Next slide.

This slide is from a study, a reference submitted by the sponsor, and this does use the mean pentagastrin stimulated peak acid output as the endpoint, and this is intended to show that there is an effect following a single does.

However, to maximize the pharmacodynamic effects of omeprazole, one needs to go out multiple doses. This study was done with a 30 milligram dose, although a similar pattern would be expected for other doses as well.

Next slide.

Now, I'd like to discuss the heartburn relief trials. To briefly review the demographics, these were frequent heartburn sufferers with a mean frequency of heartburn of 60 percent of days during the pre-study period. The average heartburn severity of participants was in the moderate range on a zero to three scale with zero being no heartburn and three being severe. Over 50 percent of the subjects had moderate to severe heartburn.

This slide shows the primary efficacy endpoint of sustained complete relief for the first episode and first dose of drug, and as you can see, the percent of subjects with sustained complete relief

is not meaningfully different between placebo, omeprazole ten and 20 milligrams in both studies.

Next slide.

Secondary endpoints for the first dose were inconsistent at those endpoints of sustained adequate relief, complete relief within an hour, adequate relief within an hour, and overall assessment.

And I would want to add here that while sustained adequate relief was a primary efficacy endpoint in previous heartburn submissions, it was not the only evidence to form the basis of approval and the totality of other submissions out of context is difficult to compare to a current submission.

Next slide.

The sponsor has discussed the secondary analysis of all treated episodes, and before we can really fully understand the meaning of those results, and that question has been alluded to earlier today, one needs to consider what the extent of exposure to drug was over the 14-day study period.

Almost 90 percent of subjects in these studies took more than three doses of medication during the 14-day period, and as we've discussed, results beyond the first episode will be confounded by

the pharmacodynamic carryover effects from prior doses.

As the next slide will show, no benefit was seen for the episodic cases. The agency requested that the sponsor do an additional analysis of all episode that were separated by at least four days from a previous dose of omeprazole. This was felt to allow for inclusion of as much data as possible, but also minimizing the extent of carryover pharmacodynamic effect and acid suppression that would be associated with prior doses for the indication of occasional relief of episodic heartburn.

And as this slide shows, the percent of subjects with sustained complete relief was not meaningfully different between placebo, omeprazole ten and omeprazole 20 milligrams at this analysis.

There were additional heartburn relief studies submitted to the IND. There were three. These were large studies with a total of over 11,000 subjects, and no efficacy was demonstrated at the study endpoints that included sustained complete relief, sustained adequate relief, overall assessment of study medication, and back-up medication usage.

In summary, there were five studies of episodic heartburn relief which failed at the primary

analyses. The all episodes analysis, taking into account carryover effect, failed to demonstrate efficacy for the occasional episodic usage.

Next we'll discussion prevention of the meal induced heartburn studies. This slide shows the primary efficacy endpoint for four-hour post meal heartburn free period, and similar to the display earlier, study 006 does show a relatively small therapeutic gain with statistical significance, while study 005 has a yet smaller therapeutic gain which does not achieve statistical significance for either dose.

Next slide.

Secondary endpoints included overall assessment of medication, maximum severity score, back-up medication use, average symptom severity, and reduction of maximum severity score. There was some supportive data -- some supportive results at the secondary endpoints for the 20 milligram dose. However, the ten milligram dose had some support only for the endpoint of maximum severity score, with the other four endpoints noted here, lacking any support for the ten milligram dose.

In conclusion, Prilosec I at a 20 milligram dose may have marginal efficacy for the

prevention of heartburn when taken one hour before a heartburn inducing meal, while the ten milligram dose lacks replicated efficacy for primary and most meaningful secondary endpoints.

Outstanding issues include the lack of replication of results; the small therapeutic gain that has been alluded to earlier today compared to placebo; the potential for consumer confusion, which I think has also been alluded to earlier in judging a product that may be approved for prevention of heartburn where there's a lack of efficacy for treatment; and finally, the pharmacodynamics as discussed do favor chronic usage of this product.

Next we'll review the 24-hour prevention studies. This is in fact, a new indication, the concept of 24-hour prevention of symptoms over a period of time, and of course, the question must be asked: is this, in fact, management of GERD or occasional episodic heartburn?

The entry criteria for these subjects included heartburn of greater than one month's duration and heartburn at least two days per week. As has been mentioned earlier, subjects had to have been responsive in the past to antacids or over-the-counter H2 receptor antagonists for enrollment which does

enrich the population for response.

Demographically, the subjects were, in fact, more strongly enriched for what we might call GERD sufferers with 80 percent of subjects having a baseline frequency of heartburn greater than 50 percent of days. Mean severity was between mild and moderate.

The primary efficacy endpoint, heartburn free over the 24 hours following the first morning does, did show meaningful differences between placebo and both ten and 20 milligrams of omeprazole.

Next slide.

The results on day 14 following 14 cumulative doses of omeprazole likewise showed meaningful difference between the placebo and omeprazole groups in both studies.

In summary, there were replicated, statistically significant differences compared to placebo for both doses, and as one might expect from the pharmacodynamics, the efficacy as measured by the therapeutic gain compared to placebo did increase over time. On day one, going across studies and across doses, the gain was nine to 17 percent compared to placebo, while by day 14 the therapeutic gain was between 23 and 30 percent compared to placebo.

This slide has been displayed earlier and does point to the fat that the efficacy is lost over the two to three days following discontinuation of a 14-day therapeutic course of omeprazole, and it of course then begs the question: what does the consumer do following day two or three when they have return of their underlying chronic symptoms with an OTC product labeled for limited usage?

In conclusion, these 24-hour prevention studies were successful at demonstrating prevention of heartburn symptoms with both ten and 20 milligram doses. The efficacy did increase over time with the therapeutic benefit lost within three days of discontinuation of the study medication.

I'd like to briefly discuss prescription versus OTC, GERD versus heartburn. The current prescription Prilosec label for GERD states that the recommended adult oral dose for Prilosec for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 milligrams for up to four weeks.

For those patients with erosive esophagitis and accompanying symptoms due to GERD, the dose is the same, but the duration is longer, extending from four to eight weeks.

Next slide.

Within the submission, the sponsor defined GERD as representing a distinct physician diagnosed chronic disease characterized by acid reflux and attendant symptoms, usually heartburn, and requires four to eight weeks of treatment with omeprazole.

A little further in the submission episodic treatment of heartburn in an attempt to distinguish from GERD is different from the treatment of GERD, although it's not well clarified how one would differentiate heartburn from GERD on a spectrum and how the treatment would best be approached.

Going outside the submission, Dr. Castell has alluded to these definitions. One appears in the American Society of Gastrointestinal Endoscopy guidelines for practice of endoscopy, and a prominent gastrointestinal disease textbook edited by Schlesinger and Fortran both point to the fact that GERD may be defined as symptoms and/or tissue injury related to the reflux of gastric contents into the esophagus with heartburn being the typical symptom of GERD.

Next slide.

In an attempt to look at an operational definition of the practitioner, one may look to

studies of GERD and heartburn to see how the clinical investigators define the population to appropriately reflect the population for extrapolation.

And in a recently published study in the Archives of Internal Medicine, entitled "Efficacy of Omeprazole for the Treatment of Symptomatic Acid Reflux Disease Without Esophagitis," the entry criteria required the patients have a history of heartburn for over 12 months and episodes of moderate to severe heartburn on four or more days of the seven days prior to endoscopy and enrollment.

In summary, heartburn is the cardinal symptom of GERD, while GERD is a chronic condition that does require some medical judgment to assess and to differentiate from what might be operationally defined as a mild occasional heartburn, and likewise management of GERD is based on medical judgment, taking into account severity, chronicity and frequency of symptoms.

The rationale that underlies the current over-the-counter treatment of episodic heartburn can be described by the points on this slide, that is, the episodes for treatment should be discrete and occasional. The symptoms have to have been shown in analysis to be responsive to low dose therapy in an

attempt to distinguish it from a chronic prescription therapy for GERD, and the currently approved over-the-counter H2 receptor antagonists are approved at one-eighth to one-quarter of the daily prescription doses.

The OTC products are all effective for both relief of acute symptoms, as well as prevention, with no repeat carryover dose effects required for efficacy, and the limitation to usage on the label is for two weeks consecutively.

Currently the approved products, as noted earlier, include relief of episodic symptoms and prevention for symptoms that may occur in association with food or beverages that are known to cause heartburn for that individual, and it's clear that the indication is linked to specific episodes of heartburn.

The proposed Prilosec label includes relief of symptoms for which the submission is not demonstrated efficacy, as well as 24-hour prevention taken any time during the day. The studies that were submitted were morning dosing and would require extrapolation to assume that dose taken any time of day would give the same results.

The label further goes on to say that if preferred, one hour before those events that are

associated with occasional heartburn, such as consuming food and beverages, where there was marginal efficacy supported, the next point the revised label addresses that.

Next slide.

The 24-hour prevention is noted, is a new indication for OTC heartburn treatment, which is not episode based. Dosing any time of day is an unsupported new dosing instruction which also pulls the consumer away from the concept of episode based management and the non-meal related symptoms we skip.

And in the original proposed dose is the prescription dose. The new proposed dose is certainly closer to the prescription dose than the other over-the-counter remedies that are approved.

Next slide.

Overall conclusions, the pharmacodynamic properties of omeprazole would predict no efficacy for acute, short-term relief with progressive improvement in efficacy for prevention over time based on the delayed pharmacodynamic effects of the drug.

The results of the clinical studies do follow these predictions with a lack of efficacy at acute treatment of episodic heartburn, marginal efficacy at prevention when taken one hour before a h

inducing meal, and a prominent optimal role in the prevention of heartburn over time in the management of GERD, which as the sponsor stated is currently a physician diagnosed chronic disease requiring four to eight weeks of therapy.

And as Dr. Castell has alluded to, moving along a spectrum from occasional heartburn to GERD would be a difficult item to label if one were to move from the occasional heartburn to GERD arena for over-the-counter management.

Thank you.

DR. CHIN: Thank you.

Testing. Can you hear me in the back?

Good morning. I trust you're still heartburn free for the FDA presentations.

My name is Dr. Chin, and I'm from the Division of Over-the-counter Drug products.

These slides were prepared by Dr. Shetty and myself.

A very brief overview of actual use studies. Typically actual use studies have the following characteristics. They are all comer studies with minimal inclusion and exclusion criteria, with minimal health professional involvement and intervention.

Actual use studies are conducted for the purpose of demonstrating that the consumer can self-select and use the drug appropriately according only to the label.

Next.

In support of the Prilosec switch, there were five studies conducted under OTC-like conditions, and they can be grouped as self-selection and usage studies which are study 003, 067, and 022, and marketing and usage studies 014 and 091.

This is a summary slide, and I'm going to skip it.

An extensive list of inclusion and exclusion criteria were applied to the enrollees before they could participate in the actual studies. The ones of more relevance to this presentation include age limitations and prerequisites for use of heartburn medications.

The only thing of note is that study 067 recruited specifically for adolescents age 12 to 17, and they had to be treated with antacids or H2 blockers in the last month.

In study 014, there had to be use of oral OTC heartburn medications in the past three months, and in study 091, antacid, acid reducer use was of at

least two times per week in the last 30 days.

Almost all of the risk conditions on the proposed label was screened out, including pregnancy, medical conditions such as peptic ulcer disease, continuous abdominal pain, dysphasia, known hypersensitivity to omeprazole, and the medications listed here.

Female subjects had to undergo two or three urine pregnancy tests before and during the study and sign an agreement that they would use a reasonable contraceptive during the study.

Next.

A key feature of actual use studies is to demonstrate the subject's ability to self-select and use appropriately. Note that the subjects in studies 014 and 091 did not determine for themselves if the product was appropriate for them to use.

Studies 003 and 022 were the only studies where subjects did self-select. The rest of this presentation, therefore, will focus only on studies 003 and 022, as well as 067 which provided information on adolescents.

Proposed uses for OTC Prilosec are for prevention and relief. Directions were provided for prevention of systems for 24 hours for any time during

the day or for one hour before associated events, as well as for relief of symptoms. Regardless of use, the directions state do not take more than one tablet a day. Do not use for more than ten days in a row unless directed by a doctor.

The primary objective of these studies you know already, and these are measured by the primary endpoints which are the percent of subjects who take only one tablet per dose, take no more than one dose per day and take no more than ten consecutive days.

Demographics. Only study 003 recruited for subjects with low literacy levels. There were about ten percent in the ITT population. There was racial diversity in studies 003 and 022, and in all studies about 60 percent were female.

These studies were useful in telling us about the kind of OTC consumers who would use this product. As far as heartburn history, most of the subjects in this study had heartburn of longstanding duration. Two-thirds to three quarters of the subjects had heartburn for more than two years, and only about eight to 15 percent had heartburn for less than a year.

More than half of the subjects had heartburn at least two times per week.

Usage patterns. Users were also characterized by their use of the product. All subjects had to record the reason for product use in the product use journal. Subjects checked prespecified boxes that were marked, taken any time during the day, taken one hour before the event or taken for relief of symptoms. These data were compiled resulting in the distribution of subjects by these five mutually exclusive groups.

Over half of the subjects used the product for prevention and relief. About a third of the subjects used it for relief only, and about ten percent used it for prevention only.

I'd like to make a note here that the three prevention subgroups, prevention any time, prevention one hour before, and dual prevention had very few subjects involved. So they will be considered as one group from here onwards, as a prevention only group.

The results on correct use. As a reminder I've put up the three dosing directions. Subjects are assessed as consistent only if they complied with all three directions, and the overall results for consistency are 58 percent to 75 percent across all three studies.

I'd like to make a comment here about sponsor's data that was presented earlier. The results presented were by dosing day and by dosing occasions. The results that are presented in this slide are by subjects. So you can see about three percent to 22 percent of subjects did not use correctly according to any one of the dosing direction.

Conversely -- can you just go back one second? Okay. I get extra time.

(Laughter.)

DR. CHIN: Conversely, in totality, if you take all the subjects in the studies, 78 to 86 percent of all subjects did dose correctly according to any of each of these directions.

If we focus only on those who exceeded the ten-day limit, this graph shows across all three studies -- oops. Sorry. Okay. I'm sorry. There was a mix-up in the order here.

If we focus only on those who exceeded the ten-day limit across all three studies and if you look at the usage groups of those who use it for prevention only, 64 percent of people in this group exceeded the ten-day limit on use.

The people who used it for relief only

very rarely did that.

Next slide.

Now, if you look further at the maximum number of sequential days that the product was used, this slide graphically shows you the pattern between the prevention only users and the relief only users. Prevention only users are in yellow. Relief only users are in orange.

Eighty percent of the people who used it for relief only used it for one to two days consecutively.

Among the prevention only users, the profile is reversed. Over 51 percent took the drug for more than 25 sequential days.

Next slide.

So in summary, these are the specific conclusions from these studies. Fifty-eight to seventy-five percent of subjects in the three studies dosed according to all three dosing directions. The relief only users were more compliant than the prevention only users. Prevention only users were most noncompliant with the ten-day sequential use limit.

Study participants had heartburn of frequent occurrence and longstanding duration. I'd

like to offer that the study results may be biased since two to six percent of subjects with a risk profile were further excluded by criteria or study personnel. Another 18 to 25 percent of subjects were excluded from the ITT population for failure to return the product use journal or failure to complete certain elements of the product use journal.

One could postulate that the subjects who did not return or complete the use journal may be less motivated and may be more likely to be noncompliant, and if included in the ITT population would have impacted on the overall consistency results negatively.

Given the possibility that study results may be overly optimistic, the overall compliance with all three dosing directions is not impressive. It is of concern that the direction to exceed ten days of consecutive use was the one direction that was most ignored, especially among prevention users, the majority of whom were using it for beyond 25 days.

This is the final slide. The 24-hour any time prevention claim has, in essence, changed the nature of using this drug product for episode linked prevention to prevention of any number of episodes of heartburn within a set time period. Therefore, people

using it for this purpose may, in fact, have more frequent and longstanding heartburn suggestive of GERD.

Our concern is that if people with self-treating for GERD, the proposed label does not provide adequate information for such use. The question is: what potential harm, if any, may affect OTC consumers from chronic long-term use without benefit of a learned intermediary in such areas as possible misdiagnosis, delay in diagnosis and treatment, and/or suboptimal treatment of a chronic condition that may result in much more serious consequences.

Thank you for listening.

DR. AVIGAN: Good morning. My name is Mark Avigan. I'm a medical officer in the Division of Gastrointestinal and Coagulation Drug Products.

Next slide, please.

As you just heard from a number of our presenters, there are a number of characteristics of omeprazole and the proposed indication for OTC use which point to a rather strong likelihood of chronic or intermittent long-term use by some consumers. These include, first, the proposed labeling does not warn against long-term intermittent use.

Second, actual usage studies that have

been performed by the sponsor indicate that a significant percentage of subjects did not follow the label instructions by treating themselves beyond ten days.

Third, the maximal asset suppression only occurs after two or three days of daily 20 milligram doses, and then there's this lingering effect after cessation for a few days.

These properties are consistent with a role of the prevention of chronic heartburn rather than immediate relief by single table of occasional episodes of heartburn.

And finally, a significant percentage of subjects recruited into the OTC studies, in fact, had GERD. Heartburn associated with GERD is characterized, as we've heard, by a high recurrence rate when treatment is stopped. Therefore, we need to take into account the safety profile of long-term drug exposure in conjunction with short-term exposure as expressed in the labeling that the sponsor has proposed.

Next slide, please.

To pursue this the following topics will be discussed, and we will have some overlap with what has been presented by the sponsor. First, the safety

profile of the magnesium formulation in the OTC trials is presented in the NDA.

Second, safety issues raised by experience from the short term administration of the prescription enteric coat formulation in which a summary of clinical studies and the post marketing experience will be discussed. Special topics of concern that will be addressed today will be omeprazole induced liver toxicity, skin toxicity, bone marrow and immune system.

Third, the post marketing experience with the magnesium formulation of omeprazole will be discussed since, as was mentioned, since 1998 this formulation has been prescribed by physicians in Sweden, and special issues that we will discuss today in collaboration with the sponsor, the potential for drug-drug interactions between omeprazole and other drugs.

Next slide.

In addition, we'll make some reference to special populations, particularly pregnant women, and then the second part of this presentation will be an analysis of special concerns that have been raised about long-term continuous or intermittent administration of omeprazole.

We've somewhat arbitrarily defined this to mean continuous or intermittent exposure to the drug for more than 12 weeks and in some cases longer than the year or longer than that even.

The special topics that will be covered include masking of medically significant diseases, tumorigenicity and the implications of gastric acid rebound upon cessation of drug administration.

Finally, a summary of the conclusions that we have drawn surrounding these issues will be given.

There are four databases that are relevant for the short-term exposure analysis. First, the magnesium formulation clinical trials, the OTC NDA, that form the body of this application. Eight thousand one hundred and seventy-nine subjects were exposed to daily ten milligram or 20 milligram doses of the magnesium formulation, 5,000 of these to the 20 and 3,000 to the ten.

In most subjects the duration of treatment range between one and 14 days. A second database relevant to short-term omeprazole exposure is that derived from the clinical trials of the prescription formulation, and as was mentioned, 5,700 patients with specifically GERD, esophagitis and dyspepsia on doses between ten and 40 milligrams who are treated over the

duration between one day and 12 weeks are in this database.

And finally, there are the two post marketing databases that have been alluded to, the SafeTNet database, which is a compilation of adverse events until 1998, a lot of adverse events from the inception of the prescription by the sponsor, and then the database about the magnesium formulation in Sweden, 1998 and 1999.

So in that database there is a small number of adverse events that so far have been recorded in a background of over 11 million prescriptions, as the sponsor has mentioned.

Now, safety information gleaned from the OTC omeprazole magnesium clinical trials is limited by the following characteristics.

First, there is brief exposure to the drug.

Second, there is short-term monitoring of adverse events.

Third, the relatively small number of subjects precludes comprehensive assessment of rare adverse events since these may not be detectable in this size of a group of exposed individuals.

It has to be pointed out that there was

negligible representation of specific demographic groups, and I think the sponsor has already alluded to the adolescents, and in addition, Asian Americans only represented one percent of the exposed individuals, and as has been alluded to, this particular group has a higher rate of slow metabolizers, and I'll come back to this point in a moment.

The findings in the omeprazole magnesium clinical trials for the OTC indication are that the profile, a general profile, common adverse events, is similar to the prescription formulation, but in the database there are also cases of drug related adverse events, including serum sickness, urticaria, and elevations of AST, suggesting that these side effects are not exceedingly rare.

There are no apparent dose related differences in these adverse events. Causes for drug discontinuation in the groups included not surprisingly headache and rash.

Next slide.

Because there are large numbers of people in the United States who may self-medicate for heartburn symptoms only, without supervision of the physician, it is necessary to insure that omeprazole meets a very high stringency of safety. In the case

of prescription usage, the benefit of treatment of significant medical conditions under the supervision of a physician outweighs the risk to develop drug toxicities, including those that are rare.

Because the benefit gained for the symptomatic treatment of occasional episodic symptoms is different, it is appropriate to revisit the profile of these toxicities which were previously found to be acceptable in the arena prescription treatment.

In synthesizing the four different sources of information concerning the safety profile, the short-term exposure to the drug, a number of toxicities have emerged as points for this discussion, and they're listed here. These are the ones we will just briefly focus on: hepatic, marrow suppression, angioedema and anaphylaxis, and finally drug-drug interactions.

The sponsor has provided a liver function assessment that was performed in four U.S. and five non-U.S. clinical trials. These studies included a rather small group of 1,400 patients. Treatment duration with omeprazole lasted between one and 60 weeks, and we can make the following general conclusions from these studies.

First, that LFT abnormalities are not dose

dependent, and secondly, most of these abnormalities are mild, transient, and not related to duration of treatment.

Nonetheless, as can be seen, a few patients with liver injury were detected in these trials. Transaminase elevations exceeded three times the upper limit of normal in five patients in the U.S. trials with respect to incidences at .58 and .18 percent.

No unexpectedly, the incidence of milder elevations of transaminase in both groups of these studies were higher. This finding supports the conclusion that there's a spectrum of transaminase elevations associated with exposure to the drug, and, in fact, the studies reveal that between 200,000 and 500,000 treated patients developed some transaminase elevations consistent with three times or greater elevations of hepatitis.

Now, in the post marketing SafeTNet database, there were 33 fatal cases, two which were assigned an A rating. This rating suggests a high probability of omeprazole toxicity since no other explanation of causality could be identified.

Of the 227 liver toxic serious adverse events, four were assigned an A rating, and it has to

be pointed out that two of these four cases redeveloped hepatocellular necrosis after drug rechallenge, demonstrating the unequivocal linkage to omeprazole.

According to the FDA adverse event reporting system, two of 57 domestic toxic liver events linked to omeprazole have required liver transplantation. Therefore, the range of liver damage associated with omeprazole rarely includes individuals who have developed severe toxicity and organ failure, and, again, it is a rare event.

Unfortunately, the incidence of omeprazole linked liver damage and hepatic failure and death cannot be extrapolated from a voluntary reporting system because of the nature of such a system.

Next.

With regards to omeprazole associated toxic epidermal necrolysis and Stevens-Johnson Syndrome, there are variable time intervals between drug exposure and onset of symptoms. In the post marketing database there are 49 cases of this severe form of toxicity. Two have an A rating, and a nonfatal case redeveloped skin lesions upon drug rechallenge showing the strong linkage to the drug.

The incidence of white cell suppression by

omeprazole is high enough to be detectable in relatively small clinical trial populations. With regards to granulocytopenia in U.S. short-term trials that have been analyzed, the incidence was .2 percent, and in U.S. long-term trials it was .7 percent. For leukopenia, the incidence in U.S. short-term trials is .9 percent and in long-term trials 1.5 percent.

Related to these observations the intensive medical monitoring program in New Zealand and one-year follow-up of omeprazole treated patients revealed that .03 percent developed granulocytopenia. In fact, there was a case of aplastic anemia.

It's important, again, to emphasize that cause and effect is not -- is provided for each of these cases.

Now, the post marketing database -- next slide -- SafeTNet has revealed that there are 122 reported cases of omeprazole linked with suppression of white cells. These include 26 fatalities.

Of the 26 fatal cases, five were assigned an A rating. Of the 96 serious nonfatal cases, 35 were assigned an A rating.

So, in summary, similar to the other toxicities we visited so far, significant marrow suppression associated with granulocyte counts less

than 1.5 times ten to the ninth per liter occurs with an incidence between .3 and five per 1,000, and in fact, there are very rare cases of fatal agranulocytosis.

As is the case of these other events, omeprazole exposure has been associated with hypersensitivity reactions in clinical trials. In these trials at least there are four cases of angioedema and one of anaphylaxis. Three fatalities also occurred that were associated with drug hypersensitivity.

But much more commonly the incidence of urticaria has been measured to be between one and two per thousand.

Similarly, the reported incidence of hypersensitivity reactions, including angioedema and urticaria in omeprazole users has been detected in New Zealand.

Not surprisingly in the post marketing SafeTNet database there were 134 cases of angioedema and anaphylaxis. Seven of these were fatal, and nine of the nonfatal cases were assigned an A rating. Again, the A rating is the high probability linkage.

Next slide.

In summary, immediate hypersensitivity

reactions, which include urticaria, angioedema, wheezing and anaphylaxis are linked to omeprazole exposure. In the number that I've given most of those are on the milder end of the spectrum.

Next slide.

As I mentioned, omeprazole magnesium has been used as a prescription drug in Sweden since 1998, and there's a database of 219 voluntary reports. The only thing I want to say about these is that we see a similar pattern of side effects, including hypersensitivity reactions, angioedema, urticaria, anaphylactic shock, and there are some liver toxicity reports.

Other serious adverse events include toxic epidermal necrolysis and interstitial nephritis. Finally, cases of agranulocytosis have been reported.

Although substantial differences between the safety profiles of the enteric coated prescription formulation and the magnesium formulation have not emerged, it should be pointed out that subtle differences in formulation associated risk to develop rare adverse events cannot be measured because of undefined reporting biases and the relative short time that the magnesium formulation has been marketed.

Now, I'm going to just go through this

quickly. This has been alluded to before that omeprazole is metabolized by CYP 2C19.

Next slide.

An important influence on omeprazole clearance is the presence of a polymorphism, which inactivates the isoform, and this slow metabolizer phenotype is identified. The homozygous genotype actually is identified in only three percent of Caucasians, but it's present in 15 percent of Asians.

Other factors as has been mentioned which decreased clearance or aging and liver disease.

Again, the concept is that a reduction in clearance of the drug may be linked to two effects: first, a longer circulating half-life of the drug; and, second, increasing circulating drug levels when it's at steady state.

Because of the relatively short half-life of omeprazole, modest effects on clearance usually have small effects in circulating drug levels.

Alterations of activities of other drugs by omeprazole occur by two distinct mechanisms. One of these, changes of drug absorption, occurs due to the effects of the PPI and gastric liminal pH, and pertinent to this mechanism, there is increased absorption of digoxin and nifedipine, which in normal

individuals is a modest phenomenon.

However, it should be pointed out that certain individuals, such as those with renal failure, might be susceptible to digoxin toxicity, for example, even with subtle changes in blood levels.

In the opposite direction, decreased absorption of the anti-fungals by as much as 80 percent during treatment with omeprazole has been observed.

The second mechanism by which omeprazole interacts with some other drugs is through the inhibition of CYP 2C19, leading to their reduced clearance. Drugs which are cleared by this enzyme include diazepam, phenytoin, R-warfarin, and tolbutamide.

And during omeprazole treatment in study subjects, decreases in clearance of these drugs has ranged between ten and 55 percent. In the case of diazepam, an omeprazole induced reduction of this magnitude may be clinically significant in individuals who are particularly susceptible, such as those with liver disease.

Although omeprazole reduces clearance of these drugs only modestly in normal subjects, the potential for more pronounced alterations in

individuals who are slow metabolizers taking multiple drugs in which alternate clearance pathways have been saturated or in individuals with underlying medical conditions, such as liver disease, has not been entirely ruled out.

Let's move on. The adolescent point I think we both agree on, and I think we can just move forward.

Thank you.

Currently omeprazole is not approved for prescription use during pregnancy. There are a number of concerns regarding the use of omeprazole during pregnancy. These include the following points. The drug is associated with embryo fetal lethality in rabbits and reduced fetal weights in rats. In some experiments the drug has been found to be classed eugenic, and I will discuss this in a moment.

Nonetheless, it has to be said that voluntary reporting of females of child bearing age who have been issued 14 percent of the total prescriptions in the U.S. before, during, and after pregnancy has not revealed a signal consistent with human embryo-fetal toxicity.

With these observations, there is a need for a prospective or nested (phonetic) case control

studies in pregnant women to confirm safety of embryo-fetal exposure.

Now, let me switch gears to talk about the safety issues that surround long-term exposure of omeprazole, defined as exposure for more than 12 weeks, in some cases longer than a year. These include the masking phenomenon that we've heard about or in the delay of diagnosis of GERD related complications or conditions which require medical treatment. Such conditions include Barrett's esophagus, advanced stages of erosive esophagitis, esophageal dysplasia and adenocarcinoma.

A second issue is the undefined tumorigenic potential of drug induced prolonged hypergastrinemia and genotoxic properties related to the drug.

Finally, a concern has been raised about the potential for rapid and/or exaggerated rebound of gastric acid secretion after cessation of treatment that is tied to recurrence of reflux symptoms and/or mucosal inflammatory changes.

As I alluded to, it is likely that the long-term use of omeprazole will be common among undifferentiated OTC consumers with heartburn since, first, the proposed labeling does not warn against

long-term intermittent use;

Second, actual usage studies revealed longer than ten-day use in a significant percentage of people who use the drug for prevention;

Third, the pharmacodynamic properties of omeprazole lend themselves to this phenomenon;

And, finally, the history of symptoms of many of the OTC users, in fact, was that they had GERD.

Moreover, the concern about masking of underlying disease is justified from a number of anecdotal voluntary post marketing SafeTNet reports, which indicate that delay in diagnosis of gastric malignancy can occur due to temporary alleviation of symptoms or improvement in the appearance of gastric lesions.

In four of 49 cases of omeprazole linked gastric adenocarcinoma, there was a one to 12 month delay in diagnosis after treatment was started.

Here I'm just going to reemphasize a point made by the sponsor that the incidence of GERD complications is not trivial. Complications include Barrett's esophagus. You heard a ten percent number, that studies range anywhere from one to six percent of people with longstanding hypernon (phonetic).

And, again, as was mentioned, the symptoms of Barrett's esophagus really are not distinguishable from the undifferentiated population, which is a problem, but the conundrum, the hook is that current medical practice includes regular endoscopic surveillance in these folks for dysplasia and cancer.

A different complication of GERD is the composite of advanced stages of erosive esophagitis whose incidence ranges between 2.4 and 47 percent, depending on the studies. These individuals are at increased risk to develop clinically significant strictures and other fibrotic changes, and they're currently treated with aggressive pharmacotherapy to suppress acid.

Another complication that we've heard about today is the dysplasia and cancer complications where the problem of delay in diagnosis may have an important impact on outcome. These individuals are less than one percent of the total pool of people.

Next slide.

Because of the complications that I have mentioned, effective triage of individuals with GERD who require further diagnostic testing plays an important role in their management. The current standard of medical care includes the following

features.

Early physician referral is recommended for individuals with one or more of the following: dysphagia or odynophagia; persistent symptoms despite treatment; hematemesis, melena, rectal bleeding, or anemia, weight loss, anorexia, unexplained chest pain, chronic cough, hoarseness, asthma, chronic symptoms in patients at high risk for a Barrett's esophagus and finally need for continuous therapy.

Therefore, early physician evaluation of individuals with GERD who have features that put them at risk for underlying diseases is part of the current standard of medical care in the United States. Endoscopic evaluation may be warranted in many of these individuals.

In summary, physician referral after a failed treatment course or recurrence of GERD symptoms after cessation of therapy is thought to provide an important margin of safety to exclude significant underlying diseases.

Consistent with this perspective, the sponsor has made the following statement, and you can read it. In order to avoid the risk of possible complications -- and I think they basically said the same thing today -- that there has to be adequate

warning, and that consumers should be made aware of the indications, dose and duration of therapy, and in addition, they should have a clear understanding of when to seek medical attention

Issues of concern that have been raised that pertain to a potential carcinogenic effect of omeprazole in a large population of chronic users, even though ambiguity still surrounds some of these issues, it is important to raise them since the proposed treatment of occasional episodic heartburn requires an appraisal of risk relative to a newly calibrated benefit.

The concerns are based on the following proposed mechanisms. First, omeprazole induced hypergastrinemia has an atrophic effect on not only ECL cells, but other cells both within and outside the GI tract.

There is a potential by omeprazole induced hypergastrinemia to cause exaggerated growth promoting effects in the gastric mucosa of H. pylori infected individuals.

And finally, the genotoxic properties of omeprazole to susceptible cells both within and outside the GI tract may promote carcinogenesis.

Omeprazole induced hypergastrinemia is

characterized in the following manner. Many individuals manifest a two to fourfold increase in serum gastrin concentrations above baseline during chronic administration of the drug. This reverses upon cessation of treatment.

Increases of this magnitude are not observed during administration of low dose H2 receptor antagonists that are used to treat heartburn over the counter. A small percentage of individuals develop pronounced responses with greater than a fourfold increase of serum gastrin concentrations, some well above the upper limit of normal. These individuals may be particularly vulnerable to drug related cancer risks.

Factors which may increase serum gastrin responses to omeprazole in some individuals include H. pylori infection, the CYP 2C polymorphism, both the heterozygous, as well as the homozygous genotype. High dose and increased dosage infrequency of omeprazole and medical or physiologic conditions in which there is a reduced level of pretreatment gastric acid secretion.

The genotoxic potential of omeprazole is predicated on the following observations. First, in vivo and in vitro clastogenic effects have been noted

in drug exposed mouse and human bone marrow cells.

Second, chromosomal aberrations in omeprazole exposed human lymphocytes have been noted. Increased sister chromatin (phonetic) exchanges in peripheral lymphocytes of treated subjects have been reported in one set of experiments, but similar reports subsequently have not been forthcoming.

Despite these findings, DNA mutagenicity testing is measured by Ames Salmonella typhimirium tests, has been consistently negative.

Taken together in the face of positive results that omeprazole has some clastogenic properties, it is not possible to rule out genotoxicity associated with long-term exposure to the drug that may be linked to an increased risk of malignancy.

Now, taking a step back and analyzing the carcinogenic potential of omeprazole in humans, there are a number of significant limitations in our analysis. These include the size of controlled studies of individuals treated for longer than one year are small; precluding detection of rare drug related tumors. There's a lack of prospective or nested cohort studies to track patients treated with the drug over a very long period of time.

Detection of malignancy is limited by a predicted long lag phase after drug exposure, and in some cases high background rates of certain GI malignancies, for example, colon cancer are expected to drown out weak signals.

The SafeTNet, as needs to be emphasized, relies on a voluntary reporting which is not comprehensive. So we don't really get incidence figures out of SafeTNet data.

Finally, there's a lack of definition of groups that may be especially vulnerable to the carcinogenic effect of omeprazole. We heard that from the table. Such subsets of the population may be diluted by individuals who are not at increased risk for malignancy when exposed to the drug.

Nonetheless, taking these deficiencies into account, at present based on the composite of the clinical studies, the SafeTNet data and the literature, the development of omeprazole induced ECL cell hyperplasia in humans, unlike rats, has not been linked to progression of carcinoid tumors with the caveats that I've mentioned.

There is no apparent causal relationship between omeprazole and carcinoid tumors, gastric adenoma carcinoma, colorectal adenocarcinoma, and

other malignancies.

And finally, in H. pylori infected subject a clinically significant contribution by omeprazole to the development of gastric mucosal atrophy, intestinal metaplasia and dysplasia, which are the precursor lesions to cancer, has not been apparent.

Finally there has been concern about rebound of gastric acid secretion after cessation of omeprazole. This is based on the following points.

First, cessation of treatment is associated with rapid reappearance of inflammatory changes in individuals with erosive esophagitis.

Second, acid rebound is reflected by increases in both basal and pentagastrin stimulated acid secretion. This effect is variable, usually in people who have been on treatment for longer than a month, but it's not unique to PPIs. It also occurs with full dose H2 blockers.

And, lastly, acid rebound is self-limited after discontinuation of treatment with omeprazole. No information has been provided by the sponsor to determine whether acid rebound plays a role in some subjects to extend the duration of continuous OTC self-medication with omeprazole. Therefore, at this time it is not possible to assess whether conditions

which affect acid secretion, such as H. pylori, for example, may influence the development of acid rebound after cessation of treatment.

In addition, pronounced acid rebound in a subset of susceptible individuals cannot be excluded. Such a phenomenon would not necessarily be detected in studies which are in real small numbers of test subjects.

In conclusion, associated with the omeprazole magnesium application, there are a range of liver toxicities, toxicities idiosyncratic, usually mild, self-limited, and reversible upon drug withdrawal.

However, the drug does cause significant hepatocellular necrosis in a small percentage of individuals and has been linked to a few deaths.

Causality of significant hepatocellular damage has been confirmed and in a few cases with rechallenge by rechallenge with omeprazole.

Omeprazole is also associated with toxic epidermal necrolysis and Stevens-Johnson Syndrome. Although very rare, some cases have been linked to death.

The drug has been linked to agranularcytosis and other disorders of marrow

suppression. Life threatening suppression of leucocytes by omeprazole is very rare. Usually drug induced marrow suppression is reversible upon drug withdrawal.

Drug hypersensitivity occurs in some cases in which symptoms of urticaria, wheezing, rash, anaphylaxis and angioedema after omeprazole exposure have appeared, and the causality in some cases has been proven by drug rechallenge.

The incidence of these responses that have been detected in clinical trials may be as high as .5 per 1,000 users of the drug.

Now, even if serious adverse events and the fatalities related to them are rare, and I think we all agree that these are rare events, in a background of millions of OTC consumers per year, a significant number of these events are expected.

For example, if there are ten million OTC courses of omeprazole magnesium issued in a year and the rate of an SAE is one per 10,000, then 1,000 SAEs are predicted to occur. SAE, that is, serious adverse events.

We can skip that.

Currently omeprazole is categorized as a Class C drug because of embryo-fetal toxicity in an

animal model. In addition, there are concerns about the clastogenic properties of the drug. Nonetheless, off label use is not demonstrated to omeprazole linked loss of fertility or teratogenicity in humans.

With regards to long-term exposure, omeprazole may mask clinically significant GERD, complications which require early diagnosis and specific management. These include Barrett's esophagus, advanced erosive esophagitis, dysplasia, cancer, and gastric cancer.

The drug may induce significant hypergastrinemia and/or manifest toxicity in some individuals. Hypergastrinemic responses to omeprazole may be more pronounced in those with H. pylori infection or in slow metabolizers.

However, based on voluntary reporting a tumor association with omeprazole administration has not yet emerged. The possibility that there are oncogenic effects of the drug in susceptible groups who are exposed to the drug for very long periods of time has not been ruled out.

Rebound of acid secretion may encourage long-term usage in a subset of consumers. Upon cessation of treatment, rapid relapse of heartburn symptoms and/or esophageal inflammatory change is

predicted in some individuals with GERD.

Taken together the prescription use of omeprazole has relied on the presence of a professional health care provider for patient assessment, triage, and for further diagnostic testing and recognition and management of significant drug toxicity.

In the OTC setting there is no learned intermediary to enact these functions so that safe and effective use entirely depends on the effect on effective consumer labeling.

We want to be convinced that serious omeprazole magnesium induced toxicity even when rare is outweighed by the benefit of OTC treatment by symptomatic heartburn.

Furthermore, we are concerned whether serious toxicity will be recognized and effectively managed by OTC consumers without physician supervision.

Chronic empirical therapy prior to physician referral is inappropriate for a significant number of patients with GERD. We are concerned whether omeprazole magnesium can be targeted in an OTC setting to only those consumers for whom self-medication will have a meaningful benefit in the

absence of a significant risk for serious adverse events.

Conversely, we are concerned whether there are adequate safeguards protecting those for whom physician referral is indicated to justify OTC approval.

(Pause in proceedings.)

DR. LECHTER: Good morning. I'm Karen Lechter with the Division of Drug Marketing, Advertising, and Communication.

I'm going to talk as fast as I can. I understand our time is running out. I'm going to be talking about the label comprehension study and the addendum study, and to give you a little context, I'd like to point out that the regulations require that OTC labels be written in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension under customary conditions of purchase and use. For this reason, sponsors for switched products often perform label comprehension studies.

For Prilosec, there was one main label comprehension study and an addendum study. I won't go over the details of this. The sponsor has already discussed those, but I will point out that there were

four cohorts, one of which were persons who should not use the product without referring to a doctor before use. They were taking medications that were indicated on the label as requiring medical consultation or they were pregnant or nursing.

I will just present the most important results, not all of the results. When asked the purpose of the product, 99 percent said that it was prevention or relief. Sixty-five percent mentioned relief only. Eighteen percent mentioned prevention only, and 16 percent mentioned prevention and relief.

These results indicate that when asked what the product is for, most consumers think in terms of relief.

The information listed here was only moderately understood. I will not go over all of these with you. If you can read them fast, you will understand that there are some issues that were understood only in the low 80 percent range and could benefit from improvement in the labeling.

There was a significant troubling result. Seventy-five percent of Cohort IV, the persons who should see a doctor before using the product, incorrectly said that they would use the product to prevent and relieve heartburn. There were two

questions on this issue, one for prevention and one for relief. Only 21 percent of persons in that group were correct in saying that they would not use the product.

Because of this troubling result, an addendum study was conducted to determine if the wording of the question about self-use in Cohort IV contributed to the high rate of incorrect responses. The addendum study compared responses to the original self-use question with responses to a new self-use question. In this study there were 58 participants, 29 in each arm. All should have asked the doctor before using the product. They were pregnant, nursing, or taking the drugs mentioned on the label.

The addendum study questions were as follows. One arm was asked the original question: if you wanted to present heartburn, would you use Prilosec I yourself? They were also asked an identical question about relief.

The other arm was asked new questions. If you were a heartburn sufferer and you wanted to prevent heartburn, would it be okay for you personally to use Prilosec I yourself or not?

A similar question was asked about relief. It did not use the word "personally."

The new questions did improve the results. For the original question about prevention, 35 percent were correct. With the reworded question, 69 percent were correct. For the original question about relief, 31 percent were correct, with the reworded question, 59 percent were correct.

However, even with the reworded question, comprehension about self-use was low among those who should see a doctor before use.

There were additional questions asked. If the prior responses were not correct in this study, they dealt with whether the persons were actually taking the medications on the label, and they also were leading questions. Is there anything you would do prior to taking this product or not? And considering your current health and medications you are currently taking, would it be necessary for you to contact a doctor prior to using this product yourself or not?

The results of the leading questions have uncertain value, and therefore, we do not use those results in interpreting the responses to the questions.

The conclusions from the addendum study are that the group that should consult a physician

before use has problems understanding that they need to see a physician first. Only 59 percent to 69 percent of this group responded correctly to the new question about self-use.

Now I'll briefly talk about the product label. The label changed substantially after the label comprehension test, and the new label has not been tested. The committee members have copies of the tested label and the NDA label in their packets. It's two sheets stapled together if you want to refer to those.

And then there's a more recent label that was submitted recently that we have not had an opportunity to review. I'll just briefly go over some of the differences in these labels because of the time constraint.

The NDA label, as opposed to the tested label had causes of symptoms, prevention, and allergy warning, a "do not use" section, a statement about not using with acid reducers, and some other additional information that did not appear on the tested label.

The NDA label specified the number of days in which to see a doctor, changed the number of days, said that to see a pharmacist as well as a doctor for certain questions; changed the wording about trouble

swallowing, pregnancy, directions for use, and storage instructions; reversed the order of other information; and bolded one of the warnings and included a symbol.

Therefore, there were many changes to the label after the label comprehension test. Because the new label was not tested, we don't know how well it will be understood by consumers.

In summary, consumers associate this product with relief. The fact that most consumers associate this product with relief is troubling, particularly since efficacy for this indication is questionable.

The data suggests a substantial use by persons who should consult a doctor first.

Some information is not strongly communicated. They were listed on the prior slides. I won't go over all of those at this time, and the most recent label has not been tested. It varies significantly from the tested label, and in light of the changes that the sponsor presented today, we particularly don't know if consumers will understand what the product is for.

CHAIRMAN BRASS: Thank you very much.

We now have time for questions from the committee to the FDA. I would again like to remind

the committee that there will be ample opportunity for general discussion this afternoon, and I would like to focus the discussion now on clarification of issues directly relevant to the FDA's presentation.

Dr. Sachs. Microphone.

DR. GEORGE SACHS: Three hundred and forty-five points on these presentations. (a) --

CHAIRMAN BRASS: Round it off to one.

DR. GEORGE SACHS: Right. Any genotoxic studies that have been performed on omeprazole in vitro have shown it to be negative unless there's an extremely high dose with conversion to the actual active drug.

Two, in pernicious anemia patients, there is no history of increased gastric cancer or increased carcinoids, and the gastrin levels in PA patients is much higher than you see with omeprazole treatment.

CHAIRMAN BRASS: Any comments from the FDA?

Okay. Ms. Cohen.

Microphone. Thank you for making me feel needed.

DR. AVIGAN: I think that the hypergastrinemia point is an excellent point. The only caveat to that is the time line of when the

hypergastrinemia occurs in life.

Someone else at the table has raised the problem of what about early in life exposure to high gastrin levels. PA is a disease typically of older people. So one of the problems with these cancer questions based upon the way we understand the disease is the long lag phase and the multiplicity of mutations that have to accrue in particular cells over time to get the phenotype.

So, again, I agree with the statement, but there is a caveat.

CHAIRMAN BRASS: Ms. Cohen.

MS. COHEN: I have one question, but since I'm the only consumer member, I hope I'll have time this afternoon to address my questions to the presenters, but I do have a question for the FDA in regards to what Dr. Waldum said about the studies of rats and the study of humans, and I don't think there was any answer. Now, do you feel that what he has presented in terms of his study, that there is a causation that you can track between rats and humans? Is this something that's essential to our understanding of what needs to be done?

I'm glad I asked the question.

CHAIRMAN BRASS: Could you identify

yourself, please?

DR. DeGEORGE: Joseph DeGeorge, Associate Director for Pharmacology and Toxicology.

Actually, I don't think we can answer your question specifically about any causal link or any specific link between the animal findings and humans. There is, it's my understanding, evidence of a hyperplasia across species, but the next step is the link that people would like to know the answer to. We just don't have that data.

CHAIRMAN BRASS: Dr. Mirsalis.

DR. MIRSALIS: Yes. I'd like to ak a question or a clarification about the statement that was made that there is in vivo genotoxicity. It's stated one place in the briefing book and again in the presentation you say in vivo chromosomal aberrations, and yet in FDA's own briefing book they state no significant increase in chromosomal aberrations were noted.

I did a National Library of Medicine search and can't find anything in the peer reviewed literature. In fact, the data is overwhelming in the literature that there is no in vivo genotoxic response, and data hasn't been provided to us.

I'm just curious what that statement is

based upon.

CHAIRMAN BRASS: Thank you all.

DR. CHOUDARY: I'm Jaspi Choudary, a pharmacologist from Gastrointestinal and Coagulation Drug Products Division.

Those statements are there in the labeling also. The in vivo tests referred to the chromosome aberration test in the mice and the micro nucleus test in the mice. Those are all there in the NDA labeling for omeprazole, and those stand up.

DR. MIRSALIS: Could I comment on that then? We haven't been provided that data at all to look at.

DR. CHOUDARY: That is there in the labeling that has been reviewed already in the NDA review dating 11 years back, and it still stands.

CHAIRMAN BRASS: Thank you.

Dr. Robinson.

DR. ROBINSON: For a long time we've all been told about the dangers of drug-drug interactions and not only with the potential drug-drug interactions with this drug, but other drugs as well, and I want to know whether either the agency or the sponsor has any data on the actual occurred on drug-drug interactions with omeprazole because it seems to me if we're going

to talk about this as a risk, we need to have some idea of what kind of quantitative risk this might be.

DR. AVIGAN: Well, I think we were not -- I was not really disagreeing with what the sponsor has said. Again, it was a caveat that I was mentioning, which was that these drug-drug interactions have been tested in a very confined way to specific kinds of subjects.

My concern is that when you take this drug out of the arena of a learned intermediary and you have an outlier individual who has multiple simultaneous reasons for abnormal clearance, there may be an additive or a synergistic effect, which is not measurable in a more simple case where there's just two drugs being tested in a normal background.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I have a couple of comments. First, on pernicious anemia, I think that it is quite clear that you have a two to three times increased risk of carcinoma in patients with pernicious anemia, and it's also well documented that you have an increased risk of ECL cell carcinoids. I think there's no doubt about that.

And so it's difficult to me to understand what you mean when you say that there is no indication

that hypergastrinemia in UCC cell lumas (phonetic) in man because also patients have Zollinger-Ellison Syndrome not only as a part of endocrine neoplasia, but also chellery (phonetic).

So patients -- every condition with hypergastrinemia in whatever species you know do develop ECL cell tumors when they have hypergastrinemia for a long enough time. It's well known that the studies on mice and dogs, that two low doses were used and, therefore, you had not adequate inhibition of gastric acid secretion, and therefore, you didn't see any tumors.

That's my first comment, and the second is relating to Helicobacter pylori. Since Dr. Sachs didn't know this Norwegian-British study about gastric carcinoma and the Helicobacter Pylori and gastrin, I suppose he does know that transgenic mice, moderately hypergastrinemic, when they develop gastric carcinoma and when they are infected with Helicobacter pylori, the gastrin value increases and the incidences of gastric carcinoma also increases.

So you have this connection both in man and in animals, and I have a question concerning this. It is claimed that you haven't seen any ECL cell tumors in patients treated with omeprazole. If you

look at the book from page 131, there are 14 cases.

CHAIRMAN BRASS: I'm sorry. Which book are you referring to?

DR. WALDUM: This white one.

CHAIRMAN BRASS: The sponsor's book.

DR. WALDUM: Yeah. On page 131, they stated that there were 14 cases of gastroduodenal carcinoids where they could not determine whether the patient had Zollinger-Ellison Syndrome or pernicious anemia, and they also state that some of them obviously have acid hypersecretion. I guess that they had gastric hypersecretion due to rebound, acid hypersecretion secondary to treatment, and also that actually these patients, these tumors actually show that the ECL cell tumors have been developed after treatment.

So it would be very interesting to have an independent look into these tumors, I think.

CHAIRMAN BRASS: Comment on that?

DR. AVIGAN: I think both the sponsor and the FDA would agree that sorting through these cases is very difficult, and when you read the narratives and look through them, just my general impression is that there are some cases which are, you know, clearly the diagnosis is made, and in other cases there's

still an open question mark.

So I think to be fair at this point it's a theoretical possibility, but I have not really so far, you know, found, you know, clear cases that could be linked by cause and effect, but that would be something that could be thought about in terms of how that could be looked for.

CHAIRMAN BRASS: Dr. Shapiro, did you have a question?

DR. SHAPIRO: I have 346 questions, but one of them was taken up already. The drug and drug interactions is one. My basic question is this: is that agranularcytosis, aplastic anemia, anaphylaxis, acute liver failure, and toxic epidermal necrolysis, and Stevens-Johnson Syndrome have all been mentioned as case reports possibly linked to the use of omeprazole. Case reports are notoriously unreliable. In my view they are sometimes, and then only occasionally, reliable for the generation of hypotheses. Beyond that, they tend to be systematically biased and exceedingly unreliable, and in all instances, they have to be confirmed by epidemiological data.

Are there any epidemiological data to indicate that omeprazole was associated with an

increased risk of agranularcytosis, aplastic anemia, anaphylaxis, et cetera? And if so, what is the magnitude of the association, and what is the incidence of these conditions among people who use omeprazole?

We know, for example, that the baseline incidence of aplastic anemia is two to four per million per year in the general population, and incidentally, none of your incidence figures included the time dimension at all, which makes them rather difficult to interpret.

Assuming even that there were an increased risk, what would be the public health implications of that increased risk for a drug which may turn out to be very useful in the management of heartburn?

CHAIRMAN BRASS: I will allow them to answer in just a second, but sine it's fresh on many of our minds, I would just like to reemphasize that the burden of proof of safety is on the sponsor, and that there's no burden on the FDA to provide lack of safety if a concern exists.

DR. SHAPIRO: Mr. Chairman, if the allegations are made that there may be a lack of safety, we need data to show that those allegations have some foundation.

DR. AVIGAN: As I alluded to, for those four rare events that were discussed, they were actually rated by the sponsor according to a lettering system A through D for causality, and I was not trying to build a case for numbers because I think we actually all agree that these are very rare events.

The most compelling A cases, which are the ones where causality has been linked, are ones where there is rechallenge, that is, single drug. For example, hives, zero to cariad (phonetic), a very clear example where there are cases where the drug is given. Hives develop within 12 hours. The drug is stopped. Hives disappear, and then the drug is given again as a rechallenge and the hives reappear.

There are similar cases, again, as anecdotal for each of the side effects that I mentioned, and the question about incidence is a fair question. On a population basis, clearly these events are rare. The reason why they were raised in this setting is that we're moving from a learned intermediary setting where rare complications might be recognized and managed to one where the OTC consumer has to take liability for recognition and for doing something about it.

And so it's a conceptual point that bears

some thought not on a population basis, but rather on an individual basis.

CHAIRMAN BRASS: Dr. Cantilena.

DR. CANTILENA: Yes. I just have two questions on the issue of drug-drug interactions, and the first one is I guess I'm hearing you say that you're not sure of the clinical significance of what could be up to, you know, 50 percent decrease in clearance as a result of the inhibition of CYP 2C19.

And I guess I heard you sort of qualify that by saying there could be subsets who have, you know, liver disease, et cetera, et cetera, but I guess I would like to sort of ask you then are your, you know, qualifications saying that in all likelihood that magnitude of a change for drugs such as phenytoin or, you know, diazepam are not likely to be clinically significant?

That is, you know, the first, you know, question because as I think all of us saw, there was a change in the label from the original label which had a couple of these drugs in there, and, you know, the final label or, you know, the one that's on the table now has, you know, dropped those drugs, and I'm hoping that they weren't dropped as a result of the FDA saying they're unlikely, you know, to be

clinically significant.

DR. AVIGAN: Let me clarify that point. There is a margin of safety in terms of the CYP ISO enzyme ability to metabolize. That's clear, and the sponsor is absolutely correct, I guess, in their data on test subjects to show that slow metabolizers still based on theoretical considerations can basically get rid of drugs through other alternate pathways.

But the problem is in a large population of users when you amplify the usage to people who have other reasons to not clear, then you have to consider different kinds of scenarios in terms of saturating those alternate pathways, and the potential that you run out of that margin of safety.

In cases where you have underlying liver disease, for example, as a concept point or people who are on multiple drugs. The idea there is if you have a learned intermediary, and I raise this as a question only, would that learned intermediary at least know or think about those issues in a patient who is a problem patient?

DR. CANTILENA: So if I could just follow, so are you in support of, you know, dropping that from a label because of, you know, low likelihood that it will be a problem?

DR. AVIGAN: I don't want to take a position on that now. I think I would rather keep away from the remedy because I would rather that that be discussed by the committee and later on.

DR. CANTILENA: Okay. Then the follow-up question is in someone who is, you know, homozygous, you know, PM for the enzyme, is, you know, the pathway that then becomes the most important, is that CYP 3A4 and are there questions in terms of interactions with substrates of the CYP 3A?

DR. AVIGAN: There might be.

CHAIRMAN BRASS: Dr. Steinberg.

DR. STEINBERG: Could you give us an estimate, if there is one, of the difference in toxicity as where it is between omeprazole and the data we have on that, and other medicines that already have been approved for OTC products, such as the H2 receptor antagonists, such as NSAIDS, et cetera?

Is this drug more dangerous, less dangerous? It appears to me it's a lot less dangerous than NSAIDS, which the FDA has approved, and multiple NSAIDS, if I'm correct, and H2 receptor antagonists have similar rare toxicities, to my knowledge.

DR. AVIGAN: You're correct, and I don't want to get into that argument.

CHAIRMAN BRASS: Well, can you comment on the order of magnitude comparisons of frequency, I think, which was --

DR. AVIGAN: Yes.

CHAIRMAN BRASS: -- I think, just in terms of information?

DR. AVIGAN: At first blush because, again, the problem that you're -- if you're asking me to be scientific, I don't have incidence data. We see with post marketing data there's a large pool of users and signals. We have no idea what the reporting bias is. So these are not incidence data. So it's a database from, let's say, one of the H2 blockers and a database for this. They're not really scientifically comparable. That's a very important point to realize.

But having said that, the general gestalt is for these acute effects which probably is not all that much difference in terms of the gestalt of it from what I see.

DR. STEINBERG: From the H2s, for instance.

DR. AVIGAN: Right. The separate issue of the longstanding exposure, chronic hypergastrinemia, that's slightly distinct and the way the

pharmacodynamic properties of the drug work; that's a slightly distinct issue.

DR. STEINBERG: I have another question of a toxicity that hasn't been or an adverse effect that hasn't been raised, and that is there have been reports of vitamin B12 malabsorption from the use of acid suppressors. Vitamin B12 as we take it is protein bound, and acid is needed to separate the B12 from the protein.

What information do we have on long-term use of omeprazole and clinically significant vitamin B12 problems, and has it been looked at even?

DR. AVIGAN: It has been looked at. There's a series of papers on that, and a general impression, and there are some experts here who could probably tell more about it than I can, but that there is not a problem.

CHAIRMAN BRASS: Dr. Lam.

DR. LAM: Is there actual safety data whether it is positive or negative in poor metabolizer that are described on the omeprazole? And if the data is negative, what would be the effect of specific inhibitor of CYP 2C19, and especially in terms of converting them into a poor metabolizer, and if that case they're more reliant on a CYP 3A4 pop way

(phonetic), what would be the effect of adding a CYP 3A4 inhibitor, which as erythromycin, which is available over the counter -- I mean not over the counter -- which is widely available to the regimen?

DR. AVIGAN: That was the point I was raising. I'm not aware of data about that. Again, the way the subjects are tested is that, you know, theoretically if you don't saturate the alternate pathways, then the patients or people who are slow metabolizers should have no effect on the drug because they don't even use that pathway.

The problem is starting to speculate about what happens when you sort of spill over and saturate pathways, and that, again, is just an open question.

DR. LAM: Okay, but we have no safety data in specific poor metabolizers at all whether it is negative or positive?

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: I'm going to go to a slightly different subject. I'm curious about whether FDA has had submitted to it to review data from an efficacy study designed for the new use label that the sponsor is proposing, specifically prevention due to food or beverage when taken only on days heartburn is expected, because I haven't seen any efficacy data

about that specifically.

And the second question is I have not heard any label comprehension data on this new proposed use, and I trust that's because you're hearing about this for the first time today as well. Can you confirm that?

DR. GOLDKIND: My understanding is the same as yours. There's no currently labeled products have that indication as you described it.

CHAIRMAN BRASS: No, I think the question was whether any of the existing submitted from the sponsor efficacy data are relevant to the indication as proposed.

DR. NEILL: Actually it's not whether they're relevant because we've got several studies that may be relevant, but none that are specific that were designed to answer the question: is the medication as proposed effective?

And while I would guess that that study, if done, might show a degree of effectiveness, my concern is for those intermittent users who might have more than a two or three day lag time between doses, who I'm extrapolating from the data that I have would not see much effectiveness, and then on the contrary, for patients who might be taking it daily, I've got

data that suggests that they're going to take it daily for a long time, and my concern in those people is they are a category of patient who would not be appropriate for OTC use because of the inability to self-select and to self-monitor for important co-morbid conditions, specifically GERD and Barrett's and are then not going to present for endoscopy and that learned intermediary intervention.

I've got no data on efficacy for the proposed indication at all.

DR. GOLDKIND: The data that would be relevant from these submissions would be the data on day one of the 14-day prevention studies. There was a difference between placebo in both doses for the percent of subjects who would be heartburn free for 24 hours following a dose at 8:00 a.m.

CHAIRMAN BRASS: Dr. Lechter, do you want to comment on the label question?

DR. LECHTER: The only label that we're aware of that was tested is the one that I described. You have the two in front of you. One was a tested label, and the other was the one submitted with the NDA, and now the one that they're discussing today is an even different one. We have not seen that one.

DR. NEILL: Just to follow up about the

efficacy data, while I agree with you that that might be the most appropriate piece of data that we have in front of us, my concern is that that data derives from a study in which that first use was not up to the consumer to choose, and the label that I have in front of me as proposed is on days when heartburn is expected.

And I don't know that my patients have the ability to know when to expect heartburn, and if that's not the case, then I would have expected studies like 171 and 183 where we would tell patients who have a history, "Don't try and predict whether it's coming. Take it every day for ten to 14 days."

DR. GOLDKIND: I share that concern and agree.

CHAIRMAN BRASS: Dr. Sachs, you had an additional comment?

DR. GEORGE SACHS: Yes.

CHAIRMAN BRASS: Microphone.

DR. GEORGE SACHS: Ms. Cohen asked a question about comparison of rats and people, and remember as well just incidentally that there are four such drugs now available on the market in the U.S. that have been subjected to not only a variety of animal studies at very high doses, approximately 100

times, even sometimes 1,000 times of what's given to people, and rats consistently give this ECL cell carcinoid carcinoma eventually because that cell in the rat continues to replicate and doesn't stop replicating. It is not an end cell, and there's much data in the dog, the mouse and man that ECL cells are end cells and, therefore, do not continue replication beyond a certain point of aging and maturation.

So I think it's very clear, given not just omeprazole from the early days, but with pantoprozole, lansoprazole, and rabeprazole, that the rat ECL cell rapid formation of ECL cell carcinoids and metastasis is a rate selector problem independent of dose given to any other animal species, and of course, all of those PPIs have had two year carcinistic studies in at least two species.

CHAIRMAN BRASS: Dr. Geller.

DR. GELLER: Hearing everything I've been hearing, what is the ideal way to take this drug if you have, indeed, heartburn and not GERD?

CHAIRMAN BRASS: If the FDA would like to answer, but again, I don't want a general discussion. I want focused on are there any issues about the FDA presentation that we can get addressed now. If you'd like to make a comment, feel free.

DR. GOLDKIND: The proposed label doesn't really address the efficacy data well, and I think a challenging discussion would be how one might label this product following the efficacy data. I don't have a solution to that problem.

CHAIRMAN BRASS: Do you have a rebuttal to Dr. Sachs or do you have a question for the FDA?

DR. WALDUM: No, only a remark.

CHAIRMAN BRASS: No. Save it for later, please.

Dr. Cohen, a general question for the FDA?

DR. COHEN: My question really focuses on the last question I was asked and a question to the FDA. Are you trying to make a distinction between GERD and heartburn? I don't see how you can do it. I don't know a difference, and I think if you filled the room with a group of Talmudic scholars I don't think they can tell you the difference.

There is no difference. GERD or gastroesophageal reflux is manifested by heartburn, and heartburn is the cardinal symptom of GERD. So it's the same, and I can't see how you can go about trying to argue this point. It's the same situation, same condition.

DR. GANLEY: Can I answer that or try to

answer that?

CHAIRMAN BRASS: Yes.

DR. GANLEY: Yeah, I think that's what we're trying to point out here, is that the current OTC market is for the treatment of episodic occasional heartburn or meal induced heartburn. This is going down another path.

I think we're coming to that agreement here. It's going to pull in people that have GERD. Our question to the committee is: is that acceptable?

We're taking a neutral position. We're asking your opinion on it. We're not taking a position. I think that's what the presentations have tried to pull out. So that's a question for the committee to answer. Is that an acceptable OTC use? And if it is, how do we appropriately label for that?

CHAIRMAN BRASS: And that will be the focus this afternoon.

Dr. Shuster, question for the FDA?

DR. SHUSTER: Yeah. First of all, I just wanted to ask Dr. Cohen what he thinks a good Jesuit priest might do with that question.

(Laughter.)

DR. SHUSTER: But I did want to address the question which had been raised here and which I

had in mind which really concerns me, and that relates not to content, but to process. Here we are now being presented with something which none of us have really directed our attention to.

When I read these tomes here, I usually have a targeted concept, a targeted approach to it, and I think that many others would, too. For example, the group now that is being proposed, which really essentially is the prevention only group for the labeling, is the group which was most noncompliant, which most misunderstood the directions. Sixty-four percent of them did.

Now, we are also given a new dosage form, and I would have to go back to all of this focusing now on ten milligram dosage rather than a 20 milligram dosage.

So what I'd like to ask is can -- and I address this to all of the FDA representatives as they're standing there, and actually it's a question that could be addressed to all of the committee members as well, and that is do you feel that you are competent at this stage to make recommendations about the new labeling or would you have to go back to look at this in a totally different sort of fashion.

I'm new to this committee and, as a matter

of fact, so new that I've been disenfranchised because I haven't been vetted appropriately yet, but I would like to ask whether the process should not be a rather rigid one; that if there is a change in labeling, and that wasn't determined yesterday, I presume, that that change be submitted to the FDA and to the committee so that they could pay attention to it.

CHAIRMAN BRASS: Well, let me respond to that and then, again, Dr. Ganley or the committee or anybody else can comment, too.

I think that the points you raised are extremely important and, in fact, will be reflected in both the questions and discussion that we will have this afternoon about reacting to this information, and I think the FDA has asked our opinion not only with respect to the studies and issues that have been presented, but because this is an evolving area, our input at this stage might be helpful to both the agency and sponsor in focusing that evolution in the future.

But I think the points you've raised are germane and recognized by all, and Dr. DeLap.

DR. DeLAP: Yeah. I think that this is a not terribly unusual circumstance for us when we're dealing with something that is a little different

paradigm than what's gone before, and there is a natural back-and-forth between the sponsor and the agency over the course of the review of an application in this kind of situation, and in fairness to the sponsor, you know, it's not their fault that they come up with some new ideas in the course of the review process because we're asking them to come up with some new ideas a lot of times.

Having said that, this did seem to us to be a good time to look at at least a large portion of the issues in the application and to get some advice from the committee rather than, you know, trying to get everything totally ironed out before it comes to you.

And, again, in terms of like labels for things, it's not unusual if the label gets changed from what was studied. That usually triggers the need to do another label study, but, again, that's not unusual.

I think there are some questions that have come up today, as you say, that we're not really competent to address because we haven't thought about them exactly in that fashion, but there are a lot of good questions, I think, that have been thought about, and we've tried to capture some of those for the

committee here, and I think we'll be very pleased if we can get some good discussion and ideas about the questions that we have addressed here. That will really help us with the process.

CHAIRMAN BRASS: With that segue, I will adjourn us for lunch to reconvene at 1:05. I don't ant to shortchange your lunch.

(Whereupon, at 12:08 p.m., the meeting was recessed for lunch, to reconvene at 1:05 p.m., the same day.)

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

(1:09 p.m.)

CHAIRMAN BRASS: If we could begin the afternoon session, after the presentations of this morning a number of issues were identified, and what I would like to do is we have been given or will be given shortly a very broad spectrum of questions quantitatively and qualitatively from the FDA to discuss, which I think encompasses the broad range of these issues, and by using the questions to focus our discussion, I think we will be able to be more productive and yet cover that broad range of issues.

So at this point, I'd like to ask Dr. Katz to give the charge to the committee.

DR. KATZ: Good afternoon. I hope everyone can hear me back there. Can you hear? Okay.

At this point in time, I'd like to welcome everyone back to the final session of our committee meeting, which is the deliberation portion of our meeting.

Before going on to kind of address some of the questions, I'd just like to go back again and just kind of remind everybody where we've been.

As part of the background, currently available now we all know that there are two products

out on the OTC marketplace for the indication or symptomatic relief of heartburn. Those would be the antacids and the acid reducers, also known as the H2 receptor antagonists.

The H2 receptor antagonists also have an additional indication, that of prevention for meal induced heartburn symptoms at a specified period of time depending upon the nature of the drug.

Today we have heard from Procter & Gamble, who has proposed moving omeprazole, Prilosec, to the over-the-counter marketplace. Currently, as we know, Prilosec is approved for 20 milligrams as a prescription drug for the treatment of gastric and duodenal ulcers, erosive esophagitis, GERD, and for treatment as well of pathologic hypersecretory conditions.

Today also we have heard that an additional proposal has been discussed for an additional indication, and in fact, at the time of the filing of the NDA, the three indications that I have here for acute symptomatic relief of heartburn, for prevention of meal induced heartburn, and the new indication of a 24-hour heartburn prevention due to a variety of causes was proposed.

Earlier today we've heard about a

modification for the labeling which would be for the treatment of frequent heartburn and a change in dosage from 20 milligrams to ten milligrams.

When you go back to deliberate over some of the questions at hand, what I'd like to remind you about are some of the important issues that go into some of the decision making process for looking at drugs that are going over the counter. These would include the benefit-risk for the population that we're talking about; consumer's ability to treat, to self-diagnose and self-treat; consumer's ability to understand the labeling instructions, including monitoring, follow-up care, and other associated treatment that they might need to receive; ability to recognize that they've attained a goal and what that goal is; and the ability to recognize toxicity.

In today's discussion, what I'd also like to do is to focus you on the areas that we've heard about, which is that we've had different studies that have been presented to look at efficacy, and in fact, we've heard about five studies that have been presented for the acute symptomatic relief of heartburn where both ten milligram and 20 milligram a day doses have been looked at.

For relief, we've also heard that there

really has not been a significant benefit shown for either the ten or the 20 milligram tablet.

We've also been presented two trials to look at prevention of meal induced heartburn, both the ten and 20 milligrams, one which was successful, one which trended but did not show statistical significance, and two additional studies for the prevention of 24-hour heartburn due to a variety of causes.

In addition, there were five actual use studies that were performed to evaluate use patterns in dosing compliance, but these were not designed specifically to look at efficacy.

We also have heard further about the indication as to GERD, and in part of your deliberations today, we'd like you to look at is GERD an acceptable OTC indication, and this gets us from the acute versus the chronic realm, and is this appropriate?

When we consider GERD, remember again we consider chronicity of therapy, safety consequences, any rebound effects, and suboptimal treatment, and by this I mean the fact that the label itself will be labeled if as we saw it for ten-day use and what do consumers need to do if the symptoms persist beyond

the ten days' duration, and this, again, should be something that should come out in some of the discussion.

The safety issues we've heard a great deal about, and at this point in time rather than spending a lot of time here, I just want to focus you on short-term versus chronic intermittent use, and in going through to the deliberations and trying to answer the questions, to have you focus on those terms, and also, again, to let us know in any of the areas that we've discussed today, such as anaphylaxis, angioedema, urticaria, liver toxicity, bone marrow disorders, severe skin reactions, and other safety concerns, which of these are of import for an OTC marketplace and which we should pay more or less attention to.

We're also coming down. Two would be the drug-drug interactions.

Finally, we get to the last area, which is that of actual use and label comprehension issues, and this is where some of the data, again, we kind of try to synthesize the whole over-the-counter picture together.

We've heard about that it's important for consumers to be able to appropriately self-select, to know which population of consumers should use this

product and which should not, their ability to use the product correctly, having the correct dosage for the time specified in the label, their ability to identify when to go see a physician or other health care provider, their ability to identify serious adverse events and what needs to be done about them, their ability to avoid interacting drugs, and whether or not populations who should not use the drug can adequately identify that they should not be taking this product.

We've also identified for you some areas of concern in that 65 percent of a subset of subjects using omeprazole for prevention only used it more than the ten consecutive days that was a limit placed on the label itself.

In addition, about 19 to 22 percent of consumers using omeprazole for both acute symptoms and prevention also exceeded the ten-day limit.

The best results did seem to go in the individuals who used it for relief only. However, again, we've heard that the product was not very effective for relief only.

At this time, again, in closing, I would just like to once more focus your attention that what we were talking about here is a new indication, as well, that would take over more of a chronic realm,

and that should focus in as part of your discussion in deliberating the questions at hand.

Thank you.

CHAIRMAN BRASS: Thank you.

We will now proceed to the questions, and again, because we have several guests, I just want to go over a few of the ground rules.

First of all, when it comes to voting, only official panel members will be able to vote, and therefore, the following people will be excluded from any voting, though they will be able to participate in the discussions. Specifically, Drs. Mirsalis, Sachs, Robinson, Blewitt, Douglas, Waldum, Shapiro, Shuster, and Cohen as all excluded from the voting.

Second, I think because of the breadth of material we need to cover this afternoon, I think it's extremely important that we stay focused in our discussion on the issues relevant to the questions, each question as it comes before the committee.

It will obviously be important for us to discuss these in as much depth as possible, and I would encourage committee members to ask questions of either sponsor or the FDA for clarifications on issues relevant to those questions.

So with that preamble -- yes?

DR. SHAPIRO: Just a point of order, Mr. Chairman. On my handout, I'm listed as a voting participant. Is that incorrect?

CHAIRMAN BRASS: I will ask for help.

DR. TITUS: You're Dr. Shapiro?

DR. SHAPIRO: Yes.

DR. TITUS: I need to check.

CHAIRMAN BRASS: We will look into that and try to get an answer prior to the first vote. Thank you for clarifying that.

So the first question is: in studies 092 and 095, those two studies specifically, the primary endpoint for efficacy was the occurrence of sustained complete relief of the first treated episode of heartburn. Based on the primary measure of efficacy, is there a clinically significant improvement of acute symptomatic heartburn in either the ten or 20 milligram omeprazole groups as compared to placebo? Please explain your answer.

I have been told that Dr. Shapiro does, indeed, get to vote officially.

Dr. D'Agostino.

DR. D'AGOSTINO: The data is quite clear. The studies did not attain statistical significance.

CHAIRMAN BRASS: Other comments or

observations?

I personally would agree with that assessment, and that on the primary endpoints there was no reason to believe that there was efficacy. Would anybody else like to comment on that issue?

Yes, Dr. Steinberg.

DR. STEINBERG: That appears to be clear for that particular question, but there were the secondary outcomes where some of this is muddied, where there is statistical significance for sustained adequate relief. Is that an important consideration?

CHAIRMAN BRASS: It's potentially important. But I would point out that in 095 it was only the 20 milligram dose, and neither dose in the 092 is my understanding for that endpoint.

DR. STEINBERG: I have all treated episodes.

CHAIRMAN BRASS: I see. The all treated episodes, that's correct.

DR. STEINBERG: It was the ten milligrams for both studies appear to be statistically significant.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: I think we could have an interesting discussion that they picked the wrong

endpoints and the primary endpoint, and I think that when you look at the sort of array of endpoints, at the secondary, and then though the FDA sort of took them to task for it, when you look at what other studies, other products have done, that there may be something of interest going on with the secondary endpoints. The question focuses on the primary, and my response was to the primary.

CHAIRMAN BRASS: Dr. Cohen.

DR. COHEN: In looking at the data, if I read this correct, with the 60 percent placebo response, I think that's beyond what --

CHAIRMAN BRASS: Which endpoint are you referring to?

DR. COHEN: Well, the sustained adequate relief. I think 60 percent placebo response is beyond what we generally see in GI diseases where you're looking for symptomatic improvement. So I would think that we brought in a lot of patients, and it's very insensitive in separating out the two groups.

DR. STEINBERG: But I think it seems that industry set a very high task to get complete -- that primary endpoint which they established was very admirable, but very tough to achieve. I think most of us in practice would be very happy if we controlled

symptoms. It would be great if we could eliminate them, but make them better. It appears that the data shows that it make the people better, but not completely better.

CHAIRMAN BRASS: Well, I think part of the issue in the endpoint discussion, which I think both of you have highlighted, and I tried to bring out earlier is whether in the endpoint that you are referring to, whether or not it is truly acute relief that's being detected or prevention, and it is more similar to some of the other studies, and I think that's also what Dr. D'Agostino is referring to in terms of differentiating the endpoint.

DR. STEINBERG: I don't think you could separate those two probably.

CHAIRMAN BRASS: But I would submit separation is important if the product was to be labeled directly so that consumers would understand which endpoint they were trying to treat.

Yes, Dr. Blewitt.

DR. BLEWITT: Yeah. Frankly, I don't think that you can ask Question A in isolation as far as the primary endpoints are concerned. I think that really you have to find out what the studies told you, and I would suggest that there were significant

learnings from the studies when you look at adequate relief compared to complete relief. Maybe complete relief was too high a bar.

And so I would suggest that the Question A be taken also in the context of the secondary endpoints.

CHAIRMAN BRASS: Yes. I would encourage such a discussion. Obviously for the purposes of the vote, we will focus on the primary endpoint, but I think your point is an excellent one, and I'm trying to bring that out in the discussion so that it would help provide insights relevant to the later questions, et cetera.

Yes.

DR. ROBINSON: My comment would be that I don't think anyone in this room would argue about the efficacy of this product in the disorder for which it's intended, and the only issue really is: is it possible to use this product in the OTC environment in a way which is easily understandable by patients or by people in the community who would want to use such a medicine.

And they really answered that question in this study, it seems to me, and I think the sponsor pointed this out quite well when they asked for the

appraisal, the overall appraisal of was this a useful medicine for you for this condition for which you took it.

And in that situation it clearly was very -- deemed by the takers of the medicine who, after all, are the only arbiters who are important in this situation as being very useful, indeed.

So I think that's really the -- from my perspective at least, that's the final point in this story, and that is this is a lot of semantics about whether we're talking about acute heartburn or relief of heartburn or treatment of heartburn, but really the bottom line for all of this is are these subjects being satisfied by a medicine that they are taking for a condition, an unpleasant condition which they are experiencing?

CHAIRMAN BRASS: Dr. Geller.

DR. GELLER: I would like to disagree with the previous speaker. I think we're talking about a disease that's both self-limiting and has a placebo effect.

Now, the primary endpoint here was clearly negative. The P values aren't even close, and I'd like to make an additional -- to .05 -- I'd like to make an additional comment that since there were

essentially two studies using the same control group, a rigorous clinical trialist will assess these data at the .025 level, not at the .05 level, and in that setting a P value of .035, which is the last treated episode P value for the 20 milligram versus placebo dose or the .032 which is the totality of evidence over the two weeks would not be considered statistically significant. At best they would be borderline.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: It's the same comment, that basically the placebo effect is so large, I mean, it's probably a badly run study as opposed to indictment of the drug, and I think that's really what the issue is.

CHAIRMAN BRASS: Dr. Sachs.

DR. GEORGE SACHS: I think you should remember that this class of drug actually made its name by its ability to treat GERD or heartburn as compared to H2 RAs, and that was its launch pad, but it's very clear from any study that had been done on this class of drug that to expect to get complete symptom relief with first dose simply isn't within the mechanics of the way this drug works.

However, in taking the drug by the second

dose you see the effect, and you see the effect also, in fact, in the evening better than H2 RAs.

So if they ask the question complete symptom relief, almost nothing does that even in long-term studies, but in terms of improvement for the patient by the first dose, second dose, that sort of question, I think, would be answered positively.

CHAIRMAN BRASS: Dr. Sachs on my right.

DR. HARI SACHS: Dr. Hari Sachs, P. Mandrix (phonetic).

In my looking at the data, actually looking at clinical significance, where I have a little trouble is at best they're showing ten to 15 percent over placebo. So I don't see this as being clinically significant in answering this, you know, for efficacy at all. Even though there may be some improvement, it's really very marginal over placebo.

CHAIRMAN BRASS: Ms. Cohen, did you have a comment?

MS. COHEN: Well, I don't know --

CHAIRMAN BRASS: Microphone.

MS. COHEN: Thank you.

I think you're going to shoot me down, but as a consumer member, I've heard a lot of things. There are almost 50 million Americans in this country

that don't have health care. Therefore, they're not even going to be able to see a doctor.

This is a multi-cultural country, and I saw that you had 86 percent Caucasians in your study. Did you advertise in different languages to find people from different backgrounds and different cultures? How are these people going to understand something if it's not going to be in their language? No one has interviewed them in their language.

Did you do focus groups in different languages for different people? Because the one thing most of us, I do, I'm a perfect example of heartburn and GERD. How do you know how these people -- it's the one thing that everybody is going to say. In the advertising that's going to happen, and all of a sudden everybody, everybody is going to think, "Well, I can come take this medication."

Well, there are all kinds of preemptive information that they need to know, and I, frankly -- this is the real world of all those Americans who aren't going to be able to go see a doctor, and we're talking about all of these things, and the end result is the kind of information that is given to consumers that's it's plain and concise, plain language in Spanish.

Is someone going to answer the phone who speaks Spanish or another language? Is there going to be someone at the phone at your place?

I'm sorry. I feel that these are issues that are very important and the heart and soul of the end product, which is the information you're going to give to people, and the advertising if this thing is passed is going to be voluminous, and I'm worried about all the people that can't go to a doctor, and they continue to take it and what's going to be the end result?

Thank you. I appreciate your allowing me to say that, but I'm disturbed.

DR. SCHACHTEL: I couldn't agree with you more, and there are several -- as you know, I've been involved in neighborhood health centers for years, and I entirely agree with you about concern for people who may not be as literate as others, whose ethnic backgrounds or even language background may be different.

We did look at the benefits for them, as well as their compliance with the label in different ways, and I can provide you in great detail if you want looking at the different stratifications. Maybe there can be a few that can be thrown up that might

satisfy you.

For example, looking even at educational level, which is a reasonable handle I think you'll agree for literacy -- we actually have it. Good. This one I don't know how to work. Oh, there it is. Good, okay.

Looking at the percent of dosing days compliant by whether a person has had a high school diploma or a GED or less versus some college and greater than a college degree; looking at whether they took one tablet per dose, one dose per day, and the overall doesn't matter. Do you have it for the ten days, please? Because I think that's a critical issue, too. No, that's not a critical issue to you? I thought it would be.

MS. COHEN: Is that where you go from Hispanic areas and you go into black areas and you find that everybody has that educational level? You know, we're all educated in this room, but this is not real America either. There are all those people out there who are not college degree or don't have advanced degrees, who really -- I mean I just saw what you gave. I mean, is that typical of the United States and in many areas of this country?

I don't think so. I'm worried about

people that have to understand what they're taking, what they're taking it for, how long they can take it. I'm worried about they might have symptoms that really are far more serious than just indigestion or GERDS

I mean, this is a serious thing, and if you're going to go OTC, you're going to start advertising, and I'm worried about the people who have symptoms that are going to be masked by other things.

I think showing me the educational level is not telling me about America.

DR. SCHACHTEL: But, in fact, the shopping centers that we purposely selected represent lower socioeconomic, Hispanic sections. If you looked in the reports -- perhaps it's not in the dossier that you received -- we did that intentionally, and that's why the averages for socioeconomic level through different indices are intentionally low.

What I was particularly interested in is that it doesn't really matter as much as some people believe because if a person wants to take a medication for their heartburn, they will learn how to use it correctly either because, in fact, they are literate or because there are other people in the home who are, and that's what I've learned at least over the past, well, 13 years that I've been doing this kind of

research.

And I don't consider this study to have been any different, in fact.

CHAIRMAN BRASS: I want to bring us back to 92 and 95 and the question on the table. So we'll come back if there is a question about the label. We can do that.

Dr. Geller?

DR. GELLER: I was going to say that I don't think you can make a very strong argument in defense of efficacy based on these trials. In fact, I think the argument is extremely weak. In fact, the people sitting around this table did not make the decision of what the primary outcome should be. The company chose this because they thought they were going to get success on this endpoint, and that's a reasonable line of thinking.

But I don't think anybody here should make the case that there's efficacy based on this trial, and I think we should go on to the other trials where you can make some argument of efficacy.

CHAIRMAN BRASS: Dr. Shuster.

DR. SHUSTER: My area of special interest in gastroenterology is gastrointestinal disorders or functions, sometimes called functional gastric

disorders there, disorders in which there is disturbed motility and disturbed contraction of sphincters that prevent reflux and so forth, and what we see in a number of these disorders of function is a very high placebo response, up to 60 percent.

Now, I think you need a pretty darn good drug to best a 60 percent placebo response, and even ten or 15 percent above that I think is a significant response. That's number one.

Number two, had these studies been carried out further, they may have shown a more impressive result because the placebo response tends to be somewhat self-limited, and if you can write out that response, I think that it might have shown we don't have that data, but I think it is a consideration.

CHAIRMAN BRASS: Dr. Neill?

Any other comments before we vote on -- yes.

DR. ELASHOFF: Well, in terms of sustained adequate relief, the difference between the ten milligram dose and the placebo is five percent in one study and two percent in the other. It's not ten or 15.

CHAIRMAN BRASS: Okay. I'm going to call the first question, and again, specifically in