reference to 092, 095. Based on the primary measure of efficacy, is there clinically significant improvement of acute symptomatic heartburn in either the ten or 20 milligram omeprazole groups compared to placebo? The options are yes, no, and abstain.

All who feel the answer is yes to that question, please raise your hand.

(No response.)

CHAIRMAN BRASS: All those who feel the answer is no to that questions, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All abstentions, please raise your hand.

(Show of hands.)

DR. TITUS: Okay. We have zero for yes, 12 noes and one abstention.

CHAIRMAN BRASS: Can we see the --

DR. STEINBERG: But I would like to add that that's not the only question that should have been asked for these studies.

CHAIRMAN BRASS: I understand, and hopefully the discussion will have brought out the information on those other points that are not ignored, and I agree they are important.

Do you want to count again.

DR. TITUS: I think the count must be, unless someone on the committee wants to correct me, one abstention and 13 noes. Anybody want to correct me? Okay. I have to get a count of 14.

CHAIRMAN BRASS: Okay. Second question: in studies 005 and 006 the primary endpoint for efficacy was the percentage of subjects heartburn free over the entire four-hour period after a provocative meal. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the ten or 20 milligram omeprazole groups compared to placebo?

Then we will also specifically discuss are the analyses of the prespecified secondary endpoints supportive of the primary study outcome. Do they add information regarding clinically significant treatment effects?

Yes, Doctor.

DR. UDEN: The product now that we're going to be approving is a ten milligram product. I am confused why we would be voting on the 20 milligram dose.

CHAIRMAN BRASS: I think that to the degree it helps both the sponsor and the agency in

future decision making, I think it would be useful information unless the agency would like to withdraw that question.

DR. DeLAP: No, I think we're interested in it. The question as it's phrase, I think, refers to both doses, and you can tell us what you think.

DR. UDEN: So are we going to be splitting our votes up?

CHAIRMAN BRASS: If the discussion so dictates, I am more than happy to split votes.

Dr. Geller?

DR. GELLER: The second study seems to show a significant difference and the first did not, and I'm kind of curious about the difference between the patients in the first and second study, say, with respect to the frequency of heartburn during the run-in period.

CHAIRMAN BRASS: Could you be more specific between first and second? Do you mean --

DR. GELLER: I presume 05 preceded 06.

DR. ZORICH: They were run concurrently, and just for the matter of convenience designated with two different numbers, and we have asked ourselves that question, of course, and cannot account for why there's a difference in the placebo.

The difference in those two studies is not the treatment effect. It's the placebo groups, and we have not been able to account for why there's a difference in placebo response.

CHAIRMAN BRASS: Other observations about these two studies?

DR. GELLER: Could I get an answer to the question about the number of days of heartburn?

DR. ZORICH: Yes, that's what I was trying to answer. We have specifically looked for parameters, and that being one of them. We've looked at every parameter we had available to us to try to account for was there some disbalance, unbalance, and had not found any.

CHAIRMAN BRASS: Yes, Dr. Elashoff.

DR. ELASHOFF: Well, I would argue that whether significant or not, the actual observed differences are five percent and four percent in one study and nine percent and eight percent in the other study, and if we assume that the truth is somewhere in between, we're talking about maybe a six percent or seven percent difference, which I don't think I would regard as clinically significant even were they both statistically significant, which they are not.

DR. STEINBERG: Unless you were one of

those seven percent that got relief.

(Laughter.)

CHAIRMAN BRASS: Dr. Sachs.

DR. SACHS: Again, the issue is this is day one initial treatment, and it's very clear from any comparative study against any other form of heartburn or GERD treatment that the incidence improves day two, day three.

In terms of patients who can't go see doctors, the 20 milligrams if that becomes available OTC will be the only effective medication for those people in terms of treating any form of GERD relative to H2 RAs. And it's not the first day. It's also the continuation of treatment that really makes the difference.

So the six or nine percent that Elashoff sees the first day translates to 20 or 30 percent by third day.

CHAIRMAN BRASS: Let me try once more to try to justify why these differentiations are being made explicit in the context of the questions and in the context of understanding the studies.

Ultimately if this product is to be approved for over-the-counter use, it will have to have a label indication that will tell a consumer

realistically when they can take it and what they should expect to have happen and how likely it is to have happen almost in fact.

And to the degree that a comparison to the other labeled products for the same type of relief of heartburn have taught consumers an expectation that when they have heartburn they can take the medication and get relief, if that is not the case for this medication, then we have to both understand that and deal with that in terms of ultimately what the instructions to the consumer might look like.

Dr. Cohen.

DR. COHEN: The provocative meal is equivalent to a stress test, and the stress test here is to provoke heartburn in a high percentage of patients, which it's done.

The very low placebo response would indicate that it was a very, very aggressive stimulus and that the drug at this dose was not adequate to overcome that, but as Dr. Sachs said, perhaps if the patient was treated longer, it probably would have prevented it.

But what we were given here with this very low placebo response or very provocative meal, it didn't have a clinically effective response.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: I guess I am having a little trouble following some of the arguments from the other side of the table because, as I understand it, this isn't something that is going to be recommended to be taken day after day after day. So I accept that maybe on third day they would have good benefit, but that's not how we're asking these people to use this drug. So I'm not quite sure what the relevance to continuous use is in the over-the-counter setting because we don't want them to use it continuously, unless I've missed something and it is supposed to be used continuously.

DR. COHEN: That was just an editorial comment. It was a negative study.

CHAIRMAN BRASS: Dr. Robinson.

DR. ROBINSON: Obviously we're sort of doing this in a peculiar order because it seems to me that the bottom line, of course, is what kind of label if this product were to be approved will it have, and it's quite likely, it seems to me, knowing what we do about the pharmacology of omeprazole, that any label that made any sense for this product is not going to be for single, one time use.

So if we are looking at the question of

should it be approved for single, one time use, the answer does appear to be no.

CHAIRMAN BRASS: Yes, Dr. Geller.

DR. GELLER: Once again, I need to remind the people on the other side of the table that the trial --

(Laughter.)

DR. GELLER: -- the trial was designed as a single dose, meal induced heartburn trial. We didn't tell them what to feed them. We didn't tell them what does to use. These are decisions they made.

And, of course, if they had had a winner, if this had been overwhelmingly successful in both trials, then we would not be having this discussion, of course.

But we only can evaluate what we're presented with, and I think the rest is extrapolation beyond the data.

CHAIRMAN BRASS: With that I'm going to call that part of Question B. So specifically for study 005 and 006, is there clinically significant improvement of heartburn symptoms in either the ten or 20 milligram omeprazole groups compared to placebo?

All who feel the answer to that question is yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All who feel the answer is no, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(No response.)

DR. TITUS: Thirteen noes, one yes, zero abstentions.

CHAIRMAN BRASS: We would like to now have some discussion on the secondary endpoints that were used in 005 and 006. Are the analyses of the prespecified secondary endpoints supportive of the primary study outcome? Do they add information?

And, again, here we would like to get insight into what can be learned from those assessments that were made that might be useful in the context of the therapeutic use of this in the OTC setting.

Dr. Johnson.

DR. JOHNSON: I have a question that I've been sort of waiting, and it looks like this might be a good time to ask the company, and that is the decision to go from 20 to ten, and I understand there's this sort of historical perspective, but,

again, if you look down the list, if I'm looking at the right Table 5.9, clear down the list there's efficacy at 20, and there's clear down the list, except for one or two exceptions, not efficacy at ten.

So I'm curious if you can tell us a little bit about that decision apparently fairly late in the game.

DR. ZORICH: Okay. Thank you.

It is a unique opportunity to come in after many precedents have been set. For instance, I think the last vote just set a very interesting precedent because when you look, in fact, at the meal induced study for H2 RAs, and Dr. D'Agostino who has lived through those can help me remember, because my recollection is that, in fact, for the H2 RA meal induced trials these differences have never been overwhelmingly clinically kind of knock your socks off.

So I think what we are working with is really looking at the over-the-counter appropriateness for drugs for heartburn within the context of everything that has come before, and in that context, it seems to me that if you look at the considerations that were given to the H2 RAs, you'll see very similar kinds of discussions about efficacy vis-a-vis dose,

and sometimes there were dose effects; sometimes there were not.

And at the end of the day it all came down to what is the most appropriate, lowest effective dose that you would put into an OTC environment, and so we felt, as you said, that if you just look at the numbers in the absolute, 20 often is numerically superior, but then when you start really to ask a more comprehensive question, as but does that mean that ten wouldn't be an appropriate dose, we found ourselves unable to give an affirmative answer.

And so in keeping that many of these same questions had been asked and wrestled with I'd say sincerely and still remembered five years later, that in that context ten was an appropriate dose for serious consideration, and we thought it had to be, and in consultation with the agency, we thought we really had to talk about both.

And so I think that's what we're doing today.

CHAIRMAN BRASS: I would just like to comment about the dose issue because I think it's one that has a lot of impact in how we think about these issues.

From our perspective, the rationale for

picking the minimally effective dose for an OTC preparation is in the context of dose related toxicity, and to balance the risk to benefit into the OTC setting, and that if presented with a product that had little or no dose related toxicity, in fact, the interest would be in maximizing efficacy, not minimizing efficacy, and so that the concept that we always need to have the lowest dose that bumps at all may be doing everybody a disservice, including you by making it more difficult to demonstrate statistically significant effects.

So I think that is a blanket concept, is not one I am comfortable saying is a biblical law, and I don't know if I've just committed a sin.

(Laughter.)

DR. DeLAP: No, we are very interested that consumers get benefits from products, and I think you don't want to focus on a low dose unless there's really a good reason for doing that. I mean, there's no reason for someone to get 20 if ten does the job, but on the other hand, if 20 looks better and there's not some real big safety issue that makes it clear that that's not a good idea, then I think we have to look seriously at the 20.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: I don't recall the exact numbers of the previous products and so forth, but one of the things that we did and did quite consistently is before we talked about clinical significance, we had to assure ourselves that there was statistical significance, and also you've separated nicely the primary from the secondary. There was lots of multiple testing, and so I think the answer to the first question, the first part of this question has a lot to do with the fact that differences are small clinically, but they're also carrying with them some statistical insignificance, and from that point of view we'd have to say that the difference could possibly be zero.

So I think that we are being consistent, and I do think that there were larger differences, but, again, they were statistically significant. Then the question became how big must the difference be.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: I agree with Dr. Brass' comments about dose, and I'm just wondering. I really haven't heard anything about dose related toxicities. I mean this is really a very unique compound in terms of its kinetic dynamic relationship. Can you tell us more about --

CHAIRMAN BRASS: Can we save that for the safety questions?

DR. JOHNSON: Oh, sure.

CHAIRMAN BRASS: Thank you.

Dr. George Sachs.

DR. GEORGE SACHS: Yeah, I absolutely agree with what Dr. Brass said. This type of drug when it came on to market, the issue was 20 versus 40. At that time there were safety issues. Every subsequent drug has been introduced -- annexium (phonetic) that just had its approvable letter is either 30 or 40 milligrams. Ten milligrams in study after study when it was being put on the market, you know, not as a prescription drug showed very, very little, if any, benefit over OTC Zantec. I think it would be a mistake for the consumer to be offered ten milligrams when 20 milligrams is clearly to me the minimal effective dose for treatment of GERD.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I would support George Sachs and that comment because I think that --

DR. GEORGE SACHS: No, no, no, please.

(Laughter.)

DR. WALDUM: A large proportion of patients do not get any effect at all on ten

milligrams. I think the company should come up with that because I think more than 50 percent do not have any inhibition of gastric acid secretion at all because you have such a steep concentration response curve for omeprazole. It's a drawback because you have this virtually none or complete inhibition of gastric acid secretion, but ten milligram, many patients without an effect at all.

CHAIRMAN BRASS: And again, you want to remember this is in the context of looking at those secondary endpoints in these trials which had suggested that relationship which Dr. Johnson pointed out.

Yes.

DR. ROBINSON: Just to remind people here, actually our data which came to the agency for omeprazole at the time that omeprazole got its original approval showed that ten and 20 milligrams were, in fact, different, and the problem was that although ten milligrams did work, it didn't work in as large a number of people. That is, each time you elevate the dose, you decrease the number of people that failed to respond, and we showed, and that was one of the reasons that 20 milligrams was chosen, that 20 milligrams was clearly pharmacologically superior

to ten milligrams. So I would agree that if I were the company I'd pick the 20 milligram dose as well.

CHAIRMAN BRASS: Other discussion of the secondary endpoints that were used.

Dr. Geller.

DR. GELLER: I would fee much better able to assess the differences shown on page 52 of the white book if I had actual P values, not just that the P values were less than .05.

CHAIRMAN BRASS: Do we have those available?

PARTICIPANT: We have a subset of it.

CHAIRMAN BRASS: Well, I guess any actual P values would be helpful. Is that fair?

DR. ZORICH: Then I would say study 006 then would -- an overall assessment even at the .025.

CHAIRMAN BRASS: I'm sorry. Table 5.9 on page 52 has a number of endpoints which are not on it.

DR. ZORICH: Right, and the only ones I have here are the last two in that list of five.

CHAIRMAN BRASS: Okay.

DR. ZORICH: Overall and back-up, and study 006, even with the consideration as you said of a more stringent P value, both doses, and 005 only 20 milligrams.

This is overall assessment. This is a secondary variable. You asked about it. It's the fifth. ON page 52, it's the bottom.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: I agree 100 percent with the notion of the P value and the size, but there is a consistency, and I think it should get into the transcript that there is a consistency across the secondary endpoints, which is quite pleasant to see and so forth, and I don't think that it -- it doesn't support -- I think the way the question is worded it's kind of hard to answer. We said we don't buy the primary and now we're supporting something that we don't buy, but I do think the secondary showed that something is going on with the drug, and maybe it's a bad design. Maybe the requirements of having the relief within an hour and sustained for two hours, all of those things are working against the drug and the study, but I do think that we can't ignore the consistency of these secondary endpoints.

CHAIRMAN BRASS: And just for the record, that is a consistency towards drug benefit.

DR. D'AGOSTINO: Towards drug benefit, yes.

CHAIRMAN BRASS: Other comments about the

secondary endpoints? Yes, Dr. Johnson.

DR. JOHNSON: Well, my only comment would be that the consistency of benefit is only at 20 milligrams.

DR. GELLER: There's no question about that.

CHAIRMAN BRASS: Okay. I don't think we need to take a vote. I think the discussion on that point addressed the issues.

We now move to studies 171 and 182. The primary endpoint revocacy was the complete prevention of heartburn between the first two doses of therapy. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the ten or 20 milligram omeprazole groups compared to placebo?

(Pause in proceedings.)

CHAIRMAN BRASS: Thank you, Dr. D'Agostino.

DR. D'AGOSTINO: Nobody wants to say it.

The primary endpoint is quite significant, and I think clinically significant.

CHAIRMAN BRASS: Would somebody like to -- since this is looking at the first episode, would we infer something about the pharmacology or biology

here, why this one was positive compared to the previous negative results? Is this expected, unexpected, logical, illogical?

Dr. Neill.

DR. NEILL: My understanding is that this is daily dose not in response to meal; take it first thing in the morning. You've had it on board for several hours, and certainly if the assessment is 24 hours in, then that's for reasons that have already been explained -- do I have that wrong?

DR. ZORICH: The assessment is whenever heartburn occurred, covering a full 24-hour period with a specific assessment of nocturnal. So any heartburn that is occurring is collected in real time, and then of course, within 24 hours there is a final assessment, and there was also an assessment of the nighttime experience.

So there actually is ongoing assessments throughout the full period. So, for instance, there was time to heartburn, and it was on a continuum, not just a static assessment at the end of 24 hours.

DR. NEILL: So thanks for clarifying that.

So my presumption, and maybe you could confirm this -- I think you did earlier -- is that the majority of the benefit that's seen within that first

24 hours, given the studies that we've already seen, does not come from the first four hours.

DR. GEORGE SACHS: Sorry. Can I ask for clarification as well?

DR. ZORICH: I would like to suggest that the only thing that we can say with clarity, and I think, Dr. D'Agostino, I would ask you to see whether or not you see this fits any kind of test of reasonableness. Since we agree that at 20 milligrams there was something in that previous one hour before the provocative meal study and ten -- I think we had debate, but at least in one study there was significance at one hour before a meal. Then I would say that if the drug was taken prior to an hour, I think that that's about the most I think we can limit.

So I don't think we could say three hours, four hours. It seems to me that one hour is just about where you're on the edge.

DR. D'AGOSTINO: I'm going to throw that over to the other side of the table and let them answer it.

CHAIRMAN BRASS: Dr. Cohen?

DR. GEORGE SACHS: Can I get clarification? With the previous studies, the patient had heartburn and swallowed omeprazole.

DR. ZORICH: Not with the ones we just talked about.

DR. GEORGE SACHS: No, no. I'm just talking about the previous ones.

DR. ZORICH: Oh, nine, two and 095.

DR. GEORGE SACHS: Yes.

DR. ZORICH: Yes.

DR. GEORGE SACHS: Now, here I assume the patient wakes up, takes his capsule, then has breakfast, and then records his heartburn for the next 24 hours.

DR. ZORICH: They were instructed to take it in the morning, yes.

DR. GEORGE SACHS: So your dosage system is different.

DR. ZORICH: Yes.

DR. GEORGE SACHS: Here you're following what we would prescribe omeprazole and how you take it, half an hour before breakfast to give you the maximal effect day one and then day two and day three.

Your previous studies sort of on the spot swallowing omeprazole have a different design.

DR. ZORICH: Right.

DR. GEORGE SACHS: And your pharmacokinetics of the drug as your acid is switching

on are completely different. So this is the way the study should be done.

CHAIRMAN BRASS: Dr. Cohen.

DR. ZORICH: This study was done that way.

DR. COHEN: This is a very positive study, and it mimics the way patients take the drug in real life, and the ten milligram dose to my looking at this is highly efficacious. It's the way patients would take it.

The provocative meal, although very sexy, is also very artificial, but this is the way patients live, and they take the medication, and in this dose range you also have an appropriate placebo response which you would expect in the 30 percent range, not 60 or 70 percent.

So to me this is a very positive study and a very real life circumstance as how a ten milligram does would be taken.

CHAIRMAN BRASS: Was there a dose ranging analysis, not necessarily statistical significance between the doses, but just a dose ranging analysis between -- a trend analysis -- in either 171, 183 or in the combined population to look at whether there was a dose response relationship?

DR. ZORICH: Could you please put up the

first day and be ready for 14 days?

We actually saw in both of these studies -- in one study, if applying statistical test -- and, of course, this is now after the fact. I don't want to, you know, pretend it was planned in. These were both separately compared to placebo, and then after we had the results, we did see differences in 171, but as you can see and not surprising, there are not differences in 183.

Now, when you look across all 14 days, what you see is in 171 there really are not differences, and there's a suggestion of difference in 183.

So this is what I was talking about in reference to wrestling with this question of dose. In this design, ten and 20, you'd be hard pressed to say definitively 20 was better.

CHAIRMAN BRASS: Well, I wouldn't be surprised if a trend analysis, not a two arm comparison, but really a three point trend analysis would not have confirmed that there was some kind of dose relationship across that range.

Ms. Cohen.

MS. COHEN: Being as we tend to eat all kinds of foods that are bad for ourselves, did you

take the worst case scenario in foods and what people might eat? They take the dosage, and then they eat something that's pretty "gucky" and pretty bad. Did you test it under the worst conditions, not under the best, but under the worst?

DR. ZORICH: The previous studies 005 and 006, I think it was pointed out here that the low placebo response rate -- these were a highly -- these diets were really design to provoke reflux, and so, yes, we did test it under high fat, other stimulants of reflux, caffeine, and these people were living freely in their homes. So we did do both, free living, but as you know, abusing themselves nonetheless, but just on their own time.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: I'll preface my comments by saying that I think that the answer to the question is, yes, there's some efficacy shown here.

Having said that, I have to disagree that this is how people take this medicine in real life. This is how people take -- let me correct myself. This is how physicians think patients take the prescription medicine, but the studies of that show that even for single dose medicines, patients at best comply only 75 percent of the time, and when the

instruction is something like 30 minutes before a meal and that meal is morning time, trying to keep people from drinking their coffee, putting food in their mouth for 30 minutes, and insuring that they get the medicine beforehand doesn't happen.

Now, so as not to sound overly negative, the nice thing about this medicine is once a patient has been on it, it doesn't matter because the pharmacodynamic effect will remain.

My concern is that in the OTC setting, none of the current parameters apply. It's not prescription. It's not continuing therapy. There are others that we'll get to later.

And so I just felt the need not to let stand the comment that this is a study of how people take it now because I have no data to support that assertion.

DR. ZORICH: Let me say though that I think I would just like to make a correction, that I think we're over applying instructions to the patients that were, in fact, not applied. They were told to take in the morning before breakfast, and if they didn't eat breakfast or if it get late, just take it before noon.

So, in fact, this is not a study that is

a strict clinical design, and I think we tried to make it more naturalistic and take it in the morning, and the reason we did that was not to try to force, again, a situation where you're being very prescriptive, but because we had built in -- and I didn't show you the data -- but we specifically built in a nighttime heartburn endpoint. We felt that we wanted to have some idea that at least since noon people had taken it. So I just want to make sure that we don't over interpret the instructions to the patient.

CHAIRMAN BRASS: Dr. D'Agostino, you had another question?

DR. D'AGOSTINO: I'm not sure that the other side of the table answered the question you addressed to me from what I heard them saying previously, that the explanation you gave sounds reasonable, and I gather that's also in agreement with other people at the table.

CHAIRMAN BRASS: And that's what I assumed by the discussion.

Dr. Johnson.

DR. JOHNSON: You can shut me off if you want because this may not fit with this question, but I guess I'd like to go back to --

(Laughter.)

DR. JOHNSON: -- slide ZC6 where it's sort of the final proposed labeling slide.

DR. ZORICH: Yes.

DR. JOHNSON: Treatment of frequent heartburn and prevention due to food and beverage. When would they be taking these to accomplish the -- I'm very confused about how the product would be taken.

DR. ZORICH: Well, to be honest, I mean, there's no criticism here intended because truly what we're asking for is, you know, something that hasn't been done before, but when you think about it, the whole -- I think the comment came over here -- is that the meal induced model was that. It was a model, but because it helped the consumer get clear direction on when to take it in reference to what they predicted would be a provocative meal, and, Dr. Neill, with due respect, ever since '95, we've been treating predictable heartburn because you have to predict that a meal is going to be provocative.

And so prediction of heartburn is operative, I would say, but so what we're saying is that the data supports that as long as it's an hour before, we're very clear that the pharmacodynamics of this particular drug, you can't get real close to when

your heartburn is going to happen. You can't get closer than an hour. That 005 and 006, I think, showed us that no closer than an hour.

Backing up from an hour is a good idea. So let's say that if you're a consumer who is not going to have a provocative lunch but will have a provocative dinner, then dosing in the afternoon is okay, but dosing in the morning is okay.

It's unfortunate, and I'm sure that you can understand from the side point that someone who really thinks this is a benefit for a person, having the luxury of knowing that today is going to be a stressful day for a lot of reasons, it's a good thing to be able to take it in the morning and have a 24-hour prevention.

So what we would be telling the consumer is to take it on the day provided it's at least one hour before the meal that would provoke symptoms. So it would have to be more than an hour removed.

But other than that, there really isn't any reason to specify exactly when, and then if the person who is the 18 percent of the people that Dr. Castell showed to us with the weekly heartburn who's currently right now taking the drugs approved for episodic heartburn, it's just that those episodes

happen to be two or three times within a week. Our data, we believe, shows that for that targeted consumer, not the person taking Mylanta once every three months; for the person who identifies with the term -- and grant you, we have to test this for clarity -- but for someone with frequent heartburn, more than once a week, this person we believe is the targeted population. They currently are taking anti-secretory therapies now, and this would be the group that we think would benefit from this product.

And in fact, perhaps our hope would be that they would even have to take fewer products in combination.

CHAIRMAN BRASS: I want to come back to 171, 183.

Dr. Geller.

DR. GELLER: I wanted to know what the frequency of heartburn during the run-in period was in these studies.

DR. ZORICH: One, seventy-one and 173?

DR. GELLER: Yes.

DR. ZORICH: Do we have a slide for that?

I think over 50 percent of these folks were having heartburn at least half of the time, but we probably have a number.

DR. GELLER: Then is it correct that this line between GERD and heartburn is, again, blurred?

CHAIRMAN BRASS: Let's hold that question. Let's hold that one. That one will come up later.

Dr. Cohen.

DR. COHEN: I'm not going to get a chance to vote, but I want to say that this is a real life indication, and I know there's some contention across the table here, but I see patients, and this is the way patients take a drug. They know when they're going to get heartburn, and if you go out and you go to Tuscany for a week or you go out for dinner and you have a cigar and a couple of drinks, people can predict this, and in real life circumstances, this is a reasonable indication.

I don't think it's artificial at all. So I think that -- and let me just make one other comment -- I think it's better to prevent heartburn than to treat established heartburn. Once you've had heartburn, you've already had mucosal exposure and possibly mucosal damage. This can prevent it. This is a reasonable indication, in my opinion.

CHAIRMAN BRASS: Do you want to show those? Do you have that data?

DR. ZORICH: Can we show that histogram?

I have something that I think -- no, that not the right one. I've got the actual number of episodes.

CHAIRMAN BRASS: Well, if you can just --

DR. ZORICH: I'm sorry. I apologize because I'm not being clear.

You know the one that plot 114, 092 and 095? Ah.

What I've plotted for you here, I think this is separate from the studies because I'm only plotting people on placebo, but it tells you about that population of people that we recruited.

No, no. You had the right one in. Hello. I was happy. I was fine.

(Laughter.)

DR. ZORICH: Okay. We'll start again. What I'm plotting here are the percent of subjects, and -- 092 --

DR. GELLER: This is 092 and 095, and I guess in trying to understand why this trial was successful and the success with the others is more mixed, I was wondering about how much heartburn these patients had compared to the other set.

DR. ZORICH: In general, it's a fair statement that because of the way they were recruited, they're all pretty comparable. There weren't any

particular studies where they were very severe and the other ones were very mild. These, in general, were tracking in about -- I think were they about 1.5?

DR. GELLER: That's the severity, which is clear in the book, but the number of days of heartburn in the run-in period isn't.

DR. ZORICH: Well, they would have had at least two minimum to qualify.

DR. GELLER: That's part of your eligibility criteria.

DR. ZORICH: Right.

DR. GELLER: I think it was far higher.

DR. ZORICH: It's okay. How about if I go off line and I'll try to get that, and I'll come back?

DR. GILLIAM: If you look at Table 5.4, it says that 70 percent -- heartburn frequency of days during run-in, and it's running 73, 74 percent.

DR. GELLER: That's five days. Is that what that means? Does that translate to five days out of the seven days of run-in?

DR. ZORICH: Yes.

DR. GELLER: Thank you.

DR. ZORICH: That's right. We just confirmed that, five days.

CHAIRMAN BRASS: Okay. I -- oh, Dr.

Cohen, did you want to make a last comment?

Okay. I'd like to call for the vote on Question C(1). In studies 171 and 183, is there a clinically significant improvement of heartburn symptoms in either the ten or 20 omeprazole groups?

And I propose to keep them lumped, not bother with separating dose. So I think we discussed that issue. Okay?

All in favor of yes for that question, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Noes, please raise your hand.

(No response.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(No response.)

DR. TITUS: There were 14 yeses.

CHAIRMAN BRASS: We're now asked to comment on the pre-specified secondary endpoints and whether they are supportive of the primary study outcome. Do they add information regarding clinically significant treatment effect?

And I would just kind of ditto Dr. D'Agostino's previous remarks that there does appear

to be consistency in favor of drug for those secondary endpoints.

Would you like to add anything else?

DR. D'AGOSTINO: No, that's fine, but this withdrawal, are we going to talk about that in this context?

CHAIRMAN BRASS: Yes, please, go ahead.

DR. D'AGOSTINO: Well, I'd like some discussion on what that actually means. The drug obviously holds itself up for a few days, which is interesting, and is there any implication in terms of interpreting the study?

There were discussions this morning. Should something get into the transcript on that?

CHAIRMAN BRASS: Do any of the -- yes, Dr. Cohen.

DR. COHEN: I would just comment that I think clinician knows that once you stop the drug, the symptoms come back, and that was the whole rationale for long-term maintenance trial, and anybody who looks at the usage of the drug, it's chronic usage. So I think that's one of the issues that comes up. They feel so good that they don't want to stop.

CHAIRMAN BRASS: That point will become very important when we talk about the labeling and the

long-term toxicity issues.

Dr. Sachs.

DR. HARI SACHS: I really was just going to mention that, you know. It seems to me that there's no question this will be used chronically because we're talking prevention, and if you stop it, you feel bad.

CHAIRMAN BRASS: Other comments on the secondary endpoints for 171 or 183?

If not, we will move on to Question D. Based on the types and frequency of adverse events reported in the clinical trials and in the post marketing adverse events database, are the safety concerns for the OTC marketing of omeprazole able to be addressed solely by labeling, identifying risks to consumers for short-term or chronic intermittent use?

And let me editorialize. That question is whether or not you believe it will actually be used that way. So I want to focus the discussion on issues related to short-term toxicity or intermittent use that is repetitive short-term use, and I want it answered that way because I want to separate the issues without any short-term toxicity from the issues with the longer term toxicity, and regardless of how we think it may ultimately be used.

In answering this question, please consider the reports of anaphylaxis, angioedema, urticaria, liver toxicity, white blood cell disorders, and severe skin reactions.

DR. SHAPIRO: Mr. Chairman, just on a point of order, are you asking us first to confine the discussion to short-term effects?

CHAIRMAN BRASS: Yes, short term as defined with ten days of exposure.

DR. SHAPIRO: Okay, but you're talking about effects within ten days of exposure.

CHAIRMAN BRASS: Or later effects that would result from only ten days of exposure.

DR. SHAPIRO: Well, that could be things like aplastic anemia and --

DR. GANLEY: Eric, let me just interject here. I think that he's picked up on some of these things. I may require longer use than ten days in, for example, hepatitis. You know, I think there was some discussion of when that occurred in the course of chronic therapy. So if you take it in the context of someone using it for short-term use or for this, you know, chronic intermittent use, you know, there may be differences in these various --

DR. SHAPIRO: Could I make a suggestion?

CHAIRMAN BRASS: Please.

DR. SHAPIRO: Could we consider short-term effects to be things like nausea, vomiting, diarrhea, and long-term effects to be cancers of various kinds, agranularcytosis, toxic epidermal necrolyzers (phonetic) and so on?

CHAIRMAN BRASS: I was hoping to avoid the cancer issue until the next set of questions, but I'm open to doing it either way, and I was trying to simplify things because I was trying to avoid the definition of intermittent in terms of -- because intermittent use becomes chronic use.

Yes, you want to try and help?

DR. RACZKOWSKI: Yes, I think that the focus of this question is really on some of this uncommon, but some of the serious adverse events that have been associated with omeprazole use. I think both the company and the agency would agree that there have been serious events associated with the drug, and that they are uncommon.

But in a prescription setting, we've made the determination that the benefits exceed the risks because the potential benefits are greater, and so the thrust of this question really focuses on serious adverse events that are uncommon.

Are those acceptable in an OTC setting, where the benefits may not be as great?

CHAIRMAN BRASS: Okay, but what I really want to do is separate the issues that are defined in Question E, for those of you who have read ahead, from those that are going to be discussed now in the context of Question D.

So whatever language is useful to separate those two I accept immediately.

Yes, Dr. Shapiro.

DR. SHAPIRO: Thank you.

The specific effects that are referred to here are anaphylaxis, angioedema, urticaria, liver toxicity, white blood cell disorders, and severe skin reactions. I think there are secure data concerning anaphylaxis to indicate that, first of all, this is a rare outcome; secondly, that its most common causes, apart from bee stings and wasp stings, are actually blood transfusions, plasma infusions, and the use of radiopaque materials, and a few selected drugs, such a penicillin.

Apart from that, the incidence of true anaphylaxis is exceedingly low, and even if this product were to increase the risk of anaphylaxis, the incidence would still be low. If you take a very rare

disease and you multiply it by a relative risk of three, it remains rare.

So I wouldn't have anxieties about anaphylaxis even if there have been reports and even if there have been reports of the occurrence of anaphylaxis on rechallenge.

With regard to urticaria, there isn't a drug on the market that doesn't cause urticaria, either over the counter or a prescription, and if one really wants to know whether urticaria or hives or conditions of that kind are a problem, one would need to do a randomized controlled trial and compare incidence rates. Without doing that, we couldn't answer the question.

But urticaria itself is not serious, and if a patient experiences urticaria and if it recurs on rechallenge, that patient can stop. So I don't think that's major.

Major hepatic toxicity, liver failure, which rather than transaminitis, I think, again is so uncommon that whether or not there should be a causal relationship, there would not be a public health problem.

White blood cell disorders, if there's a neutropenia, which is asymptomatic, it doesn't matter.

If there is agranularcytosis, this is an exceedingly rare disease. If this drug were commonly causing agranularcytosis, like some of the other agents on the market, we would know about it.

And for toxic epidermal necrolysis and Stevens-Johnson Syndrome, there are, again, acute conditions. If they were a major public health problem, we would know about that, too.

So what I take from all of this is what we currently know is reassurance. If some public health problem were to arise, there are already data banks in which these questions can be adequately examined in well formulated case controlled studies.

CHAIRMAN BRASS: Dr. George Sachs.

DR. GEORGE SACHS: I think the issues are twofold. One, are the adverse events, the idiosyncratic events under omeprazole more frequent than placebo, or, secondly, are these adverse events more frequent than any other controlled clinical trial?

And I think careful surveillance on omeprazole 12 years post launch worldwide, I don't think anybody can point to any instance of where omeprazole per se has resulted in adverse events more frequent than those found certainly in the second

category in terms of any other drug trial that's going on in this area or any other area.

So I don't believe there's any issue whatever about the safety of omeprazole relative to any other drugs, OTC or prescription.

CHAIRMAN BRASS: Ms. Cohen.

MS. COHEN: If you describe the contraindications here, would consumers know what they are, number one? And, number two, I wouldn't trust a label till I saw it.

CHAIRMAN BRASS: We're not talking about the label right now. Labeling will come up later.

Dr. Cantilena.

DR. CANTILENA: Yeah. I guess I would not sort of share the opinions just expressed concerning the toxicity to the liver. I think there seems to be, albeit very small, but a clear signal, and I guess we have some fairly well documented cases, and I was going to just ask the FDA one follow-up question that I didn't get a chance to ask this morning from the safety presentation.

Your slide number 11 talked about some of the cases were classified as Category A, which means that you're fairly tight in terms of causality. In looking at those reports, can you tell us in terms of,

you know, genetic, you know, polymorphism or anything that might suspect, you know, mechanisms in terms of the toxicity?

And as you're thinking about that, but if you just look at that list, I mean, there's a significant number of, you know, fatal cases and, you know, nonfatal, serious, not just, you know, trivial, and I guess I'm not as comfortable as you seem to be in the issue of hepatic toxicity, especially for treatment of, you know, a condition that is not, you know, life threatening.

So just to sort of put that out there, but I am extremely interested in finding out whether or not we know more, you know, about these apparently well documented cases.

DR. STEINBERG: If I'm looking at that same slide you are, you said slide 11. You said there are two cases of fatal that were A rating and two and four of nonfatal. Are those the numbers that you're talking about that I find disturbing?

DR. CANTILENA: Right. Overall, you know, 33 fatal, 227 nonfatal, serious. But I was just asking if we knew more about the cases that had the A rating.

CHAIRMAN BRASS: Yeah, let's let the FDA

response.

DR. CANTILENA: right.

DR. AVIGAN: The point I would make is that the A cases generally have had the luxury of rechallenge in some cases at least, two of the four cases that were the nonfatal cases, with clear association on rechallenge, and I think that you have to understand that there is a limitation in this kind of analysis because the information is given in a voluntary way, and when you sort through the various kinds of cases, the problem is not just the A cases. It's the B, C, and D cases, where if you look at what is given to you in the narrative, there are a number of potential explanations which cannot be dissected through because of limitation information. In fact, there may be in the total aggregate more that in reality or in truth are attributable.

So you could look at it both ways, and the second point is that this is presumably still a very rare event, but we don't know the true incidence because this is voluntary.

DR. CANTILENA: So just for a specific, if you look at that aggregate of serious and fatal, have you examined in terms of, you know, race, if it's a high, you know, percentage of like Asian, you know,

population that have that?

DR. AVIGAN: Yeah, these are idiosyncratic reactions that are not predictable a priori by any measure that we currently have.

CHAIRMAN BRASS: Dr. Shapiro.

DR. SHAPIRO: Even when a case occurs on rechallenge, adverse reaction reporting systems do not contain the requisite clinical information that you really need to make a judgment about causality. You want to know about exact timing. You want to know about other drugs that were used. You want to know about whether that person previously had hepatotoxicity. You want to know whether the person had Hepatitis B positivity or Hepatitis A or Hepatitis C. Without that information, you can reach no conclusions.

The other added difficulty here is that if there are two patients who have hepatic failure, both of whom die, one of whom was exposed to a drug and another was not, the one that was exposed will be reported to the Food and Drug Administration. The one that was not exposed will not be reported.

The bias is 100 percent the data are not interpretable.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I tried to raise an issue previously today, but that is concerning the biological effect of gastric acid. It seems to me that nobody is interested in that. After all, we have preserved the production of gastric acidity in the upper part of the alimentary tract throughout phytogenesis, and I can't understand why you want to take it away from a large million of people.

Aren't you afraid of that? What could happen with viruses and prions, as I said? Do you have that information that there is this enormous, long incubation times for these diseases?

So I'm not -- I'm asking for biological.

CHAIRMAN BRASS: Dr. Cohen.

DR. COHEN: Yeah, the thing that impressed me at the ten milligram dose, which is the recommended dose was that it was really only a very modest effect on acid inhibition. I mean it was like a 20 percent reduction, and the pHs did reach acidity at some time during the day.

So in a way, I'm pleased and surprised that the beneficial effect without having a major impact on acid inhibition is very minimal or modest, I should say.

CHAIRMAN BRASS: Dr. Hari Sachs.

DR. HARI SACHS: In a clinically relevant question, if these drugs actually cause relevant neutropenia and perhaps make you at risk for infection because of gastric acid effects, is there any data on infection, you know, incidence in people with this drug, you know, that it's higher than the average?

DR. CANTILENA: The only thing that I know, and perhaps other people can comment, is that in patients on high dose proton pump inhibitors, they're somewhat more susceptible to getting enteric infections, like E. coli or campylobacter, salmonella, and even there the association isn't that great, but that's the only thing that I know of, but that's at pretty high doses where they're virtually achlorhydric.

CHAIRMAN BRASS: Yes. Would sponsor like to make a comment?

DR. LEVINE: I believe Dr. Cohen as made the right comment.

DR. SHAPIRO: Could I answer that question? The incidence of agranularcytosis in the population at large is about six per million per year. These would be the people who are uniquely susceptible to developing infections.

With such a low incidence, it would be

impossible in any study that I can conceive of to show an increased incidence of infection among omeprazole users and nonusers.

Even if there were an increased incidence it would be of no public health importance. It might be 12 per million per year.

CHAIRMAN BRASS: Dr. George Sachs.

DR. SACHS: In relation to infection and the use of PPIs, there have been studies done in people where the incidence of overgrowth by E. coli or other enteric organisms has been followed as a function of treatment with acid inhibitory medication, i.e., Zantec at a clinically effective dose of 300 milligrams b.i.d., omeprazole 20 milligrams. o.d.

And you can show in both instances a transient overgrowth which then disappears, and remember that at this dosage nobody except for the very slow metabolizers ever shows anything close to achlorhydria.

So the benefits that you see in terms of the 20 milligrams of omeprazole are limited by the fact that you're not getting complete acid suppression, and the pH does go down to one at night, and you don't get this sort of effect at nighttime GERD that you'd like to see.

So you're not generating achlorhydria. You're not generating gastric infection by treatment either with omeprazole or b.i.d. 300 milligrams Zantec.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: Yes. There's the question of the highest pH that you have in the stomach does not allow us. When you eat something, when you drink something, if you happen to have a high pH, that is what matters, not the lowest.

CHAIRMAN BRASS: I'd like to come back to an issue on the drug interaction question because I think it impacts the consumer's ability to discriminate.

What is -- I'm sorry. Do you have specific data on omeprazole-warfarin interactions, specifically using PT or prothrombin time or INRs as the endpoint?

And I'd much prefer not to see mean data, but data on the number of patients who had their INR bumped by a certain amount. In other words, I'm actually interested in the outliers from a safety perspective, not the mean response.

DR. LEVINE: I can't provide outliers. We have mean data and did not show any differences in

coagulation parameters.

CHAIRMAN BRASS: Yeah, I think that's just always how it's shown, and it's really not helpful if you're looking for a subset of patients who may be at risk or have an exaggerated response when you expose a large population. So I think having confidence that there are less than X percent of the population who will bump their INR more than 25 percent or something like that is much more useful than mean data.

Obviously if mean data shows a change, it's important, but when it doesn't show a change, I think for safety purposes the outliers matter a lot.

DR. LEVINE: May I just make one point?

CHAIRMAN BRASS: Oh, please.

DR. LEVINE: Just it's important to recognize that warfarin is a racemate. It has two inantemers (phonetic), and in fact, the most active inantemer that affects coagulation is not -- it doesn't go through the same metabolic pathways so that what we measure is with the less active warfarin. So although we don't have all of the data, there are reassuring bits of information.

CHAIRMAN BRASS: Also, I remember at some point there being discussion of omeprazole being an

inducer of certain P450s. Did I confabulate that?

DR. LEVINE: I would have to defer to my pharmacologist, but that's data that I'm not aware of.

DR. LAM: Omeprazole definitely can induce 1A2.

DR. LEVINE: Could I ask Dr. Andersson to respond to that, please? He's one of our internal experts in pharmacology.

DR. ANDERSSON: That issue has been thoroughly studied in many, many different ways with different doses and from different labs, and there is a German group that showed that in poor metabolizers actually 40 milligram omeprazole were given over one or two weeks, had an induction of some 30 percent 1A2, which in rapid metabolizers, they had to give 120 milligram to obtain the same degree of induction.

But those data were very variable and going from negative induction, so to say, to some 60 percent induction, and we have tried to reproduce those data at our own company, and almost as I'm speaking right now, we are going to submit a study using 60 milligram omeprazole in poor metabolizers with an N of five, and there is no induction at all in that study.

So I would tend to say that there is

really no induction at least that has no clinical relevance, 1A2, of omeprazole treatment.

CHAIRMAN BRASS: Dr. Elashoff.

DR. ELASHOFF: With respect to the proportion of people who might be in some extreme area, although these studies are probably small, they also probably have standard deviation in addition to mean, and one could make some initial approximation to how many people might be extreme, using, say, two to three times the standard deviation.

CHAIRMAN BRASS: That's assuming if it's a normal population. If you're looking for a bimodal subset, you'll miss it that way.

DR. ELASHOFF: It just -- it just gives a place to start. I'm not saying that it gives an answer.

CHAIRMAN BRASS: Dr. George Sachs.

DR. GEORGE SACHS: Yeah, again, with this induction of 1A2, the issue was initially brought up as converting things to a more dangerous form, and therefore, induction of 1A2 by implication due to omeprazole increased the patient to the risk of carcinogenic metabolites.

But traditionally, historically all P450s are protective, and animal studies with increased 1A2

shows actually protection against carcinogenicity, not promotion of carcinogenicity.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: Well, I disagree. I think there's pretty clear literature for certain cancers, and I can't remember off the top of my head, with higher 1A2 activity or induction, but I don't believe that that's probably clinically relevant in this situation.

I guess I'd like to come back to the question I asked earlier, which is the data that you might have on the relationship between toxicity and dose.

I mean, I think one of the luxuries we have with OTC products is that we've got experience with millions or billions of prescriptions being filled, and I don't see really any safety concerns, but, again, to go to this issue of ten versus 20, is there any reason we should be more concerned about 20 than ten other than the acid inhibition?

DR. LEVINE: I've tried to make the point that what we've been talking about is risk potential with particular reference to something that the agency has mentioned, which is specific subpopulations. We can monitor head to head ten milligrams, 20 milligrams

in controlled trials and obviously not show any difference, and the issue, of course, is what's happening in an at risk subpopulation or what's happening with very, very rare events.

One of the issues that we've been talking about is the potential for drug-drug interactions. We think that the profile is safe, but the potential if you want to stack the deck to really assure any lack is to simply lower the dose.

But with regard to a lot of the adverse events that we've been talking about, if there is any relationship as best as we can determine it's idiosyncratic. If we wish to think about theoretical risks that have to do with disruption of gastric homeostasis, we know that there's clearly a dose difference between ten and 20, and you know, from our view looking at the studies that we've seen where we did not see substantial differences between ten and 20, that's why we've come to the recommendation for ten milligrams.

DR. JOHNSON: But it seems in terms of side effects, in particular, if there was really clear dose related relationships, the people who are poor metabolizers would jump out and have all kinds of toxicities because they have fivefold concentrations.

My impression is they don't. Is that correct?

DR. LEVINE: That we've not observed that. You're correct.

DR. GELLER: How many slow metabolizers have you studied?

DR. LEVINE: I can't cite an absolute number. We have chosen a number of, you know, subjects as part of our pharmacology studies. We have conducted studies in Japan. We have adverse event profiles from that country, and the distribution of AEs resemble exactly what we've observed in the United States and worldwide.

CHAIRMAN BRASS: Dr. Cantilena.

DR. CANTILENA: Yes. I was wondering if you can actually show the drug-drug interaction with your product and, say, phenytoin at, you know, ten or higher dosages of the omeprazole, if you have that data, and again, obviously if you have the individual data, that would be idea, but I think even for us to see the mean with phenytoin would be helpful for me.

DR. LEVINE: Could we pull slide 55, please?

These are the data that we've been able to accumulate, and what has been done is studies both in

healthy subjects here, as well as in patients with epilepsy who required phenytoin and to whom we added omeprazole dosing. The dosing in these studies as you can see were high in these, 40 milligrams over seven days, which is steady state concentrations, and we're seeing this magnitude of change. There are some differences here, and in fact, in the epileptic patients we couldn't demonstrate a change.

So we feel pretty comfortable that particularly even if there were magnitudes of changes that are, you know, in the vicinity of 15 to 20 percent, that's not going to be a clinically relevant issue with regard to phenytoin levels, but actually when we went and looked at patients, we couldn't demonstrate a change in phenytoin levels.

I'm sorry I don't have individual data.

CHAIRMAN BRASS: Dr. Sachs, do you have a question?

DR. HARI SACHS: I just can't see -- I apologize for my eyes -- the dose in the phenytoin patients with seizures, of phenytoin.

DR. LEVINE: That was 20 milligrams for 21 days.

DR. HARI SACHS: The dose of phenytoin.

CHAIRMAN BRASS: It was whatever they were

taking, but they were at steady state. So it was an individualized study.

DR. LEVINE: Yes, yes, I'm sorry. I misheard you.

CHAIRMAN BRASS: Okay. Do you want to vote on D?

PARTICIPANT: I'd like that.

CHAIRMAN BRASS: Okay. So what I'd like to do is call the question for D. Specifically are the safety concerns for the OTC marketing of omeprazole able to be addressed solely by labeling to consumers for short-term or chronic intermittent use?

All who feel the answer to that question is -- and, again, we're putting aside the issue of whether they're going to use it longer or not -- all those who feel the answer to that question is yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those who feel the answer to that question is no, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those abstaining, please raise your hand.

(Show of hands.)

DR. TITUS: There are seven noes, four

yeses, two abstentions and one member absent.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: Safety is shown. I'm not sure whether the yes or no reflects that, but my vote is cast in favor of safety having been demonstrated.

CHAIRMAN BRASS: That was a yes.

I think we're going to take A Cantilena break and --

(Laughter.)

CHAIRMAN BRASS: -- reconvene promptly at 3:00 p.m. because I don't think we're going to get through for another little while, and I don't want people getting up and walking out.

(Whereupon, the foregoing matter went off the record at 2:50 p.m. and went back on the record at 3:04 p.m.)

CHAIRMAN BRASS: I'd like to continue our deliberations, and I think that the last question may have engendered considerable confusion, and based on what comments I have received actually in both directions so maybe it was worded perfectly, that people felt that there may not have been clarity in what this question was trying to ask.

So I'm going to try to reread the question with clarification, ask for verification if my

interpretation is correct, and if so, redo the vote, and if everybody understood it before, the vote will come out exactly the same and we will see.

So specifically, based on the types and frequency of adverse events reported in the clinical trials and in the post marketing adverse events database, are the safety concerns for the OTC marketing of omeprazole able to be addressed solely by labeling to consumers?

Notice it does not say has the sponsor's label demonstrated that. It does not say whether you have been provided a randomized controlled trial on that point. It simply says based on your understanding of these safety profiles and your understanding of labelology, whether or not it is reasonable to expect that a label could be designed to insure that short-term use could be done safely.

And if our answer comes out the same as no, I'm going to ask the noes for suggestions on what would be necessary to alleviate their concerns.

Is that fair, Dr. Ganley?

Is that clarified, Dr. Blewitt?

DR. BLEWITT: I would only add that that question be considered in the context of existing products on the OTC market.

CHAIRMAN BRASS: I think the issue is not one of comparison necessarily to other agents, but in terms of whether or not there are safety concerns, whether the label is able to convey and does not even imply a risk to benefit analysis having been made.

So I don't want to get into that kind of nuance if it's clear without it.

DR. GANLEY: Eric, I just want to --

CHAIRMAN BRASS: Dr. Ganley.

DR. GANLEY: It's not only the noes we've mentioned, but the yes because the question would be then if they do think there's some problems here, could you address it in labeling, and their answer could be yes or they don't think that these are a significant enough problem to even worry about them.

CHAIRMAN BRASS: I understand the point exactly.

Dr. Shapiro, did you have a clarification?

DR. SHAPIRO: I'm one of the people who apparently voted against his own opinion a short while ago.

(Laughter.)

DR. SHAPIRO: So I wanted to be sure I understand you.

CHAIRMAN BRASS: If you vote yes, you

believe the drug can be labeled safely for OTC use, for short-term OTC use.

DR. SHAPIRO: What if I believe the adverse reactions may not even exist?

CHAIRMAN BRASS: Then you can raise both hands, but only one will be counted.

(Laughter.)

CHAIRMAN BRASS: Okay. Are we ready to vote?

All those who believe the answer to that question is yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those who believe the answer is no, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

DR. TITUS: Is somebody missing? I have to see the noes again. The noes? Thank you.

Three for no, meaning they can't do it in the label; nine for yes, meaning the label can do it; and two abstentions.

CHAIRMAN BRASS: So apropos of trying to clarify this issue further, I'd be interested from the

people who abstained or voted no what are their major concerns and what would it take to reassure them on this issue.

Dr. Geller.

DR. GELLER: I'll give this a try. I am concerned about the slow metabolizers and the fact that you didn't show us much data on that, and it seems like we infer that you don't have much data. So, in particular, in Asian populations in the U.S., I'm concerned about that.

And I'm concerned about that, and I'm concerned about seeing -- I'd like to see more data about drug-drug interactions and whether -- I don't know how you can show that such people will read the label carefully.

I guess one of my concerns is that there are so many things going on, albeit in a very low proportion of people, that that gives me a concern about being able to cover all of this in the label.

CHAIRMAN BRASS: Are there particular populations or patients who you think are at risk that would be critical to identify in the label?

DR. GELLER: Well, I think the possibility is raised somehow that Asians may be at higher risk.

CHAIRMAN BRASS: Dr. Cantilena, did you

want to comment?

DR. CANTILENA: Yeah, I think actually my concerns were quite close to that. First of all, we only studied, I believe, 48 out of 8,000 some odd, you know, Asians. So the issue of, you know, PM for CYP 2C19 is an issue.

Then the other issue with the drug interactions, you know, my question, you know, was not answered. When you show me averages without even standard deviations, I actually can't interpret that. So it was not answered. You really need to see individual data, and I think that obviously is available. There's no clear reason why that's not shown.

And so then the question that I was faced with is I have a concern about drug interactions, and we're not going to talk about the labeling now, but I'm not sure, and it certainly wasn't clear in terms of what we've seen for labeling whether or not we can handle that appropriately. So it left me with sort of enough uncertainties not only in the amount of sort of lack of information for the magnitude of drug-drug interactions, particularly in the poor metabolizers, but whether or not that could be handled by labeling.

CHAIRMAN BRASS: Yes, Dr. Steinberg.

DR. STEINBERG: I can't answer it with relation to drug-drug interaction, but in terms of slow metabolizers, it's my understanding of what must be going on with these rare events is that they're idiosyncratic reactions. That's why it occurs one in a million.

And even a slow metabolizer who may have more drug on board would not be expected to have a greater frequency of these rare reactions because they're still idiosyncratic and it's not dose related. Just because you have more drug floating around in your system doesn't mean you get a rare side effect any more frequently.

DR. GELLER: You know what the statistician says to that. Show me the data.

CHAIRMAN BRASS: Well, again, the suggested data was the post marketing experience in Japan, which is the large cohort. Now, again, it clearly has limitations.

DR. GELLER: Actually, we did see it, number one. And, number two --

CHAIRMAN BRASS: Do you have that data?

DR. GELLER: -- I'm not sure of its relevance to the American population.

CHAIRMAN BRASS: That's why they didn't

show it to you.

DR. GELLER: I just don't know.

CHAIRMAN BRASS: Would you like to comment? Only turn on your microphone.

MS. COHEN: All right. First of all, in listening to the scientists around the table, they can't even agree what goes on the label, and if you can't agree, then how does anybody know what goes on the label?

Secondly, I'm concerned about drug interaction, and more than that, I would like to know in a long-term study about the people who took these Prilosec and what happens later on. You didn't ask the symptoms. Did you follow them? Did you come back six, seven, eight months later after they took it? And was it masking some other kinds of symptoms?

So I'm not satisfied with the information. I think it has to be more long term.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: I really consider myself a pharmacokineticist by training. So I feel fairly confident in making some of these statements.

I really don't see much reason for concern about drug interactions. There's two kinds of drug interactions here. One is inhibition of other drugs

by omeprazole, and there are really not a lot of substrates for CYP 2C19. They've covered most of them, and albeit they are mean data, they don't really appear to be important effects in that direction.

So the other concern then is effects of other drugs, which is going to be those same diazepam, et cetera. There's not really good evidence of that, which to me really leaves one category for potential drug interactions, which is poor metabolizers so that they don't have CYP 2C19 activity, which means the major enzyme is CYP 3A4, and then if they have an interacting drug on board, and again I'm not convinced because the poor metabolizers have fivefold elevations in their concentrations, and it doesn't appear to matter. I just don't think we're going to see drug interactions of a magnitude similar to what we see with the genetic abnormality.

CHAIRMAN BRASS: I think there is one drug interaction that we all agree is important, and that's the ketoconazole-itraconazole (phonetic), and I think that in terms of labeling, it's clearly incorporated on the label or the proposed new label, but I think it's an example where a different kind of comprehension study is very important.

We have talked about asking patients with the

label in front of them whether they know if they're taking itraconazole or ketoconazole and whether or not they can take this drug, and 90 percent say, "No, I'm not supposed to."

I don't think we know what percentage of consumers who are taking ketoconazole know and could identify whether or not they're on ketoconazole so that even if they read the label they would know not to take it, and I think that link for any of the drug interaction warnings on the OTC products to my satisfaction have never been cemented.

And because we're talking about a from mild to moderately severe fungal infection, I think it would be very important to know with some confidence that a patient using one of those products was not going to lose the efficacy of their antifungal agent by buying this over-the-counter product.

Please.

DR. LEVINE: May I just address one question that's been raised in the poor metabolizers?

What hasn't come across in the presentation is what happens in them, and it's the concept of affinity. Omeprazole has a strong, very strong affinity for 2C19 and a weak affinity for 3A4 so that in a poor metabolizer who doesn't have 2C19

function and who undergoes -- has the omeprazole metabolized by 3A4, what's more likely is that other drugs that go through 3A4 may inhibit the metabolism of omeprazole and not the other way around.

That's obvious to some people, but may not be to others.

CHAIRMAN BRASS: Dr. Cantilena.

DR. CANTILENA: Yeah, if I could just follow that, so have you done a study in a poor metabolizer for CYP 2C19 to look at the effect of your compound on, say, cyclosporin?

DR. LEVINE: That has been done, and my understanding is that there is no interaction. What I thought you were going to ask is whether that's been done with diazepam, and there's no effect on the diazepam levels in a poor metabolizer.

DR. CANTILENA: In the presence of omeprazole?

DR. LEVINE: In the presence of omeprazole.

DR. CANTILENA: There's no change in the individuals or in the mean?

DR. LEVINE: In the mean, but it's because of the metabolism. If you don't have 2C19 function, the diazepam is going to be metabolized normally as if

the omeprazole isn't there because diazepam isn't metabolized. You know, its dominant metabolism is 2C19.

DR. CANTILENA: Right, but, again, when you talk about the mean information, I'm uncomfortable with that, and I think that you need to know that I'm used to looking at individuals, and the outliers as, you know, the chair, you know, suggested. So I appreciate that.

When you look at the overall effect and where you're obviously for your statistical analysis, but it is important, and I think just, again, I'm just commenting in response to, you know, the reasons why I voted the way I did is in that there is information out there that when you're using this as an alternate pathway, it's possible for you to have interactions, and there's a whole host of interactions that we haven't explored on the 3A side.

And if, indeed, the data show that those are extremely, you know, small and there are not outliers, then I'm a lot more comfortable, but I haven't seen that data and, you know, when I ask for it, I only hear about averages, and so that's the reason I voted the way I did.

CHAIRMAN BRASS: Dr. Robinson.

DR. ROBINSON: Not to cast aspersions on any part of the table, but it does seem to me that this all sounds very remarkably like what I heard when I was here with omeprazole the first time. Only the difference now is the 380 million prescriptions that we've heard about, and if all of these low metabolizers and people with other problems existed, doctors have been thinking about drug-drug interactions. We are all focused on that. All the other pharmaceutical companies have told us to be focused on it. We are looking for it, and if it existed, we would have seen it.

So looking for the one or two cases that might exist under some extremely peculiar set of circumstances doesn't strike me as a very productive enterprise.

CHAIRMAN BRASS: I guess we don't all share your opinion of the conscientiousness of the surveillance system.

DR. CANTILENA: And I would also say in addition to that that you're now shifting into an uncontrolled environment, and that's really the issue. So it isn't quite the same.

CHAIRMAN BRASS: Is there anybody who would like to keep Question D on the table or shall we

move on to Question E?

Dr. Ganley.

DR. GANLEY: Yeah, for the people who said yes, was there a specific adverse event that they believe a consumer should know about?

CHAIRMAN BRASS: Well, that's why I mentioned the drug interaction education as a yet vote or as something that I think it's important to verify that the label can communicate effectively to that population who's been prescribed ketoconazole, itraconazole, that they know not to take it.

Dr. Sachs?

DR. HARI SACHS: I would probably add some stop use, which probably seems obvious to people at the table, but, for example, if a rash develops and persists, abdominal pain, nausea, vomiting, things like that.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: There aren't other things that I would add to the label, but I think that's different from whether they should be added to a package insert that's included and whether or not information that would be included on the label is going to influence a decision to buy or not.

For many of the drugs that are already

available over the counter, I can't imagine that adding agranularcytosis, some of these extraordinarily rare things, agranularcytosis, some of which patients aren't going to be able to monitor for anyway -- that there would be any value in doing that both because they occur so rarely; also because they occur very rarely in comparison to the drug that's sitting right next to the Prilosec on the shelf.

DR. GANLEY: Yeah, I think if you were worried about agranularcytosis, you would label it that if you developed fevers or chills or things like that or, you know, if you were worried about hepatitis, if your eyes got yellow. I think that's how we have to label it for consumers. If you think it's so rare that we don't have to tell -- and believe me, it's amazing what you do have to tell people sometimes, although you're probably aware of that -- but that's what I'm trying to get at.

If there was one there, a concern, that we need to incorporate in labeling, that's what I was trying to address.

CHAIRMAN BRASS: Dr. Neill?

DR. NEILL: I'm trying to imagine any circumstance where as a family doctor I would want you telling more of my patients to call me if they get

chills or a fever.

(Laughter.)

DR. NEILL: And I can't.

CHAIRMAN BRASS: Moving on to Question E.

DR. GANLEY: Would you be asking them whether they'd be taking OTC drugs?

CHAIRMAN BRASS: Both in the context of the charts you're amused, but because there will undoubtedly be discussion about more chronic use of this product if it is made available in the OTC setting, there are a series of issues that have been identified in Question E which we would also like to hear discussed because of their relevance in how much we should be concerned about that chronic use in terms of its OTC use.

So specifically, do other safety concerns affect acceptability of the OTC marketing of omeprazole? In answering this question, please consider the questions raised by the FDA reviewer regarding:

One, the making of serious disease;

Two, the potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity;

Three, rebound hyperacidity reported in the literature with discontinuation of therapy;

And, four, hypergastrinemia that may be associated with the chronic or chronic intermittent use of omeprazole.

And I would add to that list any sequelae, including alterations in cobalamin metabolism that might be associated with chronic suppression of the gastric environment.

Dr. Shapiro.

DR. SHAPIRO: Mr. Chairman, one of the reasons I'm here is that I was contacted by the Food and Drug Administration in August asking me to look at fetal and developmental toxicity, and I was provided with three papers and then subsequently with an unpublished paper which I reviewed for the FDA.

These papers were not perfect by any means in terms of their methodology, and they suffered from weaknesses, particularly in terms of their statistical power and their informatively, but collectively they showed no increase, no overall increase in the risk of major malformations, although some increase could not be ruled out. They gave no indication of any evidence to suggest delayed development or I'm trying to think of -- small for deaths. There was no evidence of an increased risk of spontaneous abortion or whether there were major methodological problems concerning

that.

And also when I reviewed the evidence of which they provided relevant papers, this drug causes fetal loss and fetal death at high doses in rabbits, and it causes fetal loss at even higher doses in mice. It does not cause birth defects. So there's no plausible biological evidence to suggest that there should be an increased risk of birth defects.

Now, of course, in principle any drug is capable of being a teratogen, and sometimes the correct experimental model for observing the teratogenic effect is the human being as with, say, thalidomide, which was more effective in producing birth defects in human beings than in any other species that I know of.

But beyond that general caveat, this product ought to be monitored for birth defects as thoroughly as any other drug on the market. I could find no special reasons to single out omeprazole, and my conclusion was that this drug poses no greater public health hazards in terms of the risks of birth defects than any other drug which is currently on the over-the-counter market.

With regard to tumorigenicity, we've already this morning discussed the findings which have

been found regarding the H2 blockers, which have shown quite substantially and quite unanimously that there is initially an increased incidence of gastric cancer which appears to be due to misdiagnosis, people being labeled as having some indication for the drug who, in fact, already have gastric cancer, and that as the follow-up continues of long-term use, the relative risk declines to one and stays there after a year or two.

And I think the unanimous opinion now is that there's no increase in risk. If one extrapolates and says that suppression of acid secretion does not appear to increase the risk of gastric cancer, that presumably would apply to omeprazole, but it could also be proven.

In addition, there do exist databases that if there was some hypothesis concerning an increased risk of tumors, those databases could be examined and one could assess whether there's an increased risk, as well.

And also if there were some specific birth defect which was alleged to be caused by omeprazole as opposed to just an increase in the risk of all birth defects, once that hypothesis exists and appears to be reasonably based, that, too, could be explored in

existing databases.

CHAIRMAN BRASS: Dr. Cohen.

DR. COHEN: I don't have great concerns about any of the questions raised here in E, but now at almost 3:30 in the afternoon, we've talked about a dose of a drug of ten milligrams, and we've talked about a whole bunch of peripheral effects, but there's been no discussion of what the effects of ten milligram is on the esophagus, which is the organ that we're treating, and I would like to know if ten milligrams of omeprazole taken for two weeks or longer has any healing effect on the esophagus. Does it heal partially, does it heal completely, does it lead to more Barrett's epithelium, or does it protect against Barrett's epithelium?

And that to me is the critical issue. I think these peripheral issues are obviously important, but I think the critical issue is the esophagus.

CHAIRMAN BRASS: I'm going to hold that question because we can stay focused on E and hopefully it will come up in some of the final efficacy.

Dr. Elashoff.

DR. ELASHOFF: Yes. With respect to fetal problems, I'm always especially concerned with a drug

that sounds like it's good if your stomach is not feeling good in pregnancy because I think people are more likely to take this kind of drug in pregnancy because of the common stomach problems.

The issue of whether the data are reassuring or not has to do very, very strongly with sample size because unless you study 1,000 people or rats or whatever it is, you're not very likely to see events that occur one in 1,000 or two in 1,000.

So I personally am not reassured unless studies have been very, very large in this area.

CHAIRMAN BRASS: Dr. Shapiro, I assume those studies you referred to are registry type studies, combined exposure in them?

DR. SHAPIRO: One of them was from the GERD database in England. That's an automated database. The numbers were small nevertheless.

Another one was from the combination of data from Canada and Italy. This was more ad hoc.

But just to answer your comment, I think it's inconceivable that a prospect of study could ever be large enough to answer these questions.

There was earlier talk about case cohort studies and about nested cohort studies. A nested case control study is one in which the cases and

controls are drawn from a follow-up study and one just samples a proportion of the non-cases, a small proportion.

But they could never be large enough. One has to use case control methods.

There are case control data in existence in this country concerning omeprazole. The prevalence of omeprazole exposure is high enough that if there is any specific birth defect, let's say, an encephaly (phonetic) or spina bifida or cleft anomalies or phocomelia that could be evaluated quite rapidly and quite efficiently in existing databases or that could be evaluated pretty soon in case control studies.

DR. ELASHOFF: But apparently has not been, according to your comments.

DR. SHAPIRO: You really need a prior hypothesis first. I mean there is a whole array of 10,000 different birth defects, and you can't go just fishing for one of them because if you fish you'll find something. Just on ordinary probability theory, you need a plausible hypothesis, and as far as I'm aware none exist.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: Given your comments about the risk in pregnancy, right now as the NDA label has on

it, the one that has been submitted, if pregnant or breast feeding, ask a health professional before use. then it says, "May cause damage to your unborn or nursing child."

Those two, it would seem to me that that first statement shouldn't go along with the second statement, that it would be "do not use if you are pregnant."

DR. SHAPIRO: Yeah, there's been reference to the one. So this is another reference. No one today would dare market a drug without a warning to pregnant women even if there's no evidence that it's dangerous for pregnant women.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I will make some comments. First, comparing H2 blockers and PPI, I think there is a great difference between these agents, although they both inhibit acid secretion. It's a question of efficacy and also a question of tolerance. You have a tolerance of an H2 blockers that in a way is protected for long-term use. You have not the same degree of acid inhibition. That was my first comment.

Then I will comment on what this danger is, hypergastrinemia. I think that it was published in the late '80s by a Finnish group concerning the

occurrence of ECL tumors in patients with pernicious anemia, and it was not so that patients having higher gastrin values than 500 picamolar had more frequent -- higher frequency of ECL tumors. They occurred already at 100 picamolar. It was a question of the degree of hypergastrinemia after a certain level and the duration of the hypergastrinemia.

Then I would say to Dr. Sachs again that in the eight --

CHAIRMAN BRASS: I called on you because he wasn't in the room.

(Laughter.)

DR. UDEN: Okay. It was a study in the late '80s showing that loxtadin (phonetic), a so-called unsurmountable H2 blocker, induced ECL tumors in mouse. So it is not correct that you don't see such tumors during hypergastrinemia in rat species.

And then my last comment will be on rebound acid hypersecretion because I was the first to describe it. It may be rather high acid hypersecretion, and one of the patients had also an increase in acid secretion from 40 to nearly 70 micromolar mL, which is values that you only see in patients with Zollinger-Ellison Syndrome.

CHAIRMAN BRASS: I'm sorry. Are you

talking about one patients from these studies or one patient from your previous experience?

DR. UDEN: I have described this patient in my paper.

And the duration of acid hypersecretion, it seems we have done a study, but we haven't published it. It lasts for about two months. It is declining from two weeks to two months.

CHAIRMAN BRASS: Dr. Steinberg.

DR. STEINBERG: My only concern as a gastroenterologist is the issues of the masking of disease, and that is Barrett's esophagus, and clearly the data have shown that there are going to be a certain percentage of these patients who get efficacy who will stay on this drug and not according to the labeling.

And so the question I have is to the esophagologist. Perhaps Dr. Castell can address this. What is the danger if a large number of users of ten milligrams of Prilosec over a long period of time; what is the danger, the public health danger of not diagnosing a certain small number of Barrett's patients who might then not be found to have dysplasia, and so forth and so on there? Do you have any feeling for this?

DR. CASTELL: Thank you, Bill.

As you know, this is from my approach is the issue about masking as Barrett's and whether we'll miss something, and it's as you know a highly controversial area. There are some people who say that we shouldn't even bother to look for it because it doesn't make any difference anyway in what you find.

We know that it's out there. We know that we miss it in people that don't get in for endoscopy, and you and I would like to endoscope everybody that has any heartburn because we think it's important to find it, and that's why I said earlier I would hope that is a drug like this were available over the counter that we could label it in such a way that it would hopefully get more people that we're missing now into the gastroenterologist. I don't know if that will work.

Now, I haven't answered your question yet. Whether it will make a difference or not, I don't know. Ten milligrams doesn't do much in terms of acid control, but it does a little more probably than the already available over-the-counter drugs.

But as I showed you from that Duke study, many patients with Barrett's have milder symptoms than

patients with erosive disease. We're already missing them with the available over-the-counter medications.

CHAIRMAN BRASS: Well, I think this also makes Dr. Cohen's question now very germane because, in fact, if you're exposing these patients at ten milligrams and they either heal if they have an erosive process or have the same treatment that they would get if they went to a gastroenterologist, you're masking nothing.

The question is whether there is an in between situation.

DR. STEINBERG: The question I have, Don, though is: would more of them come in to see a gastroenterologist or would fewer because a certain percentage will go on to take this medicine? Over 50 percent did not follow the labeling advice and won't ever come in because now they have a drug to help them.

DR. CASTELL: Yeah, and again, obviously I don't know the answer to that because I don't know what I don't know, and only time would tell us that.

I think, first of all, I want to acknowledge the agency for even being willing to discuss this question of a drug like this for treating GERD, if you will, because that's what we're talking

about here, and the sponsors for bringing the question to the agency.

I would hope that we could find a way if the drug is going to be approved to make the labeling effective so that it would, in fact, result in what I think should happen: more patients coming for evaluation rather than less.

DR. LEVINE: Could I just introduce Dr. Brian Reed (phonetic), who is another Barrett's esophagus expert?

DR. REED: Hi. I'm Brian Reed from the Fred Hutchinson Cancer Center.

I would like to suggest that the situation would get better. We would see more patients with Barrett's esophagus than we do under the existing circumstances. Why do I say that? Because the published data now say we only see five percent of the patients with Barrett's esophagus who are out there who can be detected by autopsy studies.

We only see at most five percent of curable cancers. They usually come in with incurable cancers, and so there's a huge 95 percent that aren't coming in, and I think that an appropriate labeling could increase that.

So relative to what we're doing now,

there's very little down side risk and a lot of potential with good labeling.

DR. STEINBERG: But people aren't following the labeling. That's what the study shows so far. A greater percentage of those that are using it to prevent illness are not following the labeling.

DR. REED: Are you referring to these studies here?

DR. STEINBERG: Yeah, the study that was shown here.

DR. REED: Just two comments. Even if the percentage were what it is and they did follow the labeling, that would be an enormous increase over five percent, and I think people are talking about revising the labeling, but I'm not involved in those discussions.

CHAIRMAN BRASS: Well, maybe I can pose the issue a slightly different way as a standard of care issue. Let's say a primary care physician or gastroenterologist had a patient with heartburn that was suppressed with a pump inhibitor. When they went off the pump inhibitor they had recurrence. Put them back on the pump inhibitor, they're fine.

Would that patient require any additional therapy other than continuation of the pump inhibitor?

DR. CASTELL: Are you suggesting after they've been seen by a physician?

CHAIRMAN BRASS: Yes, or a physician has seen them and says, "Here's your piece of paper. Go take your" -- you know, if it makes it go away, make it go away.

So if the patient feels better on a pump inhibitor, clearly doesn't feel good when they're not on a pump inhibitor; so they have some disease, whatever label you want to call it. But if they are symptomatically relieved by a pump inhibitor, is that fine? Would a physician simply continue the chronic use of the pump inhibitor, or does the standard of care require further diagnostic evaluation of that patient?

Because to me that's the central question. If there's chronic use in the out-patient setting, you get better and you recapitulate what's seen by a physician. If you're seen by a physician, no problem. And if you're not relieved, then you'll go see the physician.

My concern is if we're denied standard of care by giving symptomatic relief or not.

Dr. Cohen.

DR. COHEN: And that's really one of the

important issues, and I don't think you can answer that question at this point without knowing the effect of the ten milligram dose, which is very efficacious. It's very good in preventing the symptom of heartburn at that dose for the two-week period.

But what I'm asking is what is the effect on the mucosa in the 30 to 40 percent of patients that Dr. Castell said may have erosions, and that would help us know what the standard of care is, and that's an easy study to do.

CHAIRMAN BRASS: But you wouldn't know that as a practitioner unless you did an endoscopy. If the patient felt better on a trial of pump inhibitor regardless of dose --

DR. COHEN: But you would know if at that dose that's a healing dose and you can leave the patient on, or you would know at that dose you're getting continued chronic erosive disease with only relief of symptoms, and you can have a discrepancy or a separation of symptom relief and healing, and that's the issue.

CHAIRMAN BRASS: We saw some data at 20 that showed a healing rate, but it wasn't 100 percent.

DR. COHEN: No, 20 heals and maintains healing, is excellent in that effect, and it's used

that way. But the question is does ten heal and can ten maintain healing or does the physician have to do something different at the end of the two weeks or four weeks.

CHAIRMAN BRASS: Does sponsor have data from your earlier development program for healing intent?

DR. LEVINE: Based on the development program, we did not test ten milligrams in erosive esophagitis.

DR. CASTELL: Dr. Brass, can I give you another perspective on what I think you were asking?

From my point of view, if, in fact, this were to occur and it brought the patients to the gastroenterologist, what did you call us, informed intermediaries or something like that? Thank you very much. I didn't know that.

If it brought the patient to the gastroenterologist and an endoscopy was performed that ruled out Barrett's -- and, by the way, we're very close to being able to do that with a skinny endoscope through the nose, a nasogastric endoscope -- and we ruled out Barrett's, then I would be absolutely comfortable telling the patient if that dose of the drug ws working for your symptoms, you can stay with

it.

CHAIRMAN BRASS: But that seems to imply that the standard of care requires a physician evaluation to make that decision. Symptom relief is not adequate to meet the standard of clinical care.

Yes?

DR. ROBINSON: As a person who knows what physicians are doing in the community because I spend my life teaching them and speaking to them, I can tell you that although perhaps a lot of gastroenterologists wish that physicians in the community were sending all of their patients who don't do well or who do well on therapy and then relapse to have endoscopy, that, in fact, is not the case.

In fact, what doctors do is some of them send their patients for endoscopy, and I would suspect the great majority do not. The great majority of doctors continue therapy that is symptomatically effective, whatever therapy it may be, and never investigate the patients unless there is some alarm symptom.

So I don't think we're going to be changing that by adding another drug which also blocks acid secretion.

DR. COHEN: But, Dr. Robinson, they're

using a dose of the drug that heals the mucosa. So they may use it. Empirically it's still healing the tissue.

DR. ROBINSON: Well, far be it from me to tell Dr. Cohen anything about the esophagus, who, after all, wrote the book, but I would say that I at least am not so sure I care whether patients are healed or not because I know of no data that shows that people who have tiny, little erosions that remain unhealed have any untoward consequences.

That is, they don't seem to develop cancer, Barrett's or anything else, and in fact, the data I'm aware of suggest -- I think Don could address this -- that people who feel well, who are symptomatic over the long haul as a group do very well, and that people who are not controlled symptomatically are the ones who do not do well.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: I guess my concern is just adding another class of drugs for heartburn that's going to be available over the counter. You know, from a primary care standpoint I would hate for somebody that's tried Maalox and then tried another antacid and then has tried an H2 receptor blocker to have another choice that's available over the counter

that might delay them coming in and getting scoped or talking with someone else about it.

And then to follow up on what Dr. Brass said about having somebody that's on Prilosec and then they go off and then they're put back on it and they get relief, does that necessarily show that they don't have H. pylori or something else that's going on that we should be treating?

CHAIRMAN BRASS: Dr. Uden?

DR. UDEN: If you want to finish this discussion, mine is going to be about rebound hyperacidity.

CHAIRMAN BRASS: Dr. Steinberg.

DR. STEINBERG: Back to your question, I don't think there is a standard of care. It really depends on the referring doc. Some internists and family physicians are very aggressive about sending to the gastroenterologist, who is the consultant, and the gastroenterologist winds up taking a look down, and some are not. And so I don't think there's a standard of care, nor should there be a standard of care because we don't have the data to even decide who we should scope, when we should scope.

We're worried about Barrett's, but having scoped a lot of people over many years, I have yet to

pick up, except for the initial endoscopy when they present with dysphasia, somebody who gets into trouble. You have to read the big studies to show a few cases.

CHAIRMAN BRASS: Well, at an internist, that's certainly been my impression of the literature, that the justification for a screen endoscopy particularly in young people is just really low.

DR. COHEN: I want to clarify my point. I am not as concerned as Dr. Gilliam about patients having a ten milligram dose to take. All I would like to know is if they're taking it what the outcome is going to be, and I think the sponsor -- if I knew that from the sponsor, it would be reassuring, and it would be helpful, but I'm not concerned about giving somebody that dose to take if I knew what was going on with the mucosa.

CHAIRMAN BRASS: Okay. Dr. Uden.

DR. UDEN: I have a question about the clinical picture of rebound hyperacidity. Let's say somebody takes either ten or 20 milligrams of omeprazole for 25 days that I saw in the study and they discontinue it. If they have rebound hyperacidity, does that present then as heartburn, and is that then a reason for them to use more omeprazole?

How does rebound hyperacidity present clinically?

DR. LEVINE: May I address that? We have data from our studies if I could share that with you.

If I could please have slide 40. Could I have the mic on, please? Can you hear me?

Okay. This is my back-up 40. That's the wrong slide set.

What I want to be able to present is just what the baseline heartburn severity was. As part of the studies where patients had the option to dose on multiple days, what we then did at the end was do a placebo run-out, if you will, a two-week follow-up to assess what happened to their symptoms.

The existing literature, just for background, looks exclusively at acid secretion with no effort to correlate to symptoms. Our studies have the weakness because we do not have pH data to look at acid hyper secretion, but we do have the ability to look at that. We may not be able to get the slide.

But the point that I wanted to make was that at baseline we measured heartburn on a four grade scale. About 30 percent of the individuals at baseline before treatment had severe. So there would be no way to assess them at run-out as to whether or not they got worse.

So about two-thirds of the patients had mild or moderate heartburn, and what we did evaluate -- I think we can just close the slides down, please -- what we were able to do is look at across the 20 milligram, ten milligram, and placebo group, look to see whether or not there was any evidence within the group for worse heartburn than baseline after treatment. We could not demonstrate that.

What we also looked at was the number of episodes that they had, again, following treatment withdrawal versus baseline, and again, across groups we could not demonstrate any difference.

DR. UDEN: But logically rebound hyperacidity does occur, correct? And -- it does not?

CHAIRMAN BRASS: Microphone, microphone.

DR. LEVINE: I can speak to that as well. I won't try with another slide, but the data that we have from the literature is that at doses of 20 milligrams one cannot measure that. So it's usually you're getting to at least 40 milligrams for sustained periods of time when you actually elicit that phenomenon.

DR. UDEN: Thank you.

DR. STEINBERG: How long does it last when you do get rebound? Is that just a very transient

phenomenon lasting a day or two or is that something that persists?

DR. LEVINE: You know, I think it's a field that, first of all, you can argue whether or not additional work should be done because it's of uncertain clinical relevance, but the available data I would say are limited. So we don't know that.

In one of the studies where we looked at acid hypersecretion following two years of very, very high doses of omeprazole, 80 milligrams a day for a year followed by 40 milligrams, there was a follow-up done approximately three months after the conclusion, and the acid hypersecretion had normalized, which had been demonstrated within the first week, but we don't know when it stopped.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: As I said, it lasts up to two months, and then a question of dose. It is a question of degree of acid inhibition and hypergastrinemia. So if you use a low dose, fewer patients will have rebound acid hypersecretion, and it's a question of duration of the treatment. The shorter the time the less the rebound hypersecretion.

But if you examine enough patients, you will see it also at the short periods, I think.

CHAIRMAN BRASS: I'm going --

DR. COHEN: I would just comment that a 20 percent acid inhibition for ten days, you're not going to get very much acid rebound. I just think it's a non-event.

CHAIRMAN BRASS: I think what I'd like to do is now call the question, please.

DR. DOUGLAS: As a non-voting member, I guess my job is to be a devil's advocate, and I'd just like to be a little devilish if you don't mind.

I don't think there's been enough discussion about the potential for genotoxicity and tumorigenicity. The question has been raised by the FDA, and as a genetic toxicologist, I look at the animal toxicology data that was given in this package from FDA. In fact, it's not data. It's just a description of the data, and it raises a number of questions in my mind.

And I presume this data was presented in support of the original request for application for prescription use by the sponsor, and I think had it been today rather than whenever it was, ten or 12 years ago, that there would be a much better data package and there would be fewer questions left in my mind.

And I think despite the fact that there has been millions of prescriptions, it's always true that if you're not looking for the right thing, absence of evidence is not evidence of absence.

Now, this chemical causes most bone marrow micronucleus and chromosomal aberrations, and it's been shown through a survey of the literature in a published paper that chemicals that cause that effect have a 75 percent chance of causing germ cell effects, causing domino lethal effects, for example.

Now, there was a study, a reproductive toxicity study that was cited here where male and female rats were treated at 5.6 to 60 times the human dose. I don't know exactly what that -- whether it's 20 or ten or 40. So these animals are treated prior to conception and then post conception and on into the next generation.

But there was no effects in the treated animals, but in their offspring it produced fetal toxicity, postnatal developmental toxicity as evidenced by dose related increase in post implantation losses, decreases in the number of viable fetuses, decreases in the number of viable pups, decreases in survival of pups, and so on, and in a further study, postnatal behavioral development

effects as well.

So the fact that there is limited evidence here of some sort of effect, you can't specify in that type of a study, in a one generation reproductive toxicity study. You can't specify exactly what the effects were due to, and I didn't have the benefit of seeing the data that was given to Dr. Shapiro. So I can't really comment further.

But taken together the fact that we have a bone marrow micronucleus study which suggests, but only suggests, that there could be germ cell effects, and there's effects in this reproductive study that have been shown. I would think I would be concerned about unrecognized pregnancy loss. So not just if you're pregnant don't take it, but pregnancies that you don't know you're pregnant but you lose the conception.

CHAIRMAN BRASS: Dr. Shapiro, would you like to provide some context or alternative?

DR. SHAPIRO: Yes. The experimental data that have been referred to were extraordinary high doses in the rat and doses which were many multiples of the human dose in the rabbit.

The sponsor argued, I think, correctly that there was a mechanistic explanation for the

increased fetal loss, which was that these animals at these doses became profoundly sick, didn't eat properly, and were unhealthy animals, and unhealthy animals have increased fetal loss.

That explanation struck me as plausible, and they may want to add to it.

The epidemiological evidence, as I've said, is inconclusive, but gives no evidence of an increase of an increased risk. If one is talking specifically about fetal loss, the issues are spontaneous abortion, inhibited development or premature birth or stillbirth.

For spontaneous abortion, at least 50 percent of spontaneous abortions have major chromosomal anomalies, well over 50 percent, which is probably why they abort. This means that if one wants to study this issue, it would call for an ad hoc case control study of women who abort and the controls, and such a study could be done, but it's up to this panel to decide whether the evidence is persuasive to warrant such a recommendation.

For the other outcomes, I don't think that the animal data provides sufficient grounds to recommend that studies be done in human beings at the moment, but others might disagree with me.

On the issue of birth defects and germ cell effects, it would be necessary to mount case control studies concerning the specific defects that are alleged to be placed at increased risk by this drug.

CHAIRMAN BRASS: If I could just let the sponsor -- if there's any information I could provide and then I'll come back to that.

DR. LEVINE: Let me introduce Dr. Lewis Kinter, who's our preclinical scientist lead.

DR. KINTER: First, we would completely concur that the results in this repro. tox. battery that has been conducted, a very extensive repro. tox. battery at very high multiples of dose and exposure in both rabbits and rats, there is only evidence of increased abortion, and these developmental effects that have been alluded to only occur in the presence of significant and substantial maternal toxicity.

This is a bioassay system, and unfortunately because it's a bioassay system, when you introduce the confounding variables of significant maternal toxicity, it's now simply not possible to separate the two, and in this particular case we know that these effects of material toxicity with the loss in body weight and the decrease in food consumption