that the incidence of confirmed elevations is similar with lovastatin 20 milligrams to that with placebo. The data also indicate that these elevations are not associated with drug-induced liver disease.

This slide shows data from EXCEL. The bars illustrate the percentage of patients in each treatment group who had confirmed elevations in ALT greater than three times the upper limit of normal.

We see that the proportion of patients with an increase in ALT with 20 milligrams per day of lovastatin was the same as that with placebo. The incidence goes up to 0.9 percent with 40 milligrams per day, and then 1.5 percent with 80 milligrams per day, but the incidence of 20 matches that with placebo.

In AFCAPS/TexCAPS, there were over 50,000 transaminase determinations during the course of the trial. Now while there are approximately 34,000 patient-treatment-years in that study, there were only 29 participants who had confirmed elevations of ALT greater than three times the upper limit of normal. There were 18 in the lovastatin group and 11 in the placebo group, and that difference is not statistically significant. This is quite consistent with the EXCEL data.

The next slide shows that the elevations in these 29 participants did not indicate drug-induced liver disease. Here we see what happened to these 29 participants in AFCAPS/TexCAPS with confirmed elevations of ALT. The data show that an increase in ALT was not indicative of liver disease that was induced by the drug.

The profile was similar in the lovastatin and the placebo groups. Most patients in both groups had a negative rechallenge or the ALT elevation resolved while treatment was continued.

Three people in each group discontinued treatment and an alternate diagnosis was established as the likely cause for their ALT elevation. There was only one person in the lovastatin group who received lovastatin and had a recurrence of the ALT elevation when treatment was restarted. But this finding is not different than the two participants in the placebo group who had what appeared to be a positive rechallenge to placebo.

Therefore, this very large, long-term trial does not provide any evidence that elevations in ALT predict the development of acute drug-induced liver disease.

Now Merck maintains a Worldwide Adverse

Experience Spontaneous Report database, referred to as WAES. This is a voluntary reporting system. All reports that the company receives are entered into the database regardless of the perceive causality with the product.

As with all spontaneous report databases, it cannot be used to calculate an incidence for a specific adverse experience. We can, however, calculate or estimate a reporting rate based on the estimated usage of the product.

The WAES database contains 232 reports where patients taking lovastatin also had clinically diagnosed hepatitis that was not attributed to a viral infection. This equates to a reporting rate of approximately 10 per million patient-treatment-years.

However, 177 of those 232 reports were received before there was a widely available sensitive assay for hepatitis C serologies. So in fact, it was really not possible to exclude hepatitis C infection in 177, or the majority of these reports.

In those reports that mention the dose of lovastatin, there was no apparent dose response. There were only two reports with 10 milligrams and both of those were confounded by other medications and concomitant medical conditions.

Biopsy results were available from 57 of these 232 reports. There were a variety of histologic patterns observed in these biopsies. There were hepatocellular injury, cholestasis, and fatty liver, but of note, there was no consistent pattern among these 57 cases to suggest a specific pathologic picture that could be attributed to lovastatin.

The WAES database also contains five reports of documented cases of acute liver failure in patients taking lovastatin where a causal relationship could not be excluded. There were no reports among those five with 10 milligrams. Five reports with an experience of 24 million patient-treatment-years equals a reporting rate of one for almost 5 million patient-years.

Now to summarize our data with regard to the liver, we have seen that the incidence of asymptomatic aminotransferase elevations with lovastatin 20 milligrams is the same as that with placebo. These elevations are reversible while continuing the drug and they do not predict the development of acute drug-induced liver disease.

Clinically-apparent liver disease with lovastatin is heterogeneous, rare, and the relationship of that liver disease to lovastatin has

really not been clearly established.

Based on all this data, we believe that routine monitoring of liver function tests is not necessary in patients taking 10 to 20 milligrams per day of lovastatin.

Turning our attention to muscle, in the context of treatment with statins, myopathy is defined as an unexplained muscle pain or weakness accompanied by a CK level greater than ten times the upper limit of normal.

This condition usually resolves promptly when the product is discontinued. Rarely, however, the condition may be severe, prompting hospitalization and we term the severe cases rhabdomyolysis.

The mechanism of statin-related myopathy is not known. Myopathy though has been reported not only with all the statins, but also with fibrates and high doses of niacin. This fact suggests that the condition is actually related to decreases in skeletal muscle cholesterol.

Data from EXCEL highlights the fact or the difference between asymptomatic elevations in CK, myalgia, and myopathy. Elevations in creatinine kinase are relatively common, even in patients receiving placebo. In EXCEL, approximately 29 percent

of those receiving lovastatin 20 milligrams or placebo had one or more instances where their creatinine kinase exceeded the upper limit of normal.

We also see that muscle pain or myalgia is common with approximately 6 to 7 percent of the patients receiving lovastatin 20 or placebo having muscle pain, but we also see that a combination of muscle pain with CPK over ten times the upper limit of normal, what we call myopathy, is quite uncommon. There were no cases with lovastatin 20 milligrams in this trial and no cases with placebo.

If we look at all the treatment groups in EXCEL, we see evidence of a dose response for the incidence of myopathy. There was one case on 40 milligrams and four cases on 80 milligrams for an incidence in this 48-week trial of one-quarter of one percent. There were no cases of severe myopathy or rhabdomyolysis in that trial.

The data from AFCAPS/TexCAPS is consistent with the data from EXCEL. There were three cases of rhabdomyolysis in AFCAPS. One case was in the lovastatin group. A patient stopped their lovastatin before they had surgery for prostate cancer. After they had the surgery, they developed rhabdomyolysis, they recovered, they restarted the lovastatin without

difficulty.

There were two cases of rhabdomyolysis in the placebo group, both in patients who were hospitalized for unrelated medical problems, one of whom had a cardiac arrest and the other who developed shock. There were no cases of uncomplicated myopathy in this study.

Now we have received 262 spontaneous reports of rhabdomyolysis in patients who have taken lovastatin, but given the tremendous experience with lovastatin, this is actually a low number. This equals a reporting rate of approximately 1 per 100,000 patient-years.

Now the review of these reports shows that the risk of myopathy is dose related and I will review the issue of whether it's increased with interacting drugs in the moment. The risk though appears to increase in patients who have complicated medical histories such as patients with diabetes and renal insufficiency.

In 135 of the 262 spontaneous reports that we receive, there was no mention of a potentially interacting drug. And when we review those cases, we see that the risk is dose related. We see that there were no cases reported with 10 milligrams, a reporting

rate of 0.2 cases per 100,000 patient-years with 20, increasing to 3 cases per estimated 100,000 patient-years with 80 milligrams per day.

So in summary, our data shows that the risk of myopathy is dose related and quite low with any dose. There have been no reported cases of rhabdomyolysis with 10 milligrams alone. Myopathy is a symptomatic condition that generally resolves when the drug is discontinued.

Our proposed label instructs users what the symptoms of myopathy are and what they should do if those symptoms occur.

Now before discussing the potential for drug-drug interactions, I'd like to briefly summarize the pharmacokinetics of lovastatin after oral administration.

The drug is moderately well absorbed and there is first-pass metabolism in both the intestine and the liver by Cytochrome P450 3A4. The drug is rapidly converted to its active beta-hydroxyacid form. There is high first-pass hepatic extraction, and this means that there is actually very low systemic exposure to HMG-CoA reductase inhibitors.

There are two types of drug-drug interactions: Pharmacodynamic and pharmacokinetic.

The pharmacodynamic interaction recognized with all statins is that concomitant use with fibrates or high doses of niacin may increase the risk of myopathy.

Now lovastatin and certain other statins also have pharmacokinetic interactions. Lovastatin does not inhibit any of the Cytochrome P450 isoforms at therapeutic concentrations. However, use of potent 3A4 inhibitors in conjunction with lovastatin will increase the concentration of HMG-CoA reductase inhibitors.

We agree that patients taking lovastatin should not also take concomitantly potent 3A4 inhibitor; however, given the very wide therapeutic index with lovastatin, we do not believe that there is a substantial risk with clinically significant drug interactions with the proposed 10 milligrams dose.

AFCAPS/TexCAPS provides data to support my statement that significant drug-drug interactions are unlikely with 10 milligrams of lovastatin. In this trial, there were 535 patients who received lovastatin and also at some point during the study were prescribed a potent 3A4 inhibitor. Approximately 500 also received a potent 3A4 inhibitor and took placebo.

Erythromycin was the most commonly prescribed 3A4 inhibitor; however, 87 patients also

took either ketoconazole or itraconazole. What I'd like to point out is that the incidence of myalgia, or any musculoskeletal adverse experience for that matter, was not higher in patients who took lovastatin and an inhibitor than in patients who took placebo and an inhibitor.

And as we've pointed out before, even though 535 patients took an inhibitor, there were no cases of myopathy or rhabdomyolysis.

So this shows that the risk of myopathy with lovastatin 20 to 40 milligrams in a primary prevention population is quite low, even on the occasion when potent 3A4 inhibitors are taken concomitantly.

Now the WAES database contains 127 reports of rhabdomyolysis where a potentially interacting drug was also taken. There were no reports of an interaction in patients who were taking lovastatin 10 milligrams. The interacting drug most commonly mentioned in the reports was fibrates, but there were 46 reports where patients were also taking a potent 3A4 inhibitor.

The most frequently mentioned inhibitor was cyclosporin which is generally only taken by patients who are under close medical supervision.

It is worth noting that rhabdomyolysis has been reported in patients taking cyclosporin alone or patients taking cyclosporin with other statins as well.

It is also worth noting that in 19 of these 46 cases, the patients were taking two drugs on this list, so one drug alone did not cause an interaction, it was two inhibitors, or an inhibitor plus either fibrates or niacin in a patient taking lovastatin.

For example, while we have six reports with an antifungal drug, in five of those cases, the patients were transplant patients on cyclosporin. There is only one report that we have of rhabdomyolysis in a patient on an antifungal, not on cyclosporin.

Now the prescription circular for lovastatin notes that the risk of myopathy is increased when patients concomitantly take potent 3A4 inhibitors, fibrates, or large doses of niacin. Our data indicate that the risk of myopathy, however, with 10 milligrams should be quite low, even if an interacting drug is taken.

Dr. Hemwall will show you that our proposed OTC label effectively warns against use of

lovastatin with potent 3A4 inhibitors or other cholesterol-lowering medications.

We have extensive experience with lovastatin 20 milligrams and that experience has shown that 20 milligrams is extremely well tolerated. There is a very low risk of myopathy or true hepatotoxicity with the drug.

Lovastatin 10 milligrams has an even larger margin of safety. The risk of dose-related adverse experiences such as myopathy or clinically significant drug interactions should be even lower with 10 milligrams than with 20 milligrams.

As Dr. Beere showed you earlier, 10 milligrams has efficacy that is clinically meaningful. Therefore, we selected 10 milligrams to be our proposed OTC dose.

Our nonprescription development program included four phase III clinical trials. A total of 2,430 individuals received lovastatin in our program, most of those for two to six months, but 389 of those people actually took drug for 12 to 18 months.

Lovastatin was very well tolerated in our OTC studies. There were no serious drug-related clinical adverse experiences in these trials. There were also no documented cases of myopathy and no

clinically diagnosed cases of hepatitis.

This slide shows the seven adverse experiences that were reported by 1 percent or more of the participants who received lovastatin. The most common adverse experiences were flatulence, headache, diarrhea, and abdominal pain. These seven adverse experiences, however, were no more frequent with lovastatin 20 milligrams in either EXCEL or AFCAPS/TexCAPS than with placebo.

That fact indicates that most of these adverse experiences were probably not truly attributable to the drug.

Now in conclusion, the safety profile of lovastatin has been very well characterized. Lovastatin 10 milligrams was well tolerated in our OTC studies. There were no drug-related serious adverse experiences in those studies.

Long-term use of 10 to 80 milligrams per day has been well tolerated both in clinical trials and during extensive marketed use. The 20-milligram dose has been shown to have a safety profile comparable to that of placebo in large long-term trials. Lovastatin has a very low potential for toxicity in overdose or for abuse.

As Dr. Hemwall will discuss, our proposed

label and adjunct materials thoroughly address these potential safety issues.

Given the data I've presented this morning, I hope you will agree with me that the 10-milligram dose of lovastatin has a very large margin of safety and provides an appropriate safety profile to this Rx-to-OTC switch. Thank you very much. Dr. Hemwall.

DR. HEMWALL: Good morning. You've heard that lovastatin 10 milligrams can provide a substantial benefit in lowering cholesterol and that the product has an appropriate profile for OTC use. I will now review the label development and consumer behavior research results that provide the basis for our conclusion that people can safely select and use this product to achieve the benefit.

As you know, a tremendous amount of data has been collected and I will briefly go through the key results in the interest of time and appreciate your patience in our long presentation today.

These two questions define our overall approach to label development and the format of my talk. The first one pertains to product selection.

How do we allow the most people to benefit from OTC cholesterol control while preventing

ineligible people from taking the product?

The second question pertains to product use. How do we encourage the appropriate use of the product in order to achieve the maximum benefit?

Our underlying premise is that consumers interested in this product are by and large well informed on the importance of cholesterol lowering and motivated to do something about it in order to maintain cardiovascular health.

Before I move on to the supporting details, let me summarize the key findings. The Mevacor OTC label and accompanying Education and Support Program effectively communicates to the consumer the necessary information for appropriate product selection and long-term use. Motivated consumers are able to comply with long-term daily dosing and achieve clinically meaningful lipid changes.

In addition, our research shows that the education and support program encourages collaboration with healthcare professionals. As depicted here, the Education and Support Program focuses before purchase on the information necessary for consumers to make an appropriate purchase decision and after purchase on the information needed to refine and extend the

understanding of the product and its use. The importance of cholesterol testing and monitoring is emphasized both before and after purchase.

Before the purchase decision is made, eligibility criteria for the initial selection of the product are introduced through informative advertising which provides the basic information about who should and should not use the product. The carton label then summarizes all information necessary for an appropriate purchase decision.

After purchase, the consumer has access to several label reinforcement tools contained within the package which refine the product selection decision. More comprehensive information is available after purchase and educates consumers on the importance of a healthy lifestyle and encourages long-term use in order to maintain the benefit.

The multiple OTC labels tested in our study program contain core elements such as those summarized here. We specify the age and stage of life when men and women are at increasing risk of coronary heart disease and therefore most likely to obtain the benefit.

Also listed are specific values for cholesterol and LDL cholesterol and those who should

not use the product reflect the warnings from the prescription labeling.

The core label lists specific drugs which should not be used when taking Mevacor OTC and is discussed by Dr. Korn in the previous talk, the potential for rare muscle-related side effects is explained.

In keeping with OTC access, consultation with a doctor is not required if the well-informed consumer fits within the stated eligibility criteria; however, all consumers are advised to inform their doctors they are using the product and to see a doctor for regular checkups in order to obtain the best medical care. And the labeling advises any consumer with questions to check with a healthcare professional or the Mevacor toll-free service before using the product.

People with higher cholesterol values than specified as appropriate or people who have medical conditions that place them at higher risk are also instructed to talk to their doctors before using the product.

The directions for use include taking one tablet per day, continuously, and to maintain a healthy lifestyle. The consumer is advised to get a

repeat cholesterol test after about eight weeks and if the cholesterol does not go down at that time, they should talk to a doctor.

All of these core label elements are included in the outer carton and inside the carton are additional materials intended to reinforce those messages.

These additional materials we call label reinforcement tools. These include the package insert, which is standard for many OTC packages, but these tools go far beyond what is standard.

Also included is a video tape which introduces and reinforces the label messages in another medium. The video was produced and tested in our clinical program. The package also contains an information booklet on cholesterol and the importance on maintaining a healthy lifestyle.

We also provide further communication links beyond the package for the purpose of further promoting appropriate use. A unique feature of our Education and Support Program is the toll-free service which was developed and tested in our studies.

Use of the toll-free service is encouraged, not only for questions, as is the case for many OTCs, but for reinforcement of the key label

messages after purchase.

By talking with the product specialists at the toll-free service, consumers can learn more about their eligibility and appropriate use of the product. Very importantly, this service recommendations that consumers with higher risk of heart disease see their doctors and there is also an information card provided to enroll them in the compliance program.

The compliance promoting features are a key element of the product which requires long-term use to achieve the benefit. Enrollment in this program is to encourage with a high-value incentive.

Once enrolled the consumer receives a series of regular newsletters with information with aids and the use of Mevacor OTC over the long term and in increasing and maintaining a healthy lifestyle. Further, it emphasizes the importance of reassessing ones risk profile over the long term.

Also provided is a wallet-sized reminder card for tracking lipid changes and avoiding potentially interacting drugs.

And of course, the product itself, which is contained in compliance-promoting calendar packaging either as a blister pack labeled by the days of the week or the bottle cap which changes the name of the

day each time the package is opened.

This is the slide you saw before which provides a conceptual overview of the Mevacor OTC Education and Support Program showing how it works before purchase, through advertising and clear labeling to guide a correct purchase decision, and after purchase by providing an array of materials and contacts which further reinforce the label messages and support the consumer in appropriate product use.

Cholesterol testing and monitoring is encouraged throughout the process and a healthcare professional can help guide the consumer at any time in the process.

For the remainder of my talk, I will take you through the sequence of events in which the consumer will interact with this product and summarize our research which supports the feasibility of successful product use.

The first things consumers will recognize is the need to know their cholesterol numbers. Our Education and Support Program encourages consumers to obtain a complete lipid profile and provides guidance on where in the community to have a test conducted.

Cholesterol testing in the United States is already quite prevalent and most of this testing is

done in clinical settings and that is an excellent option for people who choose to use Mevacor OTC.

Our program encourages collaboration with doctors and these results are often easily obtained by a phone call. And as you saw earlier today, there is increasing availability of accurate cholesterol testing within the community using options shown here.

This is a schematic which is the first component which will orient you to our level development program. It starts with the depiction of the five interations of the label.

Four increasingly improved versions of the labeling materials were tested in a series of label comprehension tests and in-home use studies. The final label, label number five, is the one submitted in the NDA and provided in your background materials.

The first three labels were tested sequentially in three in-home use studies conducted in community settings where consumers used the product under simulated real-world conditions.

Study 76 was conducted from actual retail pharmacies and allowed long-term use of Mevacor for up to 18 months. Studies 79 and 81 were conducted in rented store space in local shopping centers and tested the toll-free service I just mentioned.

Follow-up surveys were conducted in subsets of study participants in order to supplement the information collected from the clinical studies. And a fourth study, 77, not shown here, was ended early due to poor enrollment and is not included in our presentation today.

In addition, we also conducted three label comprehension tests finishing with one round of improvements to create the NDA label number five, and I'll return to this chart now several times to illustrate the source of information which I will review.

Returning to the process by which a consumer approaches this product, I will focus on the key question about product selection. Because we continually improved our labeling and support materials, study 81, which used label number three, provides the most relevant information on the consumer's product selection decisions.

This study showed that effective labeling guides most consumers to make an appropriate selection decision and that the education and support program further improves the correctness of that decision to use the product.

Study 81 was an open-label four-week study

in which all of the interested individuals had the opportunity to make a product selection decision.

Recruitment was conducted through mass media advertising in five major metropolitan areas and this design is often termed and "all-comers" study as it is intended to simulate the real-world purchase decision in a store setting. Interested participants were actually required to purchase the product in packaging which had the appearance of an OTC product. The flow of participants through the study is shown here.

Consumers who responded to advertising placed a phone call which directed them to one of the study sites. They then reviewed the outer carton label and made a purchase decision. Those who decided not to purchase the product, or who felt they could not make a decision because they needed more information, exited the study and provided a medical history.

Those who decided to purchase the product had the opportunity to review the label reinforcement tools after purchase and either used the product or return it for a refund. For those people, the medical history was collected at the end of their decision process, on the phone, or at their return visit.

As noted, all participants had the opportunity to read the label at the storefront site and make an initial purchase decision. If they made a purchase decision, they were then asked four safety questions which reflect the contraindications in the prescription labeling for statins.

If they said no, the safety questions did not apply, they purchased the product, gave informed consent, and went home with the drug. They had an opportunity to review the reinforcement tools inside the package at home, including calling the toll-free service at any time during the study. They made return appointments four weeks later.

Those participants who said "yes", one of the safety warnings does apply, were not sent home with the drug, but instead had the opportunity to review the reinforcement tools at the study site; however, they were not given the opportunity to call the toll-free service from the site.

After reviewing those reinforcement tools, those participants made a second purchase decision so that we could observe the effects of the reinforcement tools on that decision.

A total of 2,416 interested individuals came to the site and reviewed the carton label. Of

those, about half decided they wanted to buy the product. About one-third said no, they needed more information before they could make a purchase decision, and an additional 15 percent said no, they were not interested in purchasing the product.

And we believe these results so that people who were motivated enough to come to the study site in hopes of obtaining a cholesterol-lowering medication responded to the outer carton with a thoughtful decision process.

Because we chose to obtain the medical history information at the end of the decision process, we do not have that information for some participants who did not return to the study site.

Therefore, there were 2,264 participants with medical histories providing information about their eligibility and you can see that their purchase decisions were similar when compared to the overall group.

Now let's look at how those 2,264 participants decided whether or not to buy the product. There are several criteria by which a participate could have made a wrong decision. Some are of greater interest than others.

For this exercise, we will focus on three

key categories of ineligibility. This chart shows the prevalence of those key subgroups within the overall group of interested consumers.

About 5 percent said that one of the safety warnings applied to them. Many were taking one of the labeled "do not use" medications. About 12 percent were in the higher cardiovascular risk group, meaning that they already had coronary heart disease, a history of stroke, diabetes, or hypertension. And about 17 percent had no other medical reason for being ineligible except that their total cholesterol was above the label-defined limit of 240 milligrams per deciliter.

So we looked at the decision-making process behavior within those three categories.

Now we see the percent of patients in each of the three categories who made a correct decision not to buy the product after reviewing just the outer carton label.

The safety warning subset, including those taking the "do not use" medications, and the higher cardiovascular risk subgroup were in the range of 68 to 70 percent correct.

Of those with total cholesterol over 240 as their only exclusion, 54 percent made a correct

decision after initial review of the carton label.

Now, the third column shows the reviewing the label reinforcement tools either at the study site or at home, improved the correctness of decision to 83 percent in the top groups and the group with the high total cholesterol also improved substantially after exposure to the label reinforcement tools.

It seems reasonable to expect that the safety warning group would have improved even further if they had access to the toll-free service and this assumption is supported by findings on the effectiveness of the toll-free service in reversing initial product selection errors. So let's take a few minutes and look at that toll-free service.

As noted earlier, the program we are proposing has a high-value incentive for calling a special toll-free number. A trained product specialist conducts a scripted interview of the consumer and a computerized algorithm indicates whether or not that person is eligible for the product. For eligible consumers, the key label information is reinforced and they are enrolled in a compliance program.

For ineligible consumers, the specialist advises not to use the product and to return it for a

refund. Those that are in the higher cardiovascular risk groups are also advised to consult a doctor about cholesterol management. And let's look at how this toll-free service performed when we tested it in our studies.

For this, we will draw data from studies 79 and 81. We found that the toll-free service was more effective than the carton materials alone in increasing correct decisions and that the toll-free service was effective in referring people with higher cardiovascular risk to consult with their personal doctor.

In study 81, there were a total of 376 participants who were allowed to purchase the product and go home with the product, even though they were ineligible for one or more reasons.

We wanted to see if the toll-free service was effective in reducing that decision by looking at whether or not they stopped taking drug before their return visit.

Of the people who did not call the toll-free number, 26 percent decided on their own to stop taking the product before their return visit. Of those that did call the toll-free number, however, 62 percent stopped the product before the return visit.

This indicates that the toll-free service was indeed effective in reversing incorrect selection decisions.

I will now move to study 79 which showed that the toll-free service effectively steered higher cardiovascular risk consumers to their doctor. Study 79 was different from 81 in that the participants did not have direct access to the product and had to call the toll-free service before they could enter the study.

People found to be ineligible because of higher cardiovascular risk conditions, such as cholesterol over 240, were advised by the product specialists to contact their personal doctor about cholesterol management. People were not advised to call their doctor if found to be ineligible for some other reasons.

Five to six months after the study completed, a follow-up survey of 402 ineligible participants was made to find out how many of them actually did call their doctors.

Interestingly, about half of these people who did not receive advice to call their doctor, called their doctor about cholesterol management anyway.

More importantly, of those who were

advised to call their doctors, 69 percent made that call showing that the advice from the product specialists can guide people to consult their doctors about cholesterol management.

Therefore, with respect to the product selection results of our clinical studies, we have shown that effective labeling does guide most consumers to make an appropriate decision and that after purchase the label reinforcement tools further improve the correctness of that decision.

The toll-free service was more effective than the carton materials alone in improving the process and the toll-free service was also effective in referring people with higher cardiovascular risks to consult with their personal doctor.

While these results were encouraging, that it is feasible to guide consumers to know when the product is right for them, we observed that the format of the warnings on the label in study 81, could be improved.

We therefore made revisions to all the labeling incorporating information learned from the large body of data collected from all the previous studies and at this time also FDA's new Standardized Drug Facts Format for OTC labels became available and

was incorporated.

We also have graphic enhancements included in the packaging to guide the consumer through simplified steps in understanding and evaluating the label directions, and this became our so-called EASY STEPS label which gave excellent results in comprehension testing which I will summarize next.

For this, I will review the results of the comprehension study of label 4 and from the last round of comprehension testing additional refinements were made to create the final proposed label in your package.

In this standard design and mall-intercept study, a representative sampling of the American population had a very high level of understanding. Comprehension by 80 percent or more has often been termed a benchmark for target OTC label comprehension, and all of the key concepts listed here were understood by at least 80 percent and most were understood by 90 percent or more.

In addition to the overall group, the sample population in the study was augmented with people subject to the key safety warnings and those of low literacy as measured by standardized testing. And those subject to one of the safety warnings also

understood the label very well. And the subgroup which had a reading level of 8th grade or less also had good comprehension, meaning that the key concepts were understood by at least 80 percent.

Now one of objectives was to improve the understanding of the medications which one should not use while taking Mevacor OTC. This concept was much better understood in this EASY STEPS label number 4 than label number 3 which was used, as you recall, in study 81.

Although this was not a head-to-head comparison, the differences shown here are very substantial and reflect the improvement in the label format and language. The understanding of these "do not use" medication warnings was even further improved with the participants having reviewed the label reinforcement tools that are provided with label number 4.

It is also important to have a good understanding of the condition where the label directs the consumer to ask a doctor before use. In this case, these the warnings were well understood from the carton back panel and even better after the label reinforcement tools.

The low literacy subgroup also had very

good comprehension on these "ask a doctor" questions and again further improved by the label reinforcement tools. Likewise, the low literacy subgroup had a high level of understanding on which medication should and should not be used.

Thus, we have concluded that the improved label clearly communicates the key information necessary for appropriate product selection and use. Comprehension by the low literacy subgroup was acceptable and the EASY STEP label represents an improvement over label 3 which was used in study 81.

Based on these learnings, further refinements were made to the final NDA label, number five, including several to correct consumer misunderstandings which the FDA will identify in their presentation later this morning.

So, I've finished with the key issues relating to product selection and I want to move on to the second most important question, that is after appropriate product selection, how do we encourage appropriate long-term use of the product in order to achieve the benefit? For this I will use data from study 76.

This was an open-label study which was conducted in 59 functioning retail pharmacies with 722

participants receiving lovastatin. The primary protocol was designed to last six months, with two six-month extensions, for a total of 18 months of treatment.

Eligible consumers were dispensed the product by the pharmacist investigators and these investigators provided minimal support on product use in order to observe the consumer's behavior in response to label and reinforcement tools.

In a real-world setting, it is envisioned that the pharmacist and other health professionals will actually take an active role in guiding consumers to appropriate product use.

Also, unlike the OTC setting, these pharmacies were not always conveniently located and some participants had to drive large distances to reach the pharmacies when they needed a new refill or new supply of Mevacor.

Despite these conditions which were not optimal for maintaining treatment, 70 percent of the population persisted to six months and about 50 percent of the population remained in the trial at 18 months.

The 56 percent still on drug at 12 months is comparable to published data on prescription

refills for statin drugs where the 12-month persistence has been reported to be 50 percent and 64 percent in two different studies and we believe that these are good results which indicate that a substantial proportion of people who choose to self-medicate with Mevacor OTC are motivated and will maintain treatment over the long term, and as noted, we think that this can be improved upon in the real-world setting.

The dosing compliance in those that persisted was also examined and found to be high. Of those that stayed in the study, about 85 percent took 75 percent of more of their tablets throughout the duration of the trial. These excellent compliance results based on tablet counts were confirmed by the reduction in LDL cholesterol. A substantial reduction between 20 and 24 percent was maintained throughout the 18 months of treatment in those that chose to stay on the drug.

What about maintaining a healthy lifestyle? Many have wondered whether or not consumers with broader access to such drugs will relax other important health-promoting behaviors and a follow-up survey was done in study 76 assessing eating and exercise habits of participants while taking

Mevacor OTC.

After six months, the vast majority of participants reported that their eating and exercise habits had either not changed or had in fact improved while taking the product.

Therefore, regarding long-term use, study 76 shows that motivated consumers complied well with long-term dosing and achieved clinically meaningful lipid changes and that the use of Mevacor OTC did not adversely affect eating and exercise habits.

Extensive data has been collected in our study program and summarized today which demonstrate that the labeling and accompanying Education and Support Program effectively guides product selection and long-term use.

The final labeling, packaging, and support materials will be prepared in collaboration with agency experts. The program will be expanded to include not only the toll-free service, but also a website to extend interactive support.

Many higher risk patients who might otherwise not be identified will be directed to their doctors for more comprehensive medical care.

The compliance program and accompanying support materials will foster long-term compliance and

will encourage periodic reassessment of one's only cardiovascular risk profile.

These materials and other opportunities will expand the messages regarding healthy lifestyle. Cholesterol testing and monitoring will be encouraged through health professionals and continue to proliferate in the community and very importantly, collaboration with all healthcare professionals and partnerships with healthcare organizations will serve to extend the benefits of treatment to prevent heart disease in a broader population.

In conclusion, with the Mevacor OTC Education and Support Program, consumers can self-manage cholesterol-lowering treatment.

That concludes my talk on label development and consumer behavior and at this point I'd just like to take a few minutes to summarize and place into perspective the important questions you've been asked to address today.

The population we have defined as OTC eligible is at substantial risk of developing heart disease and will obtain benefit from lipid-lowering therapy. The lipid-modifying effect of the 10-milligram dose of lovastatin is well characterized, clinically meaningful, and consistent with efficacy

accepted for approval of prescription drugs.

Significant coronary heart disease risk reduction has been demonstrated directly with higher doses of lovastatin in the OTC-like subset of the AFCAPS/TexCAPS study. This does provide a sound basis for estimating the risk reduction benefit which could be achieved with long-term use of the 10-milligram dose and the complete program we propose to accompany the product will further promote overall cardiovascular health.

It is clear that this important cardiovascular benefit outweighs any potential safety concerns associated with OTC access.

Lovastatin has a vast safety database demonstrating a very wide margin of safety for an OTC drug. It is generally well tolerated, even at doses which are several times higher than the proposed OTC dose and the consequences of inadvertent errors are minimized by this overall safety profile and even at higher dose ranges or with use of drugs that might cause interactions, serious side effects are rare and the risks can be reduced further by effective, consumer-friendly labeling.

The time is right for this important shift in how we can provide healthcare options to concerned,

informed, and motivated Americans. The public is increasingly aware of cholesterol as a risk factor and accurate lipid profile testing is becoming commonplace in clinical and community settings.

Consumers are interested in playing a role in their own healthcare and already are using a rapidly expanding array of food, vitamin, and dietary supplements with claims of cholesterol lowering and healthy heart benefits.

In fact, as you know, some dietary supplements being sold today actually contain a lovastatin level that is the same as that proposed for our OTC product.

Thus, it is clear that many consumers are motivated, capable, and actively engaged in managing their own primary prevention strategy and they deserve to have better options to do so.

With the Mevacor OTC program, we are committing to a new type of consumer education and continuous support. One that has evolved through repeated testing using well established label comprehension methods and novel clinical studies which examine consumer behavior in simulated OTC settings.

The results confirm that the label messages are well understood, that the product

selection decisions are thoughtful and generally correct, and that the label reinforcement tools further improve the process.

The program encourages continued consultation with healthcare professionals and fosters adherence to a healthy lifestyle and has proven that many motivated consumers will persist with treatment and sustain meaningful reductions of LDL cholesterol over the long term.

We are eager to learn from your discussions today, and our team of scientists and outside consultants are ready to assist in adding to the deliberations. Thank you for your attention.

CHAIRMAN BRASS: Thank you very much. At this time we are going to take a very short break and reconvene at 11:20. Thank you.

(Whereupon, the foregoing matter went off the record at 11:10 a.m. and went back on the record at 11:23 p.m.)

CHAIRMAN BRASS: After consultation with both the sponsor and the FDA, I have elected to change the agenda from that which was previously distributed, and at this point, rather than continuing with the FDA presentation, we're going to spend the remainder of the morning with questions from the Committee members

to the sponsor concerning their presentation.

Now keep in mind that the FDA will be making a presentation after lunch and that a number of issues will be incorporated into their presentation, and there will be an opportunity after the FDA presentation to address questions both to the agency and again to sponsor relevant to those points.

Thus, to the degree possible this morning, if those questions could be focused on the material presented by the sponsor and clarification of those points to set the stage for this afternoon's FDA presentation.

So at this point we're open to questions from the Committee to the sponsor. Yes sir.

DR. DAVIDSON: Davidson. Four quick questions. Is there any evidence-based medicine you know of for lowering events with 10 milligrams?

CHAIRMAN BRASS: And when sponsor responds, if the representative sponsor could identify themselves for the record please.

DR. HEMWALL: You're asking if there's evidence for the 10 milligram lowering events?

DR. DAVIDSON: Yes.

DR. HEMWALL: There is not.

DR. DAVIDSON: Thank you. Second is, you

mentioned that the percentage of patients was representative for race, what is percentage of African-Americans, Latinos, and Asians in your studies?

DR. HEMWALL: You're asking about the OTC studies?

DR. DAVIDSON: Yes.

DR. HEMWALL: Okay. We have a slide for that. We are still getting the technical things back on line here.

DR. DAVIDSON: While they look for that, could you define what you meant by low literacy?

DR. HEMWALL: Excuse me, I didn't hear that?

DR. DAVIDSON: Could you define what you meant by low literacy?

DR. HEMWALL: Low literacy. That was actually tested in a standardized test called the REALM test, and that's an acronym which is Rapid Estimate of Adult Literacy in Medicine, and what that does is gives the person being tested a list of many different medical terms and then there is a standardized way of assessing whether or not they know how many of those they can actually pronounce and say and that's their --

DR. DAVIDSON: Then based on those numbers, you really don't have minorities included there because 90 percent plus of your patients were Caucasians. Thank you for that answer. The final one, do you have any Spanish material?

DR. HEMWALL: Any Spanish -

DR. DAVIDSON: Any Spanish material? You say you are going to have some education and you have somebody to answer questions.

DR. HEMWALL: Yes, when we market the product. In fact, we do with our products today work with Spanish agencies in communicating to the Hispanic community.

DR. DAVIDSON: Thank you.

CHAIRMAN BRASS: Yes.

DR. JUDELSON: I'd like ask about the definition of the OTC population. It seems to me fairly clear for men it's over 40 years old, but I wonder why you chose to define the women as postmenopausal?

I mean, for example, about 30 percent of women in this country have had a hysterectomy. If you happen to live in the Boston area, that's more like 50 percent.

And in addition to that, all of your

studies have used the definition based on age, that is over 55. So I'm a little puzzled why you didn't just stick with the over 55 rather than going through this kind of nebulous definition that many women find it difficult to know if they qualify or not.

DR. HEMWALL: Yes, that's a good question, and the answer to that relates in trying to communicate a simple message to the consumer, where in fact if they are not clear about their eligibility, we'd rather have them talk to their physician because there may be other factors that they need to consider in consultation with a physician. Therefore the simplest way to direct a consumer on that is postmenopausal and --

DR. JUDELSON: Over 55.

DR. HEMWALL: Well, over 55 could also be considered.

CHAIRMAN BRASS: Yes.

DR. GELATO: Marie Gelato. I had a question, in the women, it wasn't clear to me if you stated anywhere that they were or were not on estrogen replacement therapy. Was that, I may not have --

DR. HEMWALL: In the OTC studies?

DR. GELATO: Yes.

DR. HEMWALL: No, that was not a criteria.

DR. GELATO: That was not a criteria?

DR. HEMWALL: No.

DR. ELASHOFF: Janet Elashoff. An implicit assumption in making this OTC and the way it's being marketed is that if people go off the drug, they will return to the baseline cholesterol levels that they had before.

Because if they were to stay at the new level, then probably there wouldn't be a need to take it long term, and if people who go off were frequently to have an increase over baseline, then short-term taking might be harmful in the long run.

So what data do you have about what happens to people's cholesterol level when they go off the drug in comparison to baseline.

DR. HEMWALL: I'm going to introduce Dr. Jonathan Tobert to answer that question.

DR. TOBERT: Yes. The onsets and offsets of the action of lovastatin is about one month in each case. So it takes about a month to get the maximal reduction in cholesterol and if you stop taking the drug it returns to baseline over the course of a month without any overshoot.

DR. ELASHOFF: Data to support that statement?

DR. TOBERT: The original studies with lovastatin which I actually presented at the original medical advisory panel meeting.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: The carton label includes recommendations that patients seek physician advice if they have cholesterol over 240, diabetes, or hypertension. And in the meeting briefing material that you gave me, you indicate that the reason for that is to avoid under-treatment in higher risk populations.

I wonder if you could explain why similarly important contributors to cardiovascular disease such as smoking or family history are not included in that list of patient characteristics that might prompt you to advise this patient to consult their physicians.

DR. SLATER: This is Eve Slater. The family history issue and the other risk factors that you mentioned are clearly important. The information about considering family history is actually included inside the package.

The outside of the package, there has to be a very focused attempt to boil down exclusions and the reasons that we excluded patients with more than

one antihypertensive is not as much that we felt they were high risk, clearly they are the higher risk, but we felt that they should be under the regular care of a physician, and so that's why there was a slight difference in our categorization of the risk.

DR. GILLIAM: On your slides 28 and 41 I think it was, where you showed the graphs from the AFCAPS/TexCAPS studies, it looks like there is needed at least six months of therapy before you actually get any benefit and risk reduction and in your data from your briefing materials, it looks like at least 30 percent of the people drop out only after eight weeks of your studies.

And I'm just concerned that we're going to have a compliance problem with people being on the medication long enough to really see a benefit and if you have comments on that?

DR. HEMWALL: We agree that most people that start this drug should stay on the drug, but in reality, some people will not stay on the drug and what we are really after is getting to the motivated consumer that wants the benefit of this product and will stay on the product for the long term.

Admittedly, some will drop out early and not retain the benefit. It's the ones that have the

opportunity to stay on it and want to stay on it that we're targeting this product for.

DR. TAMBORLANE: The issue of the low HDL as an overriding risk factor has not been addressed in any of the presentations and is not included as one of your lipid profile issues. Could somebody address that issue and explain why?

DR. HEMWALL: I'm going to give this question to Dr. Beere and see if we can answer that. There is a different answer regarding what's on the label versus what's been shown in the benefit and I'll ask Polly to demonstrate that.

DR. PEERE: Is your question regarding the risk of the OTC-eligible population or the benefit?

DR. TAMBORLANE: Yes. You related the potential cardiovascular benefits to the AFCAPS which tended to have much lower HDL values than the HDL values that you presented in the patients in your studies and the suggestion came up in the public presentations that if you had a normal HDL that you would lose most of the cardiovascular benefit and therefore would be treating a large proportion of patients on the over the counter who might not get a benefit. So that's the question.

DR. PEERE: I'd just like to clarify with

regard to AFCAPS, the decision was made to enroll persons who had relatively lower HDL than the general population and the range encompasses the median for that age range in the U.S. adult primary prevention population. Only 35 percent have what would be considered a risk factor of low HDL. That is to say, less than 35.

The extent to which the results of AFCAPS are applicable to the potential benefit using long-term over-the-counter lovastatin 10 milligrams, is related to the way in which we confirm the cholesterol hypothesis, that for a 1 percent decrease in the case of AFCAPS total cholesterol, LDL, or the ratio, you have at least a 2 percent decrease in CHD risk.

So the actual risk associated with HDL does not influence that relationship, but it is true that people with low HDL have higher risks than people with high HDL, and in fact, we saw that within AFCAPS there was an inverse relationship between HDL and risk.

But we don't think it would be appropriate to take HDL out of context of global risk factors and risk assessment because a person could have a higher HDL and be a smoker and be at much greater risk than someone with a lower HDL who is a nonsmoker.

Framingham has established the relationship between risk inversely related to HDL up to a level of 60. Does that answer your question?

DR. TAMBORLANE: I'm not sure, because the AFCAPS data wasn't disproportionally weighted because of the low HDL. When you break out the data by the over 40, I thought I saw on the review documents, that the coronary risk was not altered, as a very low risk, 2.3, 3 percent, and that was not affected by therapy.

DR. PEERE: What we did was tertile analysis for all the lipid subgroups in order to look at the consistency effect across the ranges and we found, in fact, with the test of heterogeneity for any of the lipid tertiles, that within any tertile the magnitude of effect was consistent with the overall effect. The study was not powered to detect efficacy or treatment benefit within any single tertile.

DR. TAMBORLANE: Can I ask a separate question? The issue of safety comes up with this issue about hepatic toxicity. I would assume that most of the studies excluded patients who had elevated liver enzymes on entry, and furthermore, that even in clinical practice, in a prescription environment, that most physicians would do liver function studies as baseline.

Do you have any data on the effect of statins on patients who have baseline elevations in liver enzymes?

DR. KORN: Scott Korn from Merck. You are correct that most of the controlled clinical trials have exclusion criteria, known diagnosis of liver disease or marked elevations of ALT or AST at baseline. However, because of the phasing of the run-in period, there are patients in AFCAPS/TexCAPS who had normal ALTs at the visit where they qualified for treatment, but when they actually came back and started drug, they had an above the upper limit of normal elevation at that time.

They were allowed to continue through and the fact that even though there were about 150 patients -- this has the exact numbers for us -- so there were 136 patients in the lovastatin group who had an elevation of one to three times the upper limit of normal before they actually started drug and they were not at higher risk for developing any serious liver injury during the course of the trial.

CHAIRMAN BRASS: I'd like to follow up a little bit on the AFCAPS study and its extrapolation to the OTC population. Am I correct in recollecting that the AFCAPS was designed to a specific LDL target

goal of 110?

DR. PEERE: Yes, it's true.

CHAIRMAN BRASS: Could you comment philosophically about the utility of an LDL target in managing a patient with hyperlipidemia? The NCEP recommendations always are based on targets, AFCAPS is based on a target. Your recommendation is no target?

DR. PEERE: Well, our recommendation for the OTC-eligible population is that the 10-milligram dose would be efficacious and produce beneficial lipid modifications for that population. Only a minority of them would have, in fact, an LDL target less than 130, about 40 percent.

We showed that over 70 percent are able to have an LDL less than 130 with a 10-milligram dose.

CHAIRMAN BRASS: Am I also correct that in AFCAPS, titration to achieve the goal was incorporated in the design and that despite starting at 20 milligrams, fully 50 percent of the population was subsequently titrated to 40 milligrams?

DR. PEERE: Yes. I'd like to point out that the rationale for that was twofold. One, it was started with NCEP1 with the anticipation there would be an NCEP2 and we did not know what the future target goals would be.

Two, we didn't know if studying a lower risk cohort you would need more aggressive treatment in order to gain a treatment benefit.

Three, we recognized that people have variable responses to statins and in fact, those who required titration had about 6 percent less LDL reduction than those who didn't.

Furthermore, we wanted to very clearly differentiate between the placebo-controlled group that was receiving dietary instruction in a group setting every six months in clinic in a wellness clinic atmosphere.

We wanted to clearly differentiate the magnitude of lipid modifications with lifestyle or behavioral changes that were currently recommended for that cohort from what we saw with drug. And in fact, though the goal was less than 110, very few people got to less than 110, about 80 percent did get below 130.

CHAIRMAN BRASS: So, I guess where I'm becoming confused is the degree to which the AFCAPS population was enriched by OTC participant, or OTC-eligible by your definition, and the degree that data is being used as a precedent for OTC efficacy.

It seems to be that what you've done is prove the opposite, that in fact, you need a target to

achieve that degree of efficacy and you need a learned intermediary to ensure proper dose titration to get the efficacy, not that letting consumers do their own thing would yield that same efficacy.

DR. SLATER: I have a concern actually and I want to get back to a couple of other issues, because I think the Committee is not getting the right picture. We're not doing a good enough job in explaining to you.

We have presented the AFCAPS data as supportive data, but it's only one of the several lines of evidence which you can use mentally based upon the breadth of experience with the statins to provide an estimate in your own mind of what you think the proposed benefit of this drug would be in the OTC population.

We are not in any way trying to make a direct extrapolation between clearly the differences in AFCAPS that you're all well aware of, the forced titration, and the attempt to treat to goal, although as with a lot of programs, many patients don't actually achieve goal. And also the dosage which we are well aware of.

The primary use of the AFCAPS population here is to show you that since so many, over half of

the AFCAPS population are not recommended for therapy by current guidelines, not recommended for pharmaceutical therapy, and the fact that so many of them have done well, we are using this as primarily a support for safety data, and again, one of the lines of evidence that you can use.

When Dr. Beere did her estimations, her estimations were not based on AFCAPS, and as she told you, we didn't show it on the slide, but as you may have heard, the number of events prevented, if you actually calculated from AFCAPS, would be much higher than the ones that she actually presented. The ones she presented are based on the 1 and 2 percent mathematics. So that was the one point I wanted to make.

The other point about HDL, again, the AFCAPS trial had to be framed in order that we could do the trial in a reasonable number of patients, e.g., 6,000, in a reasonable amount of time, e.g., five years. It is not that these drugs would not provide benefit over longer periods of time in a broader population, if in fact we did a longer study.

So please don't get the message, some of you are not as directly involved in lipid data, that statins won't work in people with HDL. The data in

AFCAPS are limited simply because we didn't study long enough in a larger number of patients and probably if we included more women, you'd have even seen more benefit because one of the points of AFCAPS, as you know, was to try to get at least half the population, and roughly half of population being women, and this is the first trial to have shown substantial benefit over time in women.

I did also want to get back to your question, Dr. Gilliam, on compliance because I don't think we gave you a full answer on that, and I know that's another concern.

The OTC package of trials that you had were primarily designed as front-end trials so we could, as you can see, improve patient selection over time and that's why you saw a continuum of trials. They were not primarily designed to look at the issues of compliance or at motivation for compliance and the consumer package that Dr. Hemwall showed you in terms of the patient mailings and the longer term interventions that we hope to employ to improve compliance were never tested.

The compliance numbers that were drawn out of 076 in particular, which is the longest, it was the earliest trial, the first trial, and therefore the one

that we have of longest duration. These patients had to drive, many of them over an hour, just to get more medicine. So it's not a surprise that the compliance figures don't look great.

As you know, Dr. Avorn and others have published data that, generally speaking, show compliance with Rx statins is about 64 percent.

We feel that we are in about the ball park. We feel that the LDL numbers that you saw over 18 months, for those patients who remained in the trial, who were 20 percent reductions six months, 12 months, 18 months. So the people who remained in the trial, who were compliant in that sense, were really getting effective cholesterol lowering for 18 months.

The hope would be, and we just have not been able to test it, the hope would be that over time, with the mailings, with the prompts, with the Mevacard whereby people are going to be connected now to a system whereby they can actually communicate about their health, we would achieve much better numbers.

But we really don't want to stand by the compliance numbers in the package because we didn't really attempt to go after that in this program.

CHAIRMAN BRASS: If I could just continue,

and I want to emphasize how that valuable data, the primary prevention data, in AFCAPS was and how it is beginning to change the treatment and I don't think we've seen that integrated into some of the behaviors you've presented.

But would you agree then that if we take the OTC-eligible population that was in AFCAPS, again using your definition, that the efficacy of the antilipidemic treatment that was used in AFCAPS is superior to OTC treatment?

DR. SLATER: No question. Not a question.

CHAIRMAN BRASS: Then I would ask you to address the hypothetical risk, one of the hypothetical risks that has not been mentioned, that the availability of an OTC product of recognized efficacy will be viewed by the consumer as alleviating the need for intensive care and paradoxically decrease the number of patients who get optimal therapy such as was provided in AFCAPS.

DR. SLATER: That's a wonderful question and it's one that is not entirely resolvable by whatever intervention you want to use in whatever population to try to motivate them, and this is not a magic bullet, what we're proposing here. What we are proposing is to engage the primarily low-risk

population.

So, obviously in the screening process we try and shuttle patients with the higher risk to identify themselves and go seek better therapy. All of the subsequent mailings, all of the subsequent follow through that would be provided in this rather unique way would trigger patients if your cholesterol has not gone down. If it has not gone down a certain amount, call your doctor. Take advantage of this, that, or the other.

So there is no question that we would try to motivate towards improved care across the board, but this is provided for everybody, not in an absolute way, no.

CHAIRMAN BRASS: Dr. Tamborlane.

DR. TAMBORLANE: Yes, I think that segues nicely to a sort of procedural question I have. I mean, this is obviously precedent setting, as we heard, to making this OTC. If the drug becomes over the counter, there is no legal requirement that the company or other companies when these agents become generic, have the same kind of education and follow-up programs. Is that true or not true?

DR. SLATER: No, that's very, very true and I think you are well aware, as we are as well,

that many patients now, how they do it I'm not certain, but many people now can access statins easily through the internet, through webs, and through a lot of other ways, so there are a lot of other ways to get statins that are not going to be surrounded by this kind of program. If you engage to enter in this program, it's a very different sort of thing.

DR. TAMBORLANE: So while it's admirable that you have the educational program, it may not be followed through in the future once this is approved?

CHAIRMAN BRASS: Dr. Temple, you'd like to comment?

DR. ROBERT TEMPLE: It isn't necessarily true that a generic would not have to take on certain obligations. We've had two cases in which generic companies have been obliged to follow distribution limitations or educational limitations. One is ticlopidine and other is clozapine, because those were thought to be important to the safe use of the drug. So I don't think we are devoid of resources in that area.

DR. LUKERT: I was wondering from your OTC studies if you know what percentage of those patients were taking herbal preparations or dietary supplements. It seems like the "worried well," a

group of people who would be more likely to take advantage of an over-the-counter statin may be people who are also taking herbal preparations that could have some unpredictable interaction. Do have any data on that?

DR. SLATER: We're just asking. I don't know if we do. We only asked about a particular herbal. There has been, even since we started these studies, as you know, there has been a proliferation of these availabilities, so we only asked about the one that was available, I guess when we began the studies, and I'm not sure what that number is, but we'll find out. Who was taking drugs to lower cholesterol, so it's a very general question and that was 11 percent.

CHAIRMAN BRASS: Dr. Johnson.

DR. JULIE JOHNSON: I have a couple of questions that are in some ways related to the label. The first one relates to grapefruit juice, which wasn't mentioned at all, was talked about a little in your briefing materials. And the study that you seem to be relying on to suggest that grapefruit juice isn't important is frankly a rather strange design where the grapefruit juice was given 12 hours before the lovastatin, but your comparative drug was given an

hour or two after the grapefruit juice.

And I think it's very clear from the grapefruit juice literature that co-administration of the drug, drinking the grapefruit juice shortly before or with the drug is more important than many hours previous.

So I'm curious why the study was designed that way or why you chose not to just choose the safe route and include that in your exclusion list with the drugs?

DR. SLATER: Grapefruit juice is a very important topic and if it's all right with the chairman, we'd like to present a very concise presentation actually of our data. We tried to go through it very quickly for you in the primary presentation, but we have a lot of data.

People know grapefruit juice has been implicated in the 3A4 system and I'd like to introduce Jose Vega from our clinical pharmacology department and Jose can actually present the design of the studies for you compare and contrast what is as you refer to the grapefruit juice literature.

CHAIRMAN BRASS: Since I think this will be also discussed after, I just ask you to proceed succinctly.

DR. VEGA: Absolutely. One question was the design of the study, right?

DR. JULIE JOHNSON: My question is, the design is very unusual compared to most grapefruit juice drug interaction studies where the grapefruit juice is given fairly close in timing to the dose of the drug, and the second is more a global question with the recognition that grapefruit juice is a potent inhibitor of CYP3A4, why not take the safe route and include that as a warning on your label?

DR. VEGA: Well, in terms of what you just said, I would first disagree with that conclusion that grapefruit juice, across the board, is a potent inhibitor of CYP3A4.

Now something in grapefruit juice inhibits CYP3A4, but not all 3A4 inhibitors are potent. They vary. Some are weak inhibitors, some are moderate inhibitors, and some are potent.

Now grapefruit juice only in large amounts approaches the magnitude of inhibition that would be considered potent. So I think it's critical, and in fact the specific intention of the study essentially is to show that.

There was a prior study using large amounts of grapefruit juice, again in the kind of

amounts of grapefruit juice that we do not think are realistic, but large enough that you achieve levels of inhibition that would be considered potent.

In that kind of design, which is the other extreme, there is a significant effect on exposure at the lovastatin. And the reason we did the study this way was to show the other extreme, just to show in a more realistic situation where somebody takes a regular glass of grapefruit juice in the morning and lovastatin as recommended in the evening, that the effect is only 34 percent elevation, which is not felt to be clinically significant.

So in terms of the design, of course there are all the stories with grapefruit juice comparing the different separations between the grapefruit juice and the drug being tested.

Based collectively on those stories, we would expect, had we given the grapefruit juice together with the lovastatin, the effect would have been somewhat higher, but not dramatically. Maybe instead of 34 percent we would have seen a 50 percent or say 60 percent.

CHAIRMAN BRASS: What do you base that on?

DR. VEGA: There have been studies in particular with felodipine where they have actually

looked at the effect of grapefruit juice given 12, 24 hours, or together with the felodipine.

There is also a study done by a different group looking at the grapefruit juice given together with various statins.

And collectively putting that together, I'm talking about a single glass of regular-strength grapefruit juice, given together with the drug versus 12 hours apart.

It all has to do with the mechanism of action of grapefruit juice. It is not a competitive inhibitor. The effects actually do last. I can go into that in more detail if you wish, but basically we do believe that the effect would have been somewhat greater had we given it together rather than 12 hours apart, but not significantly greater in a clinical sense.

DR. JULIE JOHNSON: Well, you still haven't answered my broader question which really is why you were leaving it off. I would suspect that there are many more people in this country who drink grapefruit juice in maybe what you would consider very large amounts of grapefruit juice, than there are patients on cyclosporin for example, which is one of the drugs you have listed. And I'm really just trying

to understand why to not include that on your list of potential problems?

DR. HEMWALL: Well, after you've heard what Dr. Vega has said, our view was that the interaction with grapefruit juice was not thought to be of magnitude to warrant putting on the label.

However, having said that, I think if there is a consensus that that is still a reasonable warning and should be provided, we'd be very willing to consider that in any labeling discussions.

DR. JULIE JOHNSON: My other question about the label, and this sort of has to do with the issue of long-term use, is why there's nothing really in the label, and maybe it would be on that first sentence that says "use," there's nothing that indicates that this therapy requires long-term and continuous use to lower cholesterol and as it says "may lead to a healthier heart."

I'm wondering again, what the justification for not providing some reinforcement that this is very long-term therapy to obtain those benefits?

DR. HEMWALL: That's a very good point and in fact, that is the message that is contained within the package, within the materials that one would get

when they enroll in a compliance program and it would be a continuous reinforcing message for the product.

It's not something that's written on the outside of the package which is written in Drug Facts format, but it is certainly reasonable to consider new versions of labeling that would include that if that was felt to be important.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: Dr. Beere, in her discussion of the efficacy of lovastatin, showed several slides that presented the reductions as percent reductions. Within the briefing material that you gave us, I couldn't find any absolute numbers described as either a mean or a range for the OTC studies or the placebo-controlled studies of the 10-milligram dose and I'm looking specifically at slides 34, 35, and 36, and I'd like to know within the 10-milligram dose studies, the placebo-controlled and OTC, what were the actual numbers? What was the mean total cholesterol?

DR. PEERE: I'll show a table from the original NDA that shows both the mean by group and the percent change for the placebo-controlled study that was done, part of the OTC development program showing that in the lovastatin-treated patients LDL was reduced from 143 milligrams per deciliter to 116, mean

percent change of 17.5.

Similarly, total cholesterol was reduced from 232 to 204, percent change -11 percent. And HDL was increased from 56.5 to 59.8, or 6.7 percent.

DR. NEILL: Several times earlier today I've heard that I might not expect a benefit in patients with HDLs above 40, and one of the reasons I wanted to see that is because I see that the main HDL in those studies of the 10-milligram dose was high 50s.

Is it your contention I trust that we should believe that there will be a meaningful clinical reduction, not just in the numbers that patients will presumably come in and have measured, but --

DR. PEERE: It could include meaningful reduction in risk, even in people with higher HDL. I think we have two bodies of evidence. One is the epidemiologic evidence from Framingham and other studies showing that that relationship continues up to an HDL of 60 so that people with an HDL of 50 have less risk than 40, less risk than 30.

Two, we have a lot of clinical trials, 4S, lipid, and others, that show the magnitude of risk reductions related to LDL reduction independent of

HDL. Now both WOSCOPS and AFCAPS showed that there was more absolute benefit if your HDL was lower, but that didn't influence the magnitude of treatment effect upon LDL and we still believe that these studies considered in total support the cholesterol hypothesis and that efficacy will influence benefit.

DR. NEILL: And I remain safe in assuming that there is no data from a prospectively designed trial using the 10-milligram dose that shows that, but rather that these are taken from exactly what you said, Framingham, AFCAPS, 4S, etc.?

DR. PEERE: That's correct.

DR. EDWARD KRENZELOK: I have about three questions. I really appreciated the fact that you used the AAPCC data to show that the drug is really safe in overdose. Indeed it is, in my experience.

We know that every good drug taken excessively, as Paracelsus said 500 years ago, "The only difference between a remedy and a poison is the dose," even these things in very large amounts maybe have the potential to cause problems.

So have you done anything to conform with child-resistant packaging at all? Does this conform to child-resistant packaging, the new product that you're proposing?

DR. HEMWALL: Yes, all the packaging that we have proposed in our OTC presentations are child resistant.

DR. EDWARD KRENZELOK: And another question. One of your last slides had a very nice collage of showing really the role of the learned intermediary in implementing good care for these people. It seemed to at least in the pharmacist's role, perhaps the nutritionist's role, the physician's role, a variety of people.

Will the product then be focused for sale in, say pharmacies and in places like that compared to picking it up at our local convenience store? What's the proposed marketplace right now for the drug?

CHAIRMAN BRASS: I'll let sponsor answer if they want, but I'll just remind you that anything they say is nonbinding and they'll be able to do whatever they want within the constriction of the agency.

DR. HEMWALL: It's not in our interest to have this product available in a convenience store. We would want to have it available where there are people who have been trained and had separate education programs that would be provided by our company to make sure that the use of this product and

the answering of questions from consumers was done in a responsible manner.

DR. EDWARD KRENZELOK: Thank you. One more question. You've described a toll-free service. Can you tell us who will be answering the calls, how they'll be trained and educated, and give us a little bit of a perspective on will this be a 9 a.m. to 7 p.m., seven-day-a-week service or how it will be staffed?

DR. HEMWALL: We envision this to be a very unique service in which there would be people on call 24 hours a day. The people that are responding to the call would be trained specialists and they would be working from a computer algorithm and a script which would interview the consumer exactly on their eligibility criteria and then follow through with additional questions based on their answers.

There would also be a physician on call or within the proximity to answer more detailed questions should that need arise. But that person immediately on the phone would be a trained specialist.

DR. EDWARD KRENZELOK: So in a sense this will serve as kind of a surveillance or toxicosurveillance as well then?

DR. HEMWALL: Exactly. In fact, that is

the real additional benefit of this program is to be able to collect additional information from patients or consumers about their use and their continued use and use it also as a vehicle to gain post-marketing surveillance information.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Davidson again. Who is that trained specialist? Who is that person and how is that person going to train and what is the background?

DR. HEMWALL: I'll introduce Dr. Stephanie Larouche who is the director of our OTC studies.

DR. LAROUCHE: The requirements are not to be a medical professional, but to be a college-educated individual who has gone through a training program that relates to how to interview the consumer on the line according to the script in order to assess their eligibility criteria and give them the appropriate advice according to the script.

So they are not medical professionals, but they're educated people with a training program that makes them product specialists.

CHAIRMAN BRASS: Dr. Uden.

DR. ROBERT UDEN: While we're on the toll-free service, Dr. Hemwall, you on slide 229 presented

some information about using the toll-free service and after label reinforcement tools 83 percent of, actually 17 percent of the people who still had higher cardiovascular risks, stroke, DM, hypertension, were still using the drug and apparently incorrectly.

And so, if that's how you're supposed to interpret that slide, 17 percent of the people who were using the drug, or going to use the drug, were using it. And you think that's acceptable to have basically one out of five people using the drug when they shouldn't be according to your labeling?

DR. HEMWALL: No. Actually we think we can improve upon that and that study used an earlier version of the label which did indeed have some flaws that we identified in our studies and were corrected in the following studies where we had much better label comprehension in terms of actual understanding of the message.

It's very clear that we want these people to go see their physicians if they've already got preexisting heart disease.

DR. DONALD UDEN: But wasn't this the point where it says including the toll-free service down their higher cardiovascular risk. It doesn't seem to me then that the toll-free service was very

effective in keeping those people who had other risks from using the drug versus going to see their physician.

DR. HEMWALL: Yes, what is indicated here is that they had the opportunity to call the toll-free service, but in fact, not everybody did avail themselves of that opportunity and we also think that we did not have, in the package that you have with you, ability to incent the consumer to call the toll-free service with high-value incentive that would actually create a much greater number of people calling.

DR. ROBERT UDEN: What experience do you have then of those incentives to call the toll-free number and that that will actually do what you hope it will do?

DR. HEMWALL: Well, the incentives that we are able to offer in the clinical studies were not as I think valuable as the ones we could offer in the real world. For example, a free month's supply of Mevacor or a free cholesterol test are a number of different things.

We used incentives in our trials for an American Heart Association cookbook or a monetary cash incentive of 10 or 15 dollars. We think we can do

better in the real world with real people spending their own money on this product.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: I want to get back to the compliance issue for a minute because it goes back to some of the information that you were talking that you needed to treat 60 to 70 people to prevent one event and that only over a five-year period are you projecting that you can prevent 150 events in 10,000 people. So it gets to the compliance of how many people are really going to be affected and helped by bringing this medication over the counter.

DR. PEERE: That's hard to predict. We've based this argument to benefit based upon the benefit that the individual would have, which is to take the product and the efficacy of the product at 10 milligrams.

Certainly, in comparison to diet, where you might expect a moderate, middle ground, of total cholesterol reduction of 10 percent, which would be a good response, we would be preventing twice as many events, so that this would be an additional effective option to lower individual cardiovascular risk and maintain and promote health. And most diets do not increase HDL which would also be an added benefit for

those who had low HDL.

CHAIRMAN BRASS: Dr. Tamborlane.

DR. TAMBORLANE: The issue of making this OTC and exposing individuals to the drug that may not be appropriate actually made me think of my hat as a pediatric endocrinologist and that we know that there are many well-meaning parents out there who believe that they can deal with a lot of health issues over the internet and there is a lot of cholesterol screening going on in pediatric offices.

What's to preclude making this OTC might expose a fairly substantial number of children to inappropriate use of this agent? Could you comment on that?

DR. SLATER: The box obviously specifies age. Our concern here would be the issue of the food additives and things like that that are out there that are, who knows how many kids are taking those.

DR. TAMBORLANE: But that's sort of what my mother told me, two wrongs don't make a right.

DR. TOBERT: Jonathan Tobert. I would just add a comment that lovastatin has been studied in children and that study was published in JAMA about a year ago. The dose was 40 milligrams and was very well tolerated.

Obviously we are not suggesting this product ever be used by children, but should that happen, the results would be most unlikely to be harmful.

CHAIRMAN BRASS: Yes.

DR. GRADY: You've presented us some data on how consumers can understand if they fit the criteria for using your medication and if they can understand drug contraindications and so forth, but really the reason this is a sort of unprecedented over-the-counter medication is because it is a preventive therapy.

And it's difficult for people, doctors included, to understand the benefits of preventive therapy, and I wonder if you've done any studies to try to figure out whether your labeling conveys the real benefit that an individual is likely to accrue.

So for example, based on your own statistics, you suggested over say five years, maybe 5 percent of people in your OTC population might have a cardiac event, and with treatment, even if they have good compliance for a total of five years, you might cut that down to 3 or 4.

So of the 100 people who decide to take your product, 1 or 2 will benefit, and the other 98 or

99 will have taken it, paid for it, etc., for no real benefit, and that is kind of difficult to understand.

And your label, one of the things that concerns me a little bit about your label is you sort of suggest that all these people in your OTC population have bad cholesterol and it sticks to the arteries and it builds up and eventually it totally obstructs those arteries and it kind of implies that they're all going to have a heart attack, and I think it maybe overestimates the real benefit.

Have you asked people what they think is really going to happen to them if they take this stuff?

DR. HEMWALL: The immediate answer to your question is no, we have not asked people that, but I think you raise a very important point and this is something that we would want to do in our labeling is to communicate what exactly could be defined in terms of risk reduction.

That's a very difficult concept for consumers and it would be probably worth studying in a comprehension type of study to find out what messages work best.

Nonetheless, having said that, the message that we're still trying to get across to consumers,

and also to this committee, is that it is good and beneficial in a general sense to lower one's cholesterol and that this product lowers cholesterol. And if you have lower cholesterol, then you will have a benefit which is a lot harder to explain in the longer term, but that is the real message that consumers are getting now and that they should be getting from a product like this that will reduce risk, but that is harder to quantify and explain.

CHAIRMAN BRASS: Dr. Elashoff.

DR. ELASHOFF: The label mentions allergy. No mention of allergy was made in the safety information. What is the allergy risk or what form might that take?

DR. KORN: The prescription circular mentions that with any of the statins, occasional a hypersensitivity syndrome has been reported, unclear whether it's truly drug related. And that is an incredibly small number of spontaneous reports that that's based on. So occasionally it's a rash or nausea, vomiting, or some airway symptoms, but again, incredibly rare.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: In your study 081, 29 percent of your patients were not eligible for therapy

for different reasons. In real life, if this pill becomes an over-the-counter pill, you're not going to really monitor people to find out if they're eligible or not eligible for intensive treatment, and therefore, I'm very concerned that we're going to give a sense of security which does not exist to these patients. How do you answer that question?

DR. HEMWALL: I think one thing we have to of course do is make sure that the labeling messages are clear and understood by the consumer and measured by label comprehension testing to the best of our abilities, then it's obviously up to the consumer to heed the label and follow the directions either through the direct reading of the label or through the label support materials in reaching the toll-free service or in the other materials reinforced in the video tape that comes with the label.

Ultimately it's up to the consumer to make the correct decision and there is responsibility that is being asked of the consumer in the use of any OTC product to read and heed the label.

Having said all that, the consequences of an error are then what is of concern and we believe that the consequences of making an error along the lines of what have been discussed here, are very low

in terms of outcome of a harm to the individual.

DR. DAVIDSON: My real concern is over-the-counter products that are short-term for pain. This is serious business. When we have 29 percent of people that are not eligible, where we're treating either to prevent a condition that could be eventually very expensive. I don't think that you answered my question.

DR. HEMWALL: I'll try again. The number of people that are not eligible encompasses a lot of different ineligibility criteria including men or women that are younger than the age cutoff, people that have cholesterol lower than 200 or higher than 240, and the number of people that actually have what we viewed to be a safety warning eligibility was in fact far lower, and we hope to improve that with our improved labeling in the study that you saw using label three.

We did not get as good of a result as we would like and we believe our enhanced label number five will give a better result and is strong by the comprehension.

CHAIRMAN BRASS: Dr. Williams.

DR. WILLIAMS: One of my concerns is that one of the largest populations that utilize over-the-

counter preparations is the elderly. We've talked about the youth and we've talked about possible exclusionary individuals, but my comfort level is that if we expose this product on the shelf to a group of individuals who are geriatric bound, what is going to be our concern? Will they not be using the product with some degree of safety?

DR. TOBERT: Yes, I just want to make sure that I heard your question, it was a little hard to hear back there. Your concerned about will all the patients be able to understand the label and will they, or won't they get benefit?

DR. WILLIAMS: Secondly, the second part of it of course, but the largest users of over-the-counter preparations that we've come across have been the elderly and they want to self-medicate. My concern is having this product available for them. They see it, they want to lower their cholesterol for various reasons, they think they'll live one more year, but is the product going to be safe in that particular environment?

DR. TOBERT: Well, all the evidence is that lovastatin and statins in general in fact, are safe in the older population. Whenever we have looked we have not found any differential safety. We have

not found that older people tolerate lovastatin any worse than younger people. So I don't think there is really a safety issue.

It is true that the clinical trials with statins to date, have not included very old people. Here we have the data which I was just referring to, from EXCEL. This is as you recall a study in 8,000 patients randomized to placebo, one of four groups taking various doses of lovastatin, up to 80, for a year, and there was basically no effect of age on safety. Does that answer your question?

CHAIRMAN BRASS: I'd like to explore the drug interaction 3A4 issue just a little bit more following up Dr. Johnson's questions. I was confused. Is it your position that it is important that consumers who are consuming 3A4 inhibitors not use this product OTC and that your label conveys it, or that you will make an effort to do so, but it really doesn't matter because the drug interactions aren't clinically significant? Which was your bottom line?

DR. KORN: The bottom line is our label instructs consumers not to use lovastatin if they're on 3A4 inhibitors and we believe that that is appropriate.

However, given we are always discussing

outliers, if they don't realize that and somehow take it, we believe that risk would be relatively low to people taking 10 milligrams to have a clinical consequence from a pharmacokinetic drug interaction. So we do not want people to take it, but if they happen to misunderstand the label, we believe there is a margin of safety.

CHAIRMAN BRASS: Do you know what percentage of consumers who are taking one of those drugs could identify it when reading your label? In other words, if a consumer is taking erythromycin because it was prescribed for bronchitis and they read your label, they may know that they're not supposed to take this if they are taking erythromycin, but they may be not aware that the product they were given is actually erythromycin.

DR. KORN: While my team is looking for that answer, we'd like to point out of course that erythromycin is only available by prescription as are the other potent 3A4 inhibitors, so if the patient does his job and tells the pharmacist that he's taking a nonprescription-level statin, then the pharmacist will --

CHAIRMAN BRASS: That's exactly the problem. We know consumers don't consider OTC

products drugs and when they're giving drug histories to physicians or pharmacists, they routinely omit OTC products they are taking.

DR. KORN: Here's the slide.

CHAIRMAN BRASS: But this isn't my question. I understand they can read the label and say, "Oh, erythromycin, I shouldn't take it," but if they were given a product that has a vial, that has some brand name product on it, what's the odds of them recognizing that they're taking erythromycin?

DR. KORN: We have not tested that exact study asking consumers if they recognize the generic ingredient by brand name.

CHAIRMAN BRASS: And for many of the products I think, particularly where there is even a potentially greater risk for mechanistic reasons, the other lipid-lowering agents, I think the possibility of consumer confusion about the kind, because they're all going to be brand name products, and the ability of the consumer to recognize would seem to be a potential risk.

The other question I have is what's known about the genetics of 3A4 activity and are there populations that have very low 3A4 activity genetically that might also be at relative risk?

DR. KORN: Dr. Vega.

DR. VEGA: Yes. CYP3A4, there is no defined genetic polymorphism per se in the sense of say CYP36 or 2C19, where they are clearly defined genetically, and defined in poor metabolizer and normal metabolizer. But clearly, there is a variability, a broad variability, from subject to subject in their CYP3A4 activity, both in the guts, in the intestine, and in the liver.

CHAIRMAN BRASS: Could you estimate what the 95 percent range of, how many fold difference in 3A4 activities is encompassed by 99 percent of the population in that distribution curve?

DR. VEGA: The variability is roughly at tenfold variability.

CHAIRMAN BRASS: So that an individual on the bottom end of that curve, taking 10 milligrams per day will get the equivalent of 100-milligram dose, because of the tenfold distribution?

DR. VEGA: I wouldn't jump to that conclusion.

CHAIRMAN BRASS: Just asking. I'm trying to get a sense out of this, how big that distribution is and whether or not, when you start talking about a very broad population, how large the population

variability is?

DR. VEGA: I think the bottom line is despite the large variability in the population, this drug has been used by over 24 million patient-years and in that context, in the reality of the variability, it is still very safe.

So taking all of that into account, even for the prescription dose, it is still very safe and is proven safe. So we actually have the advantage of having the extensive clinical experience in real life, it's not hypothetical, it's real.

CHAIRMAN BRASS: Well, the other thing that appears to be real is that the incidence of significant muscle adverse events appears to be dose related, and that's why I'm trying to assess the degree of safety in a population basis that the 10-milligram dose actually represents, because in point of fact, you only have several hundred thousand years, the percentage that is 10 milligrams is much smaller compared to the higher doses, because of the rarity in which that is used.

And so the answer may be we don't know, but I'm just trying to get a sense whether or not there is known how much population variability there are as in the pharmacokinetics of this drug.

DR. VEGA: That's in terms of pharmacokinetic, yes.

DR. BLEWITT: I just wonder if I might make a comment about that. You know, there are drugs on the OTC market today that are associated with drug interactions and they're labeled as such. They are labeled in different ways and in the case of, for instance, ibuprofen, there was a mall intercept study a number of years ago which indicated that consumers understood a more generic type of statement such as, "If you're taking prescription medications then you should talk to your physician."

So I think the debate is do you have a litany, do you name every possible drug that could be an interaction? If it's erythromycin, then do you name every brand of erythromycin? That's something that really has to be worked out.

You could take it to the extreme, but I think that that is something that has to be worked out in terms of exactly how that's done.

It was done in the case of H2 antagonists, you have a certain label there, and you have it for ibuprofen products, so I don't think that you have to go off the cliff on an issue like that.

CHAIRMAN BRASS: Mr. Krenzelok.

DR. EDWARD KRENZELOK: This morning we heard the American Black Cardiologists tell us that African-American population was at a higher risk for cardiovascular disease and then they emphasized also that this population was underserved. To me, underserved would probably suggest that they don't have access to lipid profiles and to a good profile of their own health and so on.

But I guess my question is wondering whether or not you have any infrastructure in the plans, anything at all, any mechanisms in place, that might address the needs of this underserved population to make a drug like this more available to them to help reduce this risk that they described?

DR. HEMWALL: The answer is absolutely yes. We would intend to work with the communities to increase the diversity of all the populations that would have access to this product and working with experts within those communities to get the message out and devise special marketing programs to address people in those communities.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: I disagree with you, because if the company would be very interested, I would have seen 25 or 30 percent of your patients in

the clinical trials of minority origin and you have less than 10 percent.

DR. HEMWALL: That's a very true observation. In fact, when we recruited for our clinical trials, we advertised in minority communities. We advertised in Spanish media, radio, television, and print media in Spanish to recruit for our trials, and the results of the trials are the results of the people that were interested in coming after hearing those messages, as far as the demographics of the population.

DR. DAVIDSON: Then have you experienced less poor in the recruiting. What are you planning to do different than what you did in the recruiting which was very important for us to see if the outcomes will be similar?

DR. HEMWALL: Was there a question contained within that?

DR. DAVIDSON: My question is, you did poorly in the recruiting, and you are telling us that you are planning to do something in the future for our communities, and my question is if you did so poorly in the recruiting, what makes you believe that you are going to do better when you go out after your drug is in the market as an over the counter?

DR. HEMWALL: Well, there are certain restrictions in which we are able to recruit in the context of a clinical trial. In the products that our joint venture Johnson & Johnson-Merck sells over the counter now, we do use agencies which have expertise in speaking to the minority communities as part of our overall marketing programs and we would avail ourselves of the expertise of those agencies to do better than we were able to do in clinical trials.

And also I would think that we would very importantly engage thought and opinion leaders in those communities to help us get that message out. But we don't have proof at this time that that is actually going to be successful. We do have our good intentions.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: Are you going to have your packaging Spanish as well as English?

DR. HEMWALL: Yes.

DR. GILLIAM: How are you going to affect the distribution so that the Spanish packaging gets to the Hispanic community, etc?

DR. HEMWALL: There are numerous ways in which that is currently accomplished in all of the consumer arenas in the country now. I am not an

expert on that, but it is a common thing to be able to distribute to Spanish-speaking neighborhoods throughout the United States for a number of consumer products.

CHAIRMAN BRASS: I think at this point we will stop for our lunch break. I again thank the sponsor and the Committee members. We will reconvene promptly at 1:30 for the FDA presentation. Thank you.

(Whereupon, the foregoing matter went off the record at 12:32 p.m. and went back on the record at 1:32 p.m.)

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

(1:32 p.m.)

CHAIRMAN BRASS: We are ready to begin the afternoon session. The afternoon session will begin with the FDA presentations on the NDA before the Committee and the first FDA presentation will be made by Dr. Mary Parks.

DR. PARKS: Good afternoon. I'm Mary Parks. I'm a medical officer in the Division of Metabolic and Endocrine Drug Products.

Today you'll be hearing several presentations given by reviewers at the FDA on Merck's application for the prescription to nonprescription switch of lovastatin 10 milligrams.

I will first be presenting the clinical efficacy and safety review of this application. Due to time constraints, Dr. Jim Wei, who was going to be presenting the drug-drug and drug-food interactions, his presentation, or part of it, will be incorporated into my presentation.

Following me will be Dr. Andrea Segal from the Division of Over-The-Counter Drug Products and she will be discussing the actual use trials.

Finally, Dr. Karen Lechter from the Division of Drug Marketing, Advertising, and

Communications will be discussing the label comprehension studies.

Dr. Brass, members of the Joint Advisory Committee, I would like to present to you today the clinical review of Merck's application for the nonprescription availability of lovastatin 10 milligrams.

My presentation will be focusing on the following: First I will discuss the sponsor's rationale for nonprescription lovastatin and who in the population should use this product.

I would then present the studies reviewed in this division addressing issues pertaining to efficacy and safety.

And finally, I will conclude the presentation by highlighting the relevant findings from this review with respect to the benefit to risk relationship of nonprescription lovastatin.

The sponsor's rationale for nonprescription lovastatin is based on several findings. First is that elevated serum cholesterol level is an established risk factor for heart disease and for MR FIT, the Multiple Risk Factor Intervention Trial.

We see that this relationship is a

continuous and graded one with the risk of dying from heart disease increased considerably in those individuals whose total cholesterols exceed 240. And indeed, recommendations for therapy in these individuals include that of drug therapy.

However, it's also evident that the risk of dying from heart disease is also present in individuals whose total cholesterols fall between 200 to 240 and what are the recommendations in this subgroup of the primary prevention population?

Base on the National Cholesterol Education Program, or NCEP, the recommendations are first lifestyle modification, diet, exercise, and risk factor reduction. If this is not successful at lowering the cholesterol level, then drug therapy is recommended for those whose HDL cholesterols are less then 35 or there are two or more risk factors for heart disease and the LDL cholesterol is 160 or greater.

Do we have evidence that initiating drug therapy is beneficial in these individuals prior to their developing this profile?

Well, this morning you've heard a lot about AFCAPS/TexCAPS. The sponsor conducted the study which was a five-year placebo-controlled trial

involving lovastatin 20 to 40 milligrams.

The population study included men over age 45 and postmenopausal women whose total cholesterol levels fell between 180 to 264, LDL between 130 to 190. Importantly, an HDL cholesterol inclusion criteria was a part of this selection process such that men had to have an HDL less than 45, women less than 47, in order to be randomized to treatment.

Two-thirds of this cohort had two or more risk factors for heart disease and only 17 percent of this cohort would have qualified for drug therapy based on baseline risk factors and lipid profile. The primary endpoint was a composite endpoint of fatal or nonfatal MI, unstable angina, or sudden cardiac death.

And after five years, with an approximate 70 percent study completion rate, the lovastatin group had a 3.5 percent event rate for acute coronary events and the placebo group 5.5 percent. The difference between the two, which is the attributable risk, was only 2 percent; however, it was found to be highly significant.

So from AFCAPS, we have evidence that initiation of drug therapy in this subgroup of the primary prevention population can reduce cardiovascular events.

From this, the sponsor proposes that by making lovastatin at the 10-milligram dose available as a nonprescription drug, we will be increasing the availability of drug to many individuals in the primary prevention population, many individuals in which current guidelines do not recommend therapy.

And who in the population should be treated? According to the sponsor's definition, the OTC target population include men above age 40 and postmenopausal women, regardless of hormonal replacement status, no evidence of cardiovascular disease, diabetes, or significant hypertension. Significant hypertension here meaning on more than one antihypertensive medication.

The individual should not be on prescription lipid-lowering drug and the total cholesterol level should fall between 200 to 240 and an LDL cholesterol should be 130 or greater.

I need to emphasize that the sponsor's definition does not include HDL cholesterol as part of the OTC eligibility.

By taking this definition here and applying it to the NHANES III database, National Health and Nutrition Examination Survey, the sponsor estimated that there are about 15.5 million people in

the United States who meet their definition of being OTC eligible.

Several studies were conducted and submitted to support the nonprescription proposal and these studies were reviewed in this division.

Protocol 075 was a placebo-controlled trial looking at the lipid response to lovastatin 10 milligrams treatment in the OTC target population. Protocols 076 and 079 were both actual use, open-label study also looking at the lipid response to treatment at the 10-milligram dose in the OTC target population.

And finally, a subgroup of the AFCAPS cohort meeting the sponsor's definition of OTC eligibility was also evaluated.

The following issues were addressed in this review with respect to efficacy, we looked at LDL cholesterol reduction, and clinical cardiovascular benefit. With resect to safety, we looked at safety in the clinic trial setting and also in post-marketing spontaneous reports.

LDL cholesterol reduction was evaluated in three studies in the OTC clinical development program. There is some difference among these studies that I'd like to point out in this slide.

For protocol 075, this was a double-

blinded, placebo-controlled trial in which a low-fat diet was reinforced throughout the treatment period. Lipid efficacy determination was obtained off of serum samples after a 12-hour fast at baseline, 6 and 12 weeks.

In contrast, protocols 076 and 079 were both open-labeled, uncontrolled studies in which there was no diet reinforced throughout the treatment duration. Lipid measures were obtained not off of serum sample, but off of finger-stick samples at a much shorter duration of fasting, two hours in protocol 076, a minimum of two hours, and a minimum of six hours in protocol 079.

This slide here is summarizing the percentage of treated individuals across the three trials contributing to efficacy analysis. Again, protocol 075, which is the placebo-controlled trial, we see that by 12 weeks, we still have about 90 percent of the treated population contributing to efficacy analysis.

In contrast, in protocol 076, one of the actual use studies, we see that by eight weeks there is only 80 percent contributing, but this drops further such that by 16 to 24 weeks we have about 64 percent contributing to efficacy analysis.

And finally in protocol 079, by eight weeks we only had about 63 percent contributing to efficacy analysis.

This difference in dropout rates is such that presenting LDL cholesterol reduction in only the completers and in a time point in which patient retention rate is the highest, and that is what is summarized in this slide.

If we look at first the protocol 075, the placebo-controlled trial, at week 12 we see that 91 percent of the treated population had a mean reduction in LDL of about 18 percent. At week eight in protocol 076, the actual use study, 79 percent of the treated population had a mean reduction of 22 percent. And by week eight in the other actual use study, protocol 079, 63 percent of the treated population had a mean reduction of 18 percent.

So what are our conclusions about LDL cholesterol reduction? In the compliant and adherent individual, we can expect about an 18 percent reduction in LDL cholesterol.

But what about in the actual nonprescription setting? What about in the OTC population? Not the individual, but the population. Well, the effectiveness of this treatment program