all by itself without -- okay.

Dr. Johnson, do you have another follow-up?

DR. JOHNSON: Yes. I guess I just have a comment. I understand there is limited space to put drugs. I guess my impression would be that it's much more likely you would have a clinically significant interaction with itraconazole and this drug than with, for example, warfarin and this drug.

If you feel there is only room for three drugs, I think there has to be a really critical assessment of what are the three most clinically significant drug interactions because I'm not sure

those three are the three that are on the list.

DR. CANTILENA: How about if we do this? As we're going around with the questions, if someone has the actual slides that show the data for warfarin, ketoconazole, phenytoin, for example, that would be helpful for us to actually see that. If you don't have it handy, then we can start with that after lunch.

Dr. Goldstein.

DR. GOLDSTEIN: I don't have a question per se but I have a passing observation that I would like to make. The presentation on communication contained in it both a touch of irony and a touch of perhaps unfairness in the sense that the irony being the sponsor making a good faith effort to include various diseases for this heartburn medication on the label.

The unfairness perhaps is that it is the only one of this group, or any heartburn group. Neither the antacids nor the H_2-RA antagonists have been required to include the series of diseases to the best of my knowledge. I think that needs to be taken into consideration by the panel.

DR. CANTILENA: Okay. Dr. Geller and Dr. Cryer.

DR. GELLER: I have two questions about labeling. The first is in all the references to your doctor here. The verbs are "ask, discuss, and notify" and "see" is not used. I would think "see" is much stronger. I guess my question to the FDA is do you have a distinction about how strong the recommendation to contact the physician should be.

My second question --

DR. CANTILENA: How about if we hold on there and then we'll ask the second one after we hear that.

DR. ALFANO: Well, this in a sense highlights the clinical problem of management of patients with chronic heartburn generally and what the purpose of the labeling is. It really ends up being a rhetorical question for discussion.

Part of the context of that question really has to do with what is the optimal management for GERD and chronic heartburn. As perhaps will be raised later, there is in this algorithm many physicians do empirically treat individuals with a history prior to undertaking if they don't have alert symptoms and so on for a period of time prior to undertaking diagnostic studies.

I think that question should be to some

extent asked to the sponsor what their intention is with regard to that wording. Is it to simulate management of patients who otherwise might have seen a physician? Or is the intention as a primer to get into the healthcare system?

DR. CANTILENA: Would the sponsor want to comment on this?

DR. PEURA: I think the purpose of the labeling is really to try to provide as clear a direction as possible to the consumer who might be using this product. In that regard, we do have testing that shows that the word "notify" is actually a more action provoking verb than the word "see." When you show those words to consumers, "notify" gets them to do more.

Since our intent here is to be sure that people who use this product understand that it is important to keep their doctor in the loop for this condition, that would be our choice of wording probably.

DR. GELLER: My other question concerns the process of deciding on what a label should say in an OTC setting. It seems to me that there should be an iterative process if you don't get it right the first time.

When you change the label, it seems to me you should satisfy -- attempt to satisfy all the conditions or questions that have been raised and then go and test it again. It might take more than two attempts. The label change, as I understand it, hasn't been tested again. Is my assessment of the process correct and my assessment of what's happened here correct?

DR. SHETTY: Usually it's not tested if we approve the drug. Now we know the label comprehension and actual use study and the proposal for marketing labels are already close. They are very similar so we know that these people will use the drug that's used in actual use study.

If the decision will be to approve this drug for over-the-counter marketing, unless the committee feels that we need to do another study or do like Phase IV commitment to test the new level before approval, we can request the sponsor to do that study.

DR. GELLER: So you're saying it's not usually an iterative procedure?

DR. SHETTY: No.

DR. GELLER: Okay. Thank you.

DR. LECHTER: Very frequently the sponsor will do a series of tests and change the label and

retest. They don't always do that. In this case the last label used in the label comprehension study was, as Dr. Shetty mentioned, tested to some extent. '

Well, actually it wasn't the last label used. It was kind of a cross between the last label used and the label comprehension study and the new proposed label was used in the actual use study.

Ideally if there are concerns after the actual use study, perhaps the label should be looked at again, changed, and retested but that is an ideal situation. It isn't often done.

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

DR. CRYER: So the data that Dr. Avigan reviewed for us were data that were directed towards the initially proposed indication for OTC omeprazole. I'm trying to place that data in the context of newly requested proposed indication which has changed since the previous review.

The question is how do your conclusions change in light of the revised proposed labeled indication?

DR. ALFANO: I don't think that -- I mean, you can discuss these slight nuisances in the proposed changing of wording, the for-24-hours insertion. I

think that there are different ways of understanding what for 24 hours means and that becomes a point of language.

I think that the prevention concept in the study is applicable. Basically the difference between the first and the second meeting is that we have excised out the first two indications and we have come back with a focus on the third. I think that, in my view, it follows.

DR. UDEN: I would like to get back and follow up just a little bit on what Dr. Geller started here. I'm going to follow up on my question that I asked the sponsor earlier on. I was not completely satisfied by the answer that I received in terms of endpoints.

I don't know if this is the time to talk about it, and maybe we should talk more about it later, but I think the FDA or the sponsors need to set out some definable endpoints in terms of what is understandable.

When the FDA started their presentation, it started that labeling is likely to be read and understood. What does understood mean? Does it mean understood by 80 percent of the people, 90 percent of the people, 40 or 50 percent of the illiterate people

and 90 percent of other people?

I think if sponsors went in with predefined, "This is what we want. We want 80 percent of the people to understand the label of all people," then we would be able to get back and design a label and only 50 percent don't understand it. You design another label and you change the wording. We're talking about these are minor words and these are not minor words.

I would argue that notify your physician is not understandable to somebody who has low literacy. Notify is not a great word for that group of people. Probably not. I think we may need to talk a little bit more about that later on.

One other comments here. When sponsor put up -- I don't see it in the label but when sponsor put up the supplemental educational materials they had three circles up there and comparing omeprazole with antacids and H_2-receptor antagonists and basically a marketing piece which antacids work for an hour or two and H_2-receptors will work for 12 hours. This drug will work for 24. Nowhere do I see in the label any statement that you will not see this medication work for one to two days.

There is nothing in there to tell people

that if you take this for a day and you are expecting a response in six hours or 12 hours you're not going to see a response. I would like at some point in time us to discuss about the addition of what they should expect from this drug.

DR. CANTILENA: Thank you. I'm sure that will come up this afternoon in our discussions.

Dr. Alfano, do you have a question for the committee -- I mean, for the FDA? Not the committee.

DR. ALFANO: Yes. It's a question for Dr. Shetty. At one point, Dr. Shetty, you criticized the actual use study because the sponsor didn't contact physicians to confirm that, in fact, they had been contacted by the participants. I guess my question is if it's an all-comer study, how would you do that and not infringe on the doctor-patient confidentiality and violate HIPA and things like that.

DR. SHETTY: We've seen studies in the past when they wanted to check whether people really went to the physician. They asked who is their primary physician and asked permission to contact their physician to ask whether really that patient saw that physician and whether the physician approved of what was the decision made. Here there was no -- they didn't have to go to see their particular physician

those subjects.

They could have asked anybody who is a healthcare professional, a friend or a relative, "I'm taking this medicine for my heartburn. Is it okay?" They would say okay and that was considered that they consulted a healthcare provider.

DR. ALFANO: So then you're suggesting that releases would be sent to whomever?

DR. SHETTY: I don't know the particular --

DR. ALFANO: -- contacted on an all-comers basis? I guess my point is it seems to be an unrealistic requirement.

DR. SHETTY: Maybe it's unrealistic but that would be perfect or realistic to know whether really physician approved that medication for that patient to use. It could be done at the end of the study after the study is completed and contact made to the physician.

DR. CANTILENA: Some sponsors have actually handled that in a different way on other applications.

Any other questions? Dr. Davidoff.

DR. DAVIDOFF: Yes. I have a question primarily for Dr. Lechter. It has to do with the

wording of the label. It says, "Do not use with other acid reducers." I wondered if that statement is clear to you? Whether the meaning of that statement is clear to you? It's not clear to me because I think the intent is directed at H_2-receptor antagonists.

On the other hand, we've heard that the data either are missing on whether there is a reaction or that, in fact, H_2-RA errors are, in fact, make a difference because they diminish the efficacy of this drug.

We've also heard that people apparently took both H_2-RA antagonists and antacids during the course of the trial, although that -- well, I don't know about during the course of the trial because that wasn't asked for but that has apparently been true in some of the other data that was presented.

It seems like this is an ambiguous statement not just to me but perhaps to others. Do you have any notion of how clear that meaning is?

DR. LECHTER: That particular issue is not tested in the materials that I have received. However, I might note that I believe, and the OTC Division can correct me if I'm wrong, that all the over-the-counter products that are acid reducers will say acid reducer on the drug facts label.

If they are not an acid reducer, they might be called something different. Is that correct? So that if consumers look at the drug facts label for the other products they are taking it will say acid reducer if that is what it is. I agree in general the term is probably not clear to the lay people.

DR. DAVIDOFF: That is helpful because if it does say that on the HRA package, that is fine. If you just ask 100 people what they understand what is an acid reducer, I don't think that would be a highly germane point because not everybody reads the package of the H_2-RA.

DR. CANTILENA: Okay. Thank you. One more question, Dr. Camilleri.

DR. CAMILLERI: I would like to ask Dr. Shetty her advice with regard to the correct self-selection. I see from the table you have provided us that 134 of these 1,251 patients had contraindicated symptoms.

In the context of risk management, I would have thought that a much larger study would be helpful to understand whether people with contraindicated symptoms would deselect the option of using omeprazole.

I guess from a design perspective or from

the numbers that we have, is this a sufficient number to reassure us that deselection is going to occur appropriately?

DR. SHETTY: Well, I don't know. We don't have any endpoints for what is acceptable or not acceptable failure on those subjectives. We know that some people deselected in this study also those who had contraindicated conditions and didn't buy the product or refused to participate for that reason.

This was around 10 percent of that population that had those contraindicated conditions. We can discuss about that more whether it is acceptable or not. Certain conditions are more serious than the others if they are not reported to the physician.

DR. CANTILENA: Okay. Dr. Zorich, did you want to make a comment? Either that or you have to leave the room.

DR. ZORICH: Well, maybe. Considering how confusing this is becoming, maybe leaving the room is good.

The reason you saw me kind of jump up is that this is an area that is confusing to me just how the sponsor should handle appropriately. These contraindicated symptoms have really nothing to do

with omeprazole. They have to do with people misconstruing heartburn for something else.

Whether it's frequent heartburn or episodic heartburn, it's really -- I don't think that it's germane because if we are talking about people having anginal like symptoms, then the fact that is happening to them at that point when they are making a purchase decision at a Walgreens, it has nothing to do with the purchase decision of omeprazole or an acid reducer or an antacid.

We were trying -- now I see sometimes that no good deed goes unpunished. We were trying in a very responsible way to communicate to people that anytime you have heartburn, there should be this other constilation of symptoms that you are considering in making a purchase decision.

I would like to clarify that I do not believe that they are uniquely related to a purchase decision about omeprazole. They are instead the AGC warning signs which could be -- somebody could be experiencing whether or not they are having a frequent or infrequent heartburn.

DR. CANTILENA: Right. I understand your point but if it happens on your study, then you have it.

Why don't we -- actually, I would just like to go over sort of the homework assignment. I would propose that right after lunch just before the charge to the committee by Dr. Katz if we can get a copy of the ICD.

Then we would want to see the actual pharmacokinetic interaction data for warfarin, ketoconazole, and then the drug-food interaction data because that was a question that came up earlier this morning. These can just be slides with the curves to show us the effects. Does anyone else on the committee want to see any other pharmacokinetic data?

Dr. Brass, did I leave anything out?

DR. BRASS: No. I think you covered it but I'm sure when we see it there will be questions about its limitations.

DR. CANTILENA: Very good. Let's pause and we will actually start on time this afternoon at 1:30. The committee is reminded during lunch not to discuss issues that are before the committee. Talk about the soccer game and see if you can catch a replay.

(Whereupon, at 12:26 p.m. off the record for lunch to reconvene at 1:30 p.m.)

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

(1:35 p.m.)

DR. CANTILENA: I will start the afternoon with some follow-up items that we listed just before the break. I'll turn it over to Dr. Triebwasser from Procter and Gamble. Can I have your attention, please? Thank you.

DR. TRIEBWASSER: We're going to present now the data, looking at the drug-drug interaction, the specific data on warfarin.

We're not on? Do I have it turned on? I have it turned on. Let's try it again. There we go. All right.

We're going to p resent now some data on the drug-drug interaction questions regarding warfarin and also the food interaction studies which were asked for earlier. Dr. Levine from AstraZeneca will present this data.

DR. LEVINE: Thank you. Can I have slide 58, please? We'll start with the data requested regarding drug-drug interaction studies involving omeprazole and warfarin. This is from my slide set, please. Thank you.

These are data that were shown at the October 2,000 advisory committee meeting. I would

like to refresh people's memory. Warfarin is a racemate that includes two optical isomers, the R and S form. It turns out that the anticoagulant effect delivered by the racemate is primarily through the S-isomer which does not share CYP-2C19 as the primary metabolic pathway with omeprazole.

The R-isomer, which is metabolized through 2C19 does not contribute nearly as much of the anticoagulant effect. These are group data, two studies, the first in healthy subjects. One can see if one looks at the S-isomer, which is clinically more important with regard to delivery of the anticoagulant effect, there is no change in serum concentration with a 20-milligram dose of omeprazole after 14 days. There is a very small clinically insignificant effect, mean effect, of about 12 percent.

I'm not going to use the pointer. Thank you.

The bottom study was performed in anticoagulated patients. I'll show you additional data and a couple of additional slides. Similar effects were seen. Again, no changes in the S-isomer concentration with omeprazole, in this case 20 milligrams over a 21-day period, whereas with the R-isomer there was almost a 10 percent change.

We have data looking at the pharmacokinetic effect which is of greater clinical importance. What I want to show you on the next slide, which is slide 59, I need to walk you through this.

This is a rather old study in which a coagulation test known as a thrombo test was used. This was a study conducted in Sweden and this is not a test that we have presentationality with so we don't have data using prothrombin times or INRs. The TT values were a clinically relevant means of following anticoagulation in patients treated with warfarin.

What you have on the X axis are the initial run-in values with patients who are treated with warfarin but they are not yet on omeprazole. Just to give you a guide, the therapeutic range that is aimed for using this test is with a value of between five and about 18. If you look carefully all the way to the right, there is one outlier with regard to, you know, just during the run-in whether or not they were within therapeutic range.

Now, what we had the opportunity to do in this study was have a couple of run-in values. What we have done on the Y axis is run-in value at week one and run-in value week 2 and looked at the difference

just to give you the measurement variability in coagulation function just on warfarin. You can see that there is a very wide range. This has to do with the variability and warfarin effects and measurements of anticoagulation.

Now, keep this in mind. You can see that there's a range of plus or minus at least five to six points using the TT value but outliers that are even greater than that.

Now, in the next slide what I'm going to show you is the actual study slide. We had data on 28 patients. This was a randomized placebo controlled crossover study which in one period patients were randomly allocated to receive placebo or then were allocated to receive omeprazole obviously being maintained on what was thought to be their stable warfarin dose based on the run-in values.

Here what we have again like in the previous slide on the X axis below this is showing what the last run-in value was using the TT test. On the Y axis what we have here is the difference.

These are individual patients, the differences in the TT value on omeprazole with warfarin or on placebo with warfarin. Again, you can see that the nature of the variation is actually

within measurement variability of the TT test if you recall the previous slide.

The other point that I would simply make and, again, I apologize if this is confusing. The lower the TT value the higher the -- the greater length of time it would take for coagulation to occur so there is a bit of an inverse value.

My point is if you were looking down closer to the four to eight range, if omeprazole was having significant interaction, you would be seeing the differences trail up into the left and you do not see this.

Our interpretation of these individual data are that, in fact, when you look at omeprazole effects on warfarin, the changes in the pharmacodynamic effect of the drug is actually just within measurement variability as when you are looking at warfarin alone.

Would you like me to proceed through the other drugs or take questions?

DR. CANTILENA: How about if you go through the rest of the data and then we'll do it all at once.

DR. TRIEBWASSER: Okay. Next slide 55. This is looking at phenytoin. Again, I don't want to

take too much time. This is a slide also shown at the October 2000 Advisory Committee Meeting. Here we have three studies with healthy subjects and a fourth study in individuals with epilepsy that required phenytoin treatment.

What we showed with coadministration of omeprazole in the healthy subject's doses of 40 milligrams either at seven days or three days, or in the epileptic patients 20 milligrams of omeprazole for 21 days, we did not see any clinical significant changes in phenytoin levels.

Now, on the final study in epileptic patients there were eight patients. We have individual point values that we can show you on slide 57. I apologize because this is more raw data and a little bit difficult to see but the patients are one through eight down below.

If you read across on the top, baseline phenytoin levels were obtained at week zero, week one, and week two before omeprazole treatment was introduced. Omeprazole was then added during weeks three, four, and five, and then stopped. Then we have washout values off of omeprazole at week six or seven.

These are all phenytoin levels. The therapeutic range for phenytoin was approximately 40

to 80. What one can look at is really no significant movement of individual values on omeprazole that are clinically significant. I'll leave that up if you would like to look at it carefully or we can make it available later in a hardcopy.

Slides off just for a moment. Ketoconazole, I apologize, we do not have data. The data that were looked at with regard to the interaction between ketoconazole and omeprazole were actually not sponsor related studies.

In the prescription label we indicate -- this is essentially a concession that because of the known effects of acid, the requirement for acid for absorption of certain drugs, the prescriber is to take that into advisement.

Now, we are aware of published data where omeprazole was given to individuals with ketoconazole as part of the drug interaction study. The OUC levels of ketoconazole actually declined by about 80 percent.

We think that it is very important from a medical standpoint to know that if one is treated with acid suppression, the therapeutic value of the antibiotic, in this case, is not going to be very high. I'll defer to others to speak about the labeling contingencies for the OTC product. We

recognize that omeprazole will significantly decrease the absorption of antifungal agents like ketoconazole.

Finally, you asked about food effects. If I could have slide 68, please. There are three curves here. This is a standard plasma concentration time curve for the use of omeprazole tablet at 20 milligrams in the dark squares and the omeprazole tablet 20 milligrams after food.

What is not relevant here is the third curve which is the omeprazole capsule. If one wants to understand the food effect on the tablet, if one looks at the very first curve on the left compared to the second curve, which is the fasted versus fed administration of 20 milligrams of omeprazole magnesium, one can see that the c-max declines at the time the c-max extends. But the area under the curve stays the same. I can show you on a table, new slide 247.

Again, if we are looking at the mean values for AUC, c-max and t-max for either the MUPS, omeprazole magnesium tablet administered in the fed state versus the fasting state. On the right column there is the ratio. What we show is that if you compare areas under the curve there is unity.

There is a difference for c-max so based

on the way bioequivalence is interpreted, this may not be judged by equivalence. Our position is that AUC is a very good surrogate predictor of acid suppression and the fact that one sees no difference in the area under the curve. There is an element of equivalence here.

DR. CANTILENA: I just have one quick question if you can just go back one slide, SBU-68. The way in which the area under the curve remains the same is the slowing in the absorptive?

DR. TRIEBWASSER: That's correct. One would reasonably predict that in the fed state digital and gastric emptying by essentially the bioavailability based on AUC. There are different criteria that you are well aware of. Based on AUC they are the same.

DR. CANTILENA: All right. And so the title of your slide really is just referring to AUC then?

DR. TRIEBWASSER: Yes, but we also have other data that shows that the AUC is a good predictor of acid suppression.

DR. CANTILENA: Right. But there is an effect on c-max as well as t-max.

Now, just from a scientific standpoint,

can you tell us what you think is most important in terms of the ultimate pharmacodynamic effect? Is it c-max or is it area under the curve?

DR. TRIEBWASSER: We think that the most relevant factor is the AUC based on the relationship to acid suppression.

DR. CANTILENA: Okay. Other questions?

MS. COHEN: Yes.

DR. CANTILENA: Go ahead.

MS. COHEN: I see that you have to take it in the morning. Now, what happens to people who don't take breakfast or people who just have coffee or people who do have to eat after it, before it?

The other question I have along with it, can you take it with, say, orange juice or grapefruit juice or should it be taken with water? I am concerned about consumers, whether they take it without having breakfast or they take it after breakfast or how they should take it because this only says in the morning and that doesn't mean anything.

DR. TRIEBWASSER: Not all the studies have been done to specifically address each of the contingencies that you addressed. Based on the bulk information we don't think that there is really a lot of difference whether or not the drug is taken with

food or other beverages that you mentioned.

MS. COHEN: Suppose someone doesn't eat any breakfast at all and take it?

DR. TRIEBWASSER: We think the drug would still be effective.

MS. COHEN: What would it react with?

DR. TRIEBWASSER: I don't understand.

MS. COHEN: Isn't there something that --

DR. CANTILENA: I think on the slide the answer to your question would be that you would be looking at the fasting curve.

MS. COHEN: Fasting curve.

DR. CANTILENA: So he has that information. It's a higher c-max but the area under the curve doesn't change.

MS. COHEN: Thank you.

DR. CANTILENA: Dr. Brass.

DR. BRASS: Yeah. I would like to return to the focus of relating this information to the question posed by the reviewer as to the adequacy of the warning label and which of these drug interactions, in fact, need to be communicated effectively to avoid a public health problem.

First, I would like to thank the sponsor for providing the individual subject data to allow us

to understand the outliers as well as the mean response which is quite helpful. It is clear in that relatively small population that with warfarin there wasn't any evidence of a clinically meaningful effect. The question is how does that small sample effect extrapolate to a large population and whether or not there are at risk populations that are identifiable.

At the same time coming back to the point that was raised, I'm a little bit concerned about over extrapolating spontaneous reports because we all know that in any cohort followed on warfarin there will be individuals who will go out of whack for no clear reason at various times.

If they happen to be on omeprazole and happen to be reported, there may be a link. What I'm trying to gauge in terms of whether or not -- I do believe any patient on warfarin should talk to their doctor before they take any medication.

In terms of the standard of effectiveness of the warfarin warning, is the review team comfortable that based on this data that this is not a large population concern or do they remain concerned that there are specific subpopulations or stronger data to suspect this is a risk.

DR. CANTILENA: Charlie, does someone from

your team want to handle it?

DR. GANLEY: Yes. I guess the point that I would make is that we've seen a pattern, a cluster of such reports in the class, as I mentioned. In some cases some of the reports actually indicated a salutatory response to dechallenge so that basically in some cases not only is there a theoretical interaction based on the CYP-2C19 metabolism but in some cases empirically there was improvement after cessation of the proton pump inhibitor.

DR. BRASS: I mean, were there any rechallenge in any of those in terms of doing formal study?

DR. GANLEY: That I would have to go back and look at that. There was enough concern to decide to change the labeling in the prescription formulation. By the way, again, I think the other point is that we wouldn't necessarily in a small test population see it but for a variety of confounding reasons you have outliers in a large population of users.

DR. BRASS: No, I understand completely. What about phenytoin? Do you still believe that phenytoin requires a warning in the general population?