appears to be poor due to poor drug adherence as observed in the actual use studies with more than 30 percent dropout rate by week eight in protocol 079 and week 24 in protocol 076.

The second measure of efficacy is that of clinical cardiovascular benefit and the question that we're asking here is the following: Does LDL cholesterol lowering with lovastatin 10 milligrams in the OTC target population confer a clinical benefit? Simply stated, there is no evidence from controlled clinical trials.

Although there are no data from controlled trials to support clinical benefit with drug treatment in the OTC target population, the sponsor turned to AFCAPS, and from AFCAPS, they selected out 3,805 individuals meeting their definition of OTC eligibility and again that definition include total cholesterols of 200 to 240, LDL cholesterol of 130 or greater, no evidence of diabetes or significant hypertension. Again, HDL cholesterol is not part of this definition.

So these 3,805 individuals were included in a post-hoc analysis of which the same acute coronary event rate, or approximately the same acute coronary event rate, was observed in the lovastatin

group of 3 percent and in the placebo group, about 5.3 percent.

So from these results, the sponsor concluded that this is suggestive of clinical benefit in their OTC target population. But can we extrapolate from this post-hoc analysis to the sponsor's OTC target population, and in order to answer that question, I'd like to point out the differences between these two populations.

The first difference is that of dose. In AFCAPS, the dose used was 20 to 40 milligrams, and indeed more than half of this subgroup required their dose titrated to the 40-milligram dose in order to achieve an LDL less than 110.

In contrast, in the OTC target population, the proposed dose will be 10 milligrams. And as expected, the 20-milligram dose results in a greater LDL cholesterol reduction.

After 12 weeks we see a mean reduction of 24 percent for the 10-milligram dose, a mean reduction of about 18 percent.

The second difference between these two populations lies in the HDL cholesterol. I've mentioned now on several slides during the presentation, that HDL cholesterol was not part of the

selection process for OTC eligibility.

Furthermore, AFCAPS specifically recruited a population with low HDL cholesterol levels. So how does HDL affect the event rate in the AFCAPS OTC subgroup?

Well, let's first look at the placebo event rate in this slide here. We see that the risk of heart disease is highest in those whose HDLs are low. And that this risk of heart disease decreases as one's HDL increases. And this makes sense given that HDL cholesterol is a negative risk factor for heart disease.

But now let's look at the event rate in the lovastatin treatment group compared to the placebo group. We see the reductions in risk associated with lovastatin treatment is only observed in those individuals whose HDLs are less than 40. For those individuals whose baseline HDL cholesterol levels were 40 or greater, there was not observed risk reduction here with lovastatin treatment.

If HDL cholesterol is such a significant determinant of baseline risk for heart disease and if any potential benefit with lovastatin treatment in this population, we must ask, what is the HDL cholesterol distribution in the sponsor's OTC target

population?

In other words, is the sponsor's OTC target population comprised primarily of individuals in this category here in which the HDL cholesterol levels are lower, there is a greater risk of heart disease, and there is a potential for benefit, or is the sponsor's OTC target population comprised primarily of individuals in this category in which there is a lower risk for heart disease and no offer of benefit from lovastatin treatment.

This slide here summarizes the proportion of several populations in which the HDL cholesterol is greater than 40. The populations I'm talking about are the AFCAPS OTC subgroup, the three studies reviewed in this division, and the NHANES subgroup which are representative of the OTC target population.

Indeed, only about a third of the AFCAPS subgroup population had HDLs greater than 40. This is expected. The study recruited specifically individuals with low HDLs.

In the three studies reviewed in this division for the OTC clinical development program, because HDL cholesterol was not part of the selection process for study inclusion, we see that a majority of these individuals had HDLs greater than 40.

But more importantly, in the sponsor's OTC target population right here, we see that 78 percent, close to 80 percent, had HDLs greater than 40. In other words, of the sponsor's estimated 15.5 million people who are eligible for lovastatin OTC, about 12.5 million people, there was no evidence of benefit from drug treatment.

And in the remaining three million, we're not certain about the benefit of the 10-milligram dose because prospectively it has never been studied in a clinical trial.

The final difference I want to point out between the two populations is that of adherence to drug therapy and why this is important. It's important because dyslipidemia is a chronic asymptomatic condition and so too its management requires long-term adherence to therapy including nonprescription lovastatin.

In the AFCAPS cohort, I've mentioned that the five-year study completion rate was about 70 percent. What would we expect in the actual use population?

This is actually a slide of a study completion rate in another actual use study that Dr. Segal will be discussing momentarily, but I chose this

actual use study because this is a study, it's the only actual use study in which consumers were asked to purchase medication. The other consumer use studies, the consumers were actually dispensed medication. So this study here more closely simulates a nonprescription environment.

And we see that after three months, including a two-month extension period, that the study completion rate was only 40 percent, a sharp difference to the AFCAPS five-years 70 percent study completion rate.

So what can we conclude about clinical cardiovascular benefit? We cannot rely on AFCAPS as evidence of clinical benefit for drug treatment in the OTC target population. We cannot rely on it because it is not representative of the OTC target population, particularly with the HDL cholesterol level.

AFCAPS is comprised of a population with an HDL cholesterol level that is low and a greater risk for heart disease. The OTC target population is comprised of individuals with an HDL that is much higher and a lower risk for heart disease.

It was also evident from the actual use studies that adherence to drug therapy for this chronic asymptomatic condition is poor, such that any

measure of efficacy, whether it be LDL cholesterol reduction or that of clinical cardiovascular benefit, will be compromised by so many individuals in the population not remaining on therapy for long term.

In the absence of established clinical benefit for drug treatment in the OTC target population, what are the risks of drug treatment? And the risk of drug treatment was evaluated in the safety review in this application.

Now the safety in nonprescription lovastatin should not be limited to just the 10-milligram dose because in the nonprescription setting we're talking about unrestricted access to a medication, so individuals will self-titrate.

Not everybody, but there will be some who will self-titrate up and so safety was looked at across the approved dosage range of lovastatin.

First it was looked at in the clinical trial setting. At the 10-milligram dose we found that the safety and tolerability of the 10-milligram dose of lovastatin to be comparable to that of placebo. And the incidence of myalgias is low and is similar across the studies. There were no cases of rhabdomyolysis, myoglobinuria, or liver toxicity reported.

Interestingly, the discontinuation rate of study medication due to reported adverse events was slightly higher in the actual use studies compared to the controlled clinical trials. The reasons for this we do not know, but it may speak to the poor adherence to therapy observed in the actual use setting.

At the higher dose of lovastatin, we see that consecutive elevations in liver enzymes to more than three times the upper limit of normal is dose related and at the highest approved dose, the instance was about 1.5 percent, but there were no cases of liver toxicity associated with this enzyme elevation.

Myopathy, defined as skeletomuscle symptoms and CPKs greater than ten times the upper limit of normal, was also rare with no cases observed at doses less than 40 milligrams and none of these cases here actually resulted in rhabdomyolysis. And in the entire clinical trial experience with lovastatin, there has only been one case of rhabdo reported at the 20-milligram dose.

However, we acknowledge that there are limitations to safety assessments from clinical trials and those limitations relate primarily to the exclusion of high-risk individuals, particularly exclusion of patients on interacting medications,

exclusion of patients with co-morbid medical conditions.

And furthermore, in many clinical trials, with the exception of the actual use trials in this clinical development program, there are scheduled physician visits and scheduled safety monitoring such that at the earliest sign of trouble patients are asked to interrupt their therapy or discontinue medication, so that the safety findings from clinical trials are often not predictive of the real-world use of a product, particularly in a nonprescription environment where we would expect fewer physician visits and little to no monitoring.

To get a better grasp on the safety concerns in the real-world use of a product, we often turn to the spontaneous post-marketing reports. And in collaboration with the office of post-marketing drug risk assessment, we looked at the following safety concerns.

We first looked at liver toxicity with respect to liver failure and then we looked at muscle toxicity with respect to rhabdomyolysis. In particular we looked at drug-drug interactions and drug-food interactions.

The following case definition was used for

liver failure. Unduplicated domestic cases in which a clinical diagnosis of liver failure was reported or the individual received a liver transplant.

The time period was from marketing until recently in this year, February of this year, approximately 13 years. And given an estimated background rate of idiopathic liver failures being 1 per million person-years, the estimated four-year reporting rate for lovastatin-associated liver failure was only slightly increased at 1.4.

So in conclusion, lovastatin-associated liver failure cases have been reported, but these are extremely rare cases and often assignment of causality is complicated by individuals be on other medications or having co-morbid medical conditions.

The other safety concern was that of muscle toxicity with rhabdo being the most concerning safety aspect of this toxicity. Now this is something that is seen not only in lovastatin, but across all the statins. And we used the following case definition.

We used the unduplicated domestic cases again in which there was a clinical diagnosis of rhabdo reported and a CPK elevation of greater than 10,000. The time period was again about 13 years from

marketing until recently this year. And of note, the background rate for this adverse event is not known.

Using that case definition, we found 191 cases of rhabdomyolysis. And this slide here is summarizing the percent of cases reported by dose.

Of note, there were no cases reported for the 10-milligram dose; however, again, we don't want to limit the safety review of nonprescription lovastatin only to the lowest proposed dose. At the high dose, indeed, we see that there were cases of rhabdo.

Furthermore, about 18 percent of these cases did not have a dose reported, so it is quite possible that some of the 10-milligram cases could have fallen into this category. But it is also possible that we're not seeing any toxicities or rhabdo cases reported at the 10-milligram dose because of its limited use in the general population. And that is suggested from this slide here obtained from IMS HEALTH.

This slide here summarizes the number of prescriptions dispensed for lovastatin in the United States last year and we see that indeed, the 10-milligram dose is the least prescribed dose of lovastatin. And it's conceivable that the

availability of lovastatin as an OTC drug at the 10-milligram dose could result in increased use at that dose and possibly more adverse events reported.

I want to point out that this is the number of prescriptions written, not number of people using the medication, so incidence rates cannot be calculated for adverse events obtained from spontaneous reports.

I mentioned earlier that when we were looking rhabdomyolysis we want to look specifically at drug-drug interaction cases and drug-food interaction cases. This slide here breaks down the 191 cases of rhabdomyolysis by lovastatin and the fibrate interactions, drugs that were nonfibrates, lovastatin food interaction, in this case here it was grapefruit juice, and most monotherapy lovastatin use.

If we combine the fibrate and the nonfibrate drugs together, we see that more than half, about 61 percent of the 191 cases were due to a drug interaction. And these were the drugs that were listed as concomitantly used in these lovastatin-associated rhabdo cases. Most of them are drugs which interact through the 3A4 metabolic pathway.

The mechanism of rhabdomyolysis in the setting of lovastatin use with some of these

medications, which are the potent 3A4 inhibitors, have been evaluated in several PK studies, particularly that of erythromycin, itraconazole, and cyclosporin. And the combination of those two products in these studies has been observed to increase lovastatin drug levels by anywhere from sixfold up to 20 fold.

The interaction between gemfibrozil and niacin and lovastatin causing rhabdo is thought to be more through the pharmacodynamic mechanism.

In recent years it has become recognized that grapefruit juice is an inhibitor of a 3A4 isoenzyme, particularly in the small intestine. And several studies have also looked at the effects of grapefruit juice on lovastatin pharmacokinetics. And particularly one study in which lovastatin, a single dose at 80 milligrams, was co-administered with grapefruit juice at the same time, the drug level of lovastatin increased to about 15 fold.

Despite these studies, however, we only have one clinical case reported of grapefruit juice that could have potentially caused rhabdomyolysis in a patient who was on lovastatin. And after discussing this case, the reporting physician, I have to point out that there were baseline risk factors in this individual that put this individual at risk for

myopathy and those risk factors included high-dose combination therapy with lovastatin and a fibrate, and baseline renal impairment.

But what really made this case compelling was the onset of rhabdomyolysis. The onset of rhabdomyolysis in this patient occurred two weeks after he switched from a daily consumption of orange juice to grapefruit juice.

In conclusion for rhabdomyolysis, most reported cases are associated with drug-drug interaction and many of these interactions are due to competition with a 3A4 metabolic pathway.

Now the sponsor does acknowledge that this is a safety concern, and they propose that the safety concern can be adequately conveyed through consumers through proper labeling and the proposal is to warn/advise consumers not to take nonprescription lovastatin if they are on one of these medications.

These include erythromycin or clarithromycin, ketoconazole or itraconazole, nefazodone, cyclosporin, protease inhibitor, niacin, gemfibrozil, one of the prescription statin drugs. This is quite an extensive list and it's not complete, but more likely it's going to increase with time as more drugs are approved.

So we feel that this is challenging to consumer. This method of risk communication will be challenging. And why do we think that it's challenging? From our own experience in the prescription setting.

These are the drugs that have been withdrawn from the United States market due to a toxicity related to 3A4 metabolic pathway. And these withdrawals occurred despite changes to the label warning section, dear healthcare professional letters, and block box warnings.

This method of risk communication in the prescription setting was apparently not effective enough to avoid some of the drug-related toxicities. so it raises concern that the proposed method of risk communication for nonprescription lovastatin will also be ineffective.

In conclusion for safety, there are rare, but serious adverse events associated with lovastatin use, particularly that of muscle toxicity which can be potentiated by certain drugs or substances which impair lovastatin's metabolism through the 3A4 isoenzyme.

The safety concern is further compounded by the use of lovastatin as a nonprescription drug.

As an OTC drug it would be in an unsupervised, unrestricted, unmonitored setting such that the safety of OTC lovastatin is really dependent upon the consumer's comprehension that the label, the use of the product according to label instructions, such that there would be no self-titration to higher doses, and no use by individuals at risk for drug-related toxicities.

In conclusion, in evaluating the prescription to nonprescription switch of lovastatin 10 milligrams, we need to ask the following question: What is the balance of benefit versus risk of nonprescription lovastatin? And I'd like to address that question by highlighting the issues that were addressed in this review.

On the benefit side of this equation we could talk about LDL cholesterol reduction and indeed, lovastatin does reduce LDL cholesterol. But the effectiveness of this treatment approach in the OTC population will likely be diminished by poor adherence to drug therapy.

Another part of the benefit side of this equation is that of clinical cardiovascular benefit. Will treatment, drug treatment, in the OTC target population result in reductions in cardiovascular

mortality and cardiovascular morbidity? And there is no evidence from controlled clinical trials to suggest that. And furthermore, any potential benefit again may be offset by poor adherence to drug therapy.

On the risk side of this equation, I just mentioned, and the safety concerns are again rare, but the serious concerns about primarily of muscle toxicity potentiated by certain drugs and furthermore compounded by the unrestricted, unsupervised use of this product in the OTC environment.

That concludes my presentation. I now would like to turn the podium over to Dr. Andrea Segal. Thank you for your attention.

DR. SEGAL: Good afternoon. My name is Dr. Andrea Segal. I'm a physician in the Division of Over-The-Counter Drug Products and I'm going to be talking to you today about three actual use trials.

You just heard Dr. Parks describe efficacy and safety issues for trials 076 and 079. I'm going to be discussing self-selection and compliance issues for 076, compliance issues for 079, and self-selection and safety for 081.

But before I get into the individual trials themselves, I want to talk about a little bit of important background material.

Why do we need actual use studies? We need to be able to simulate the over-the-counter use of a product so that we can understand what will happen if it becomes available in the drug store for people to buy.

Therefore, the fewer exclusion criteria in these trials the better, so that we can understand that a person will self-select properly because there will be no physician standing between the purchaser and the product to inform or to screen.

So we need to know, are people choosing the product properly based on indications and contraindications? Are dosing and duration of use according to directions? What are the adverse experiences? Efficacy information is often limited in actual use trials by the open-label uncontrolled design.

There are many actual use issues for lovastatin and I'd like you to try to bear these in mind as I go through them. They comprise several slides. I've grouped them according to topic. The first topic is cholesterol.

Do people know their values? Do they understand total cholesterol, LDL cholesterol, and HDL cholesterol? Do they understand when to treat? What

is the treatment goal? And do consumers understand it?

Cholesterol measurement. Can over-the-counter desktop cholesterol screening offer accurate cholesterol measurement? What is the appropriate duration of fasting prior to measuring cholesterol? How many measurements should be performed to obtain an accurate value? If averaging multiple cholesterol values is recommended, can consumers do the math?

Self-selection. Can consumers understand what underlying conditions and concomitant medications put them at safety risk if they take lovastatin? Do consumers know when they are taking contraindicated drugs? Do consumers understand when to seek the counsel of a physician?

Compliance issues. Are consumers sufficiently compliant in the over-the-counter setting to derive clinical benefits of lovastatin treatment over the long term?

Benefit and risk. Is monitoring needed to determine of there has been a benefit of use as well as no adverse safety events? Can consumers identify symptoms associated with adverse events?

Labeling. Can a label adequately convey all necessary information about lovastatin so it can

be used properly?

These three trials had many criteria in common, both inclusion and exclusion. Because there were so many criteria, in the interest of brevity, I've decided to list the inclusion criteria in common on this slide and the exclusion criteria in common on to subsequent slides.

In common for inclusion criteria were a total cholesterol value of 200 to 240 milligrams per deciliter and an LDL cholesterol of at least 130 milligrams per deciliter. HDL cholesterol was not an inclusion criteria for these trials.

Exclusion criteria in common were recent participation in a drug study, allergy to lovastatin, current or history of liver disease, contraindicated drugs, other cholesterol medication, a history of heart disease, a family history in parents or siblings prior to the age of 55, pregnant or breast-feeding women, or women of child-bearing potential, and inability to read English.

The sponsor provided two definitions that were common to these trials and I'll just state these now. Persistence was defined as the number or percent of subjects who returned for a follow-up visit having taken any of the study tablets.

Compliance was calculated in persistence subjects and was defined as the number of tablets taken divided by the number of days drug was taken during the specified time period, and this was expressed as a percentage.

So a person could be less than 100 percent compliant or more than 100 percent compliant in these trials and not follow the dosing instructions.

Let's talk about study 076. This was an open-label, uncontrolled multicenter study conducted in 59 pharmacies. It lasted 24 weeks and there were four visits during that period. There was an extension trial option. The purpose was to evaluate LDL cholesterol, self-selection, compliance, and adverse experiences.

The inclusion criteria were as described already for cholesterol, plus men had to be at least 45 years of age and women at least 55 years of age. They had to be in general good health without any disabling disease and had to have tried a low-fat diet during the previous year.

The exclusion criteria were as described, but also included corticosteroid use, peripheral vascular disease, and drinking at least three alcoholic beverages on most days.

The label for this trial was entitled the pharmacy label. It listed the inclusion and exclusion criteria. It did not list all possible interactive medications. People were told to dose one tablet in the evening and to retest their cholesterol after eight weeks and contact a study doctor if the level did not decrease.

People were recruited via advertising and were asked to review the pharmacy label and make a self-selection decision. Is this product right for me, and if it is, what should I do next? Should I obtain it and use it? Do I need to ask my doctor about it? Do I need to have my cholesterol tested? Do I need to talk to my doctor and test my cholesterol? Or, I'm not interested in this product.

Then they were asked to complete a history form and a pharmacist triaged them and determined who was potentially qualified and who was not. Everyone had a cholesterol test after a minimum two-hour fast and qualified people received study drug.

At the return visits, unused pills were counted, adverse events were recorded, lipid profiles were repeated, and new drug was provided at visits two and three.

The results of this trial for self-

selection. Seven hundred twenty-two of 6,095 study participants qualified to receive drug. Nine hundred eight-one of study participants self-selected to obtain and use the drug, but only 119 of this self-selection group actually did receive lovastatin.

Six thousand eighty-one people completed the self-selection process. Eighty-two percent felt they needed more than the pharmacy label to decide whether to obtain the drug. Fifty-three percent thought they met criteria for total cholesterol level, but in fact did not.

There was no information about how well consumers understood the meaning of the components of the lipid profile. One hundred twenty-four, or 5 percent, who were likely to buy lovastatin were in the safety risk group. In other words, they had liver disease, were taking medications that were prohibited as per the label, remembering that the label did not include all prohibited medications, they were allergic to lovastatin, or they had a pregnancy risk.

Results for compliance. Five hundred twenty-three, or 72 percent of people completed the study. Five hundred four were persistent at the last visit, or visit four. Four hundred forty-one were taking 75 to 100 percent of medicine at visit four.

There was no diary in this trial, so precise information about how people actually dosed is unavailable.

Study 079. This was a multicenter, open-label, uncontrolled trial conducted in storefront sites, it lasted eight weeks, and there was an extension trial option. The purpose was to test a mean change in LDL at eight weeks, the ability of consumers to remain on lovastatin and the tolerability of lovastatin as measured by incidence of adverse events.

People were recruited via advertising and this time there was a telephone history screening process. There was no self-selection in this trial.

The inclusion criteria were as described for cholesterol. In this study men could be 40 or over, women had to be 55 or over.

The exclusion criteria were as described, plus drinking at least three alcoholic beverages on most days, having diabetes, angina, peripheral vascular disease, TIA, stroke, having had angioplasty or coronary bypass grafts, taking more than one blood pressure drug, diastolic blood pressure equal to or greater than 100, or a systolic greater than or equal to 180 millimeters of mercury, and subjects who knew

that their total cholesterol was less than 190 milligrams per deciliter or more than 250. Anyone taking corticosteroids was also not allowed to participate.

The label for this trial was called the restricted access label. It was designed to reinforce appropriate post-purchase behavior, but not to guide self-selection according to the sponsor.

It contained the trial inclusion and exclusion criteria. It had a more expansive list of contraindicated medications than the pharmacy label did. And the label recommended that people see a doctor at least yearly to discuss their cholesterol that plan.

People who potentially were eligible for this trial via the telephone screening, had a storefront appointment. This was visit one.

At this time a lipid profile was done after a minimum six-hour fast. Blood pressure, weight, and height were measured, and eligible people received drug with the restricted access label, a study information card, package inserts, and stickers to remind them to take the medicine.

Visit two occurred eight weeks later. Another lipid profile was performed after a minimum

six-hour fast. Remaining drug tablets were collected and adverse experience information was collected.

The results of this trial were that 4,878 people called the telephone number. Thirteen hundred twelve were potentially eligible and visited the storefront. Sixty percent of these were not qualified on the basis of cholesterol. Ultimately 460 people received study drug.

Of that 460, 363 took some drug during the study course, 265 were compliant between 75 and 100 percent of the time over the eight-week study. There was no diary, so precise information about how people actually dosed is unavailable. This trial did not test the ability of consumers to properly self-select.

Study 081. This was an open-label, uncontrolled, multicenter trial conducted at storefront clinical sites. It lasted four weeks and there was an extension trial option. The purpose was to test the effectiveness of another label called the "Red Arrow" label and some additional reinforcement tools including a video tape, a pamphlet, and a package insert.

This label and tools were looked at for effectiveness in three risk subsets. The drug risk group, the primary prevention subjects who were those

with cholesterol over 240 milligrams per deciliter, and the high cardiovascular risk group. Tolerability of lovastatin was measured by incidence of adverse events.

Inclusion criteria for this trial were as described for cholesterol, plus men at least 40 years of age, and this time women at least one year postmenopausal. People also had to express an interest in purchasing lovastatin.

The exclusion criteria were as described and also included people employed in healthcare, diabetics, people who had had a stroke, those taking more than one antihypertension medication, and those who had participated in another cholesterol-lowering study within the previous two years.

The "Red Arrow" label for this trial was different from the previous labels in that it had a flip-up back panel design. It had warnings that were emphasized loudly with red arrows and stop signs.

Examples of muscle pain, tenderness, and weakness were added to the drug interaction warnings. The warning section preceded the "who should use" section, and there was a box warning to carefully read the package before self-selecting and to call a product specialist for help understanding the label.

People were recruited for this trial via advertising and visit one was at the storefront site. There participants read the product concept and label and then made a self-selection decision.

If they said yes, this product is right for me and I would like to obtain it and use it, they paid $15 for lovastatin 10 milligrams and answered specific safety risk questions which were about contraindicated medicines, current liver disease, child-bearing potential, and allergy to lovastatin, so at this point there were additional exclusion criteria.

If a participant self-selected yes, but was excluded for safety risk, this person was given a second chance to review the label and the reinforcements and to make a self-selection decision. No drug was provided.

A cholesterol test was offered to those who needed it before they could decide if this drug was right for them, and then they were given an opportunity to repeat their self-selection decision and answer safety risk questions. A medical history was performed on all people who left the storefront site without receiving drug.

This group included the self-selection

group that said no, I'm not interested, those who failed the safety risk exclusion questions, and those who did not want to purchase.

Eligible participants received a four-week supply of open-label lovastatin 10 milligrams and were told to take the drug according to the label. They were given a gift certificate incentive to call a toll-free number and those who did that were asked their medical history by the person on the phone.

If that person deemed that the participant was inappropriate to take drug, the person was told to discontinue taking the drug and return the remaining drug and packaging at the second visit.

At visit two, return packaging and unused drug were collected and for those who had not called the toll-free number, a medical history was performed by a nurse who then determined appropriateness of treatment. Lipid testing was performed on those who were interested in going into an extension trial.

The results for this trial were that the 2,416 subjects were screened overall. Fifty-one percent of them self-selected yes. One thousand one hundred forty-four received drug. Eighty-six did not because they were felt to be at safety risk. Seventy-four percent of people completed the four-week study.

The reasons the rest discontinued were that they were found not appropriate by history, they had an adverse experience, they were lost to follow-up, returned the drug by mail, or withdrew their consent.

Self-selection errors among the 1,144 were hypertension, other cholesterol treatment, a history of hepatitis or liver disease, drinking too much alcohol, diabetes, heart disease, and stroke, or TIA.

One thousand one hundred twelve consumers with a known medical history, in other words, it was known whether or not they were eligible, said that they would purchase the product. Thirty-nine percent of them self-selected erroneously after seeing the label. This number decreased to 22 percent after they saw the label and the reinforcement tools.

Sixty-one percent of subjects with known medical eligibility status did not call the toll-free number. Thirty-six percent of them were ineligible to take lovastatin.

Safety group self-selection errors after seeing the label are on this slide. Eighty-three people took an interacting medication, 30 percent of them self-selected incorrectly to take lovastatin.

Sixteen women were less than one year

postmenopausal, half of them self-selected incorrectly. Fourteen people had liver disease, 36 percent self-selected incorrectly, 8 were allergic, 13 percent self-selected incorrectly.

There were 381 subjects with cholesterol greater than 240 milligrams as their only contraindication, 46 percent of them self-selected incorrectly. Two hundred sixty-two participants were in high cardiovascular risk categories, 32 percent self-selected incorrectly to take lovastatin.

For safety. Fifteen percent of people who received drug had an adverse experience likely related to lovastatin treatment. Four percent discontinued due to drug-related adverse events. None of six serious adverse events were likely to have been study drug related. But we have incomplete information because liver function tests and CPKs were not done and this trial only lasted four weeks.

What are the overall conclusions that can be drawn from these three actual use trials?

For cholesterol. Many people lack accurate knowledge of their cholesterol values. The trials do not assess if consumers understand LDL and HDL cholesterol.

The NCEP guidelines were not used to

determine cholesterol values, so it is not known if OTC consumers would comply with standard fasting recommendations and more than one blood test prior to using OTC lovastatin.

There is no identified treatment goal for the individual consumer, even for lowering cholesterol, and it is not clear that consumers understand this.

For self-selection. Self-selection errors were very common. It was not demonstrated that subjects know when to involve their physicians. Compliance in the OTC setting is less than desired over the short term.

Benefit and risk. Because of the many exclusion criteria, the lack of blood tests, and the short duration of these trials, these studies could not demonstrate that lovastatin is safe in conditions of actual use. Studies do not answer whether monitoring is needed to determine if there has been a benefit of use or adverse events.

And finally, for the label. There were three iterations of label that were used in these three trials. There was a self-selection error in more than a third of people. The four-step label which is proposed for over-the-counter marketing with

some small changes has not been tested in actual use. Necessary inclusions and exclusions may be too complex for the unmonitored over-the-counter population to understand.

And that concludes my presentation and now I'd like to introduce Dr. Karen Lechter.

DR. LECHTER: Good afternoon. I'm Karen Lechter with the Division of Drug Marketing, Advertising, and Communications. I'm discussing label comprehension study 201 which is a culmination of labeling studies, each of which resulted in label changes and further testing.

The study looked at the four-step label which the sponsor has referred to earlier as label number four. This is the last label test that was conducted.

I'll first talk about the purpose and methodology of label comprehension studies in general. I'll discuss the Mevacor study characteristics and results, and I'll finish with some comments about the potential for misuse, comparisons with other labels, and conclusions.

The FDA regulations state that over-the-counter labels shall be written in such terms as to render them likely to be read and understood by the

ordinary individual including individuals of low comprehension, under customary conditions of purchase and use.

For this reason, sponsors need to provide the agency with evidence that the proposed label is understood if it's read by a sample of ordinary individuals including those of low comprehension.

For these purposes, we define low comprehension as a reading level of 8th grade or below. The reading level is usually tested by a short literacy test that is given to participants in the studies before they see the labeling.

Most studies are conducted in shopping malls and in other locations where prospective participants are recruited on the spot.

In some cases, when special populations are needed, participants are recruited by telephone from existing lists of such persons or by advertisements. For some products it makes sense to recruit persons who would not be eligible to use the product as well as those who are to see if they can select appropriately.

The first step in most label comprehension studies is to ask participants to read the carton label as if they were considering buying the product.

Participants then answer questions about the information on the label.

Generally, the label remains in view during the questioning for reference; however, in some cases some questions are asked when the label is removed to test memory of certain label information.

Once the outer carton is tested, some sponsors ask questions about the materials inside the package which can include items such as inserts, brochures, audio, or video tapes.

Questions can be of two kinds. Open-ended, which require the respondent to generate his or her own answer, or closed-ended, which provide a list of choices of responses such as multiple choice or true/false. Questions vary in their quality and in the level of cognitive effort they require.

In designing questionnaires, it is best to use questions that are not leading, that do not suggest the response in the question. Questions should not provide information that should be tested by assuming the respondent knows something he or she may not know. A series of questions should not require responses that are all the same.

The Mevacor study had six open-ended and 24 multiple choice questions relating to the label.

The label was present at all times. Similar questions were also asked about at materials inside the package.

The results of the study must be explained in the context of the quality of the questions. If questions are biased in some way, the meaning of the results is questionable. While it is almost impossible to create a bias-free questionnaire, there are certain types of questions that should be avoided to the extent possible.

In this study, two sets of questions were biased series with most responses identical for all the questions in the series. There were four leading questions that suggested the answer to the question, and there were 12 questions composed in a way that it made it difficult to interpret the results.

These questions asked for example, whether a person in a particular category could use the product, should not use the product, or the label doesn't say.

It is impossible to tell whether those who responded the label doesn't say understood whether these persons could use the product.

Five questions assumed respondents knew information that they may not have known. For example, how long after beginning use cholesterol

should be checked. Such questions assume participants understood the need for testing at some time after use.

And three questions asked information at the lowest possible cognitive level of effort. They asked if something was or was not on the label. There was no test if that information was understood.

Due to the nature of the questions asked in this study, we do not know if consumers can apply the information to a variety of situations. There were no questions involving the application of the information to hypothetical situations. If such scenario type questions had been used, biasing questions could have been avoided and we could have been more comfortable about accepting the results of some of the questions.

There were no questions about whether participants could use the product themselves, which would have been crossed check against their medical history to determine of they could self-select correctly.

The design of label comprehension studies should begin with a set of communication objectives based on the information on the label. The objectives serve as the basis for designing the questionnaire.

All communication objectives should have questions associated with them and the objectives should cover all the major messages in the label that consumers should understand. Some objectives may be designated as key or primary.

The next four slides show the communication objectives for this study. The ones that are designated as key appear in yellow and most of these were presented by the sponsor earlier under the title Core Label Elements, so I won't deliver them in detail, I'll just scroll through them slowly.

The sponsor stated that the goals for the primary or key elements were 80 percent comprehension and for the other elements 51 percent; however, the FDA does not use numerical goals to determine if information is adequately understood.

Instead, the agency examines the importance of the information, the way in which the question was asked, and the label text to determine whether labeling requires modification. For some items 80 percent may not be enough, for others, less than 51 percent may be sufficient.

There were 502 participants, all age 18 or older. They were not necessarily concerned about their cholesterol. Eighty-four were low literate.

There were 96 safety risk participants. These were taking contraindicated medications, were allergic, or had hepatitis or liver disease.

Some participants were classified as "other ineligible" if they were not in the safety risk group. They should not take the product for other reasons than the safety risk people. However, responses for this group were not analyzed separately, and therefore we don't know from this study if people who have risk factors that require a doctor's care will apply the label appropriately.

What can we conclude from the tested label about the tested label from this study. The results of the study suggest that some concepts are well understood; however, the results are not clear about whether some of the other important concepts are understood and for some concepts appropriate questions were not asked.

Despite the shortcomings of some of the questions, it appears that participants understood the purpose of the product and the dosing instructions. They probably understood what information they needed before use, to know their total cholesterol, names of prescription drugs they take, and that they should call a toll-free number if they're not sure about

whether or not they should take the product.

However, these responses were based on a multiple choice question that did not require participants to generate their own list of things they must do before using the product. So we don't know if they would realize these items without prompting.

About 92 percent understood that persons with heart disease, stroke, diabetes, and high blood pressure should see a doctor before use. And it appears that there is adequate understanding of the age for men and menopausal status for women for using the product.

Participants also understood not to use the product if they are pregnant or breast-feeding, using 500 milligrams of niacin or more daily, or using other cholesterol-lowering drugs. They recognized that the label said to talk to the doctor if they drink three or more alcoholic beverages a day, and that there are potentially serious side effects if they take the product with other medications.

However, these last two questions required only that they respond whether or not these messages were on the label and did not test understanding.

They understood moderately they should not use the product if they have or have had hepatitis or

liver disease or are taking erythromycin or cyclosporin.

However, the results regarding which men and women should not use the product were low. Only 59 percent said premenopausal women cannot use the product with 28 percent saying the label doesn't say. Similarly, for use by men under 40, only 56 percent correctly said they cannot use it, but 33 percent said the label doesn't say.

We can't be sure if people who said these messages were not on the label knew that these men and women should not use the product.

Only 70 percent correctly answered that persons with total cholesterol above 240 should talk to a doctor before use. Eighteen percent said these persons could use the product.

These responses suggest substantial proportions of consumers may take the product when they should see a doctor instead or not use it at all.

Although scores were 85 percent for checking cholesterol after eight weeks, this question assumed participants knew they needed to check their cholesterol after beginning use and merely asked them when the checking should occur. We do not know if they really knew they needed a cholesterol check

without prompting.

There were two questions about diet and exercise, but these were leading.

There are important messages that were not tested at all. There were no questions about self-selection, whether they could use the product.

We generally like to see these questions to determine of consumers can apply the label information to their own circumstances correctly; however, the question about self-selection was not asked.

There were no questions asked about applying multiple criteria for use or nonuse at once, which is an important task since there are multiple requirements for use. Consumers must understand they must apply total cholesterol values, plus LDL, plus age criteria for men and menopausal criteria for women, and they must simultaneously apply the nonuse criteria.

The 84 low-literate participants scored lower than the non-low-literate participants on 16 questions at the P equal to or less than 0.05 level with no adjustments for multiple comparisons. The range of differences between the two groups and these questions was 8 to 22 points with the average being 12

percentage points.

The 96 safety risk participants scored similarly to the non-safety risk group with the exception of three items.

After exposure to the materials inside the package, participants were asked most of the same questions again. After seeing the materials on the package, participants achieved higher scores for just a few items based on T-tests at P equal to or less than 0.05.

After all materials were read, correct scores increased for questions about women who were premenopausal, going from 59 to 77 percent, for men less than age 40, going from 46 to 74 percent, and use if total cholesterol is above 240, going from 70 to 87 percent.

This morning the sponsor discussed the score increases after all the materials were examined. However, these consist of mostly nonsignificant differences at P of 0.05.

The methodology used to compare knowledge before and after reading the internal materials confounded the results which may have been affected by exposure to the first test of the label resulting in higher scores after the second test on the materials.

A better methodology would have been to give some participants only the outer label and others all the materials, test each person only once, and compare the results of the two groups. Thus, it is questionable whether the materials inside the package enhance comprehension.

There are several concepts in which participants did not score well that could be the basis for misuse of the product.

These were use by premenopausal women and men under 40 as well as those with a cholesterol above 240. And as I mentioned before, we do not know if consumers can simultaneously apply the various use and nonuse requirements.

As a result of this study the label was changed slightly for the NDA submission to put information about men before information about women and to state that men under age 40 should talk to their doctor before use.

The sponsor compared the results of this study of the four-step label with comprehension results in studies of the earlier "Red Arrow" and pharmacy labels to demonstrate improved scores through the four-step label. However, because these labels were not tested head-to-head we cannot rely on these

comparisons to show the superiority of the four-step label.

Despite the shortcomings of many of the questions, we can conclude that consumers probably understand some of the important concepts; however, some issues were moderately or poorly understood or the results were unclear. Further, some critical information was not tested.

Due the nature of the questions or lack of questions, we do not have a complete picture of how well consumers can use the information and interpret it. Significant numbers may not understand who should not use the product.

In addition, we don't know if consumers can simultaneously apply the use and nonuse criteria including information about total cholesterol, LDL, age for men, menopausal status for women.

We have inadequate information on the need for further cholesterol checks. We do not know whether consumers can appropriately apply the information to hypothetical situations or self-select whether or not to take the medicine.

Many of the relatively high scores may be due to the simplicity of the questioning. If there had been questions about hypothetical situations as we

prefer to see, and about other issues we would like to know about, we would have a better idea how consumers could apply the label information.

In conclusion, this study does not provide us with sufficient information to conclude confidently that consumers can self-select to use the product appropriately or whether they understand key information about safe and effective use.

CHAIRMAN BRASS: Thank you. At this point the FDA presentation is open to questions from Committee members. Dr. Johnson.

DR. JULIE JOHNSON: I have several questions for Dr. Parks. My first question is really to serve as a point of reference and that is what the current bar is within the FDA for approval of an antihyperlipidemic drug in the Rx setting and I guess specifically I would be asking about fenofibrate which I think is the most recently approved drug and was approved after most of the statin morbidity-mortality trials were published.

DR. PARKS: You're talking about the most recent application with fenofibrate and the approval -- I'm sorry --

DR. JULIE JOHNSON: I guess I'm asking, was the basis of approval of the drug that it lowered

cholesterol or was it that it had important clinical benefits such as reduced cardiovascular endpoints or reduced mortality?

DR. PARKS: Yes, the approval of lipid-altering drugs in our division is based on its demonstration of a significant lowering of the LDL cholesterol without an alteration in the other lipid profile in adverse direction and in the absence of clinical benefit, then the drug would be labeled as such, that this product has not been shown to result in a significant reduction or any reduction in cardiovascular mortality or morbidity.

There are certainly several statins on the market right now that lower LDL cholesterol and they meet the bar of a minimum 15 percent reduction in LDL cholesterol compared to that of placebo, but have not demonstrated any clinical cardiovascular benefit.

So the approval of those drugs in that setting there is based on the surrogate marker of LDL cholesterol which has been demonstrated to be a reliable surrogate marker based on initially epidemiologic data, but then confirmed by many statin trials, five megastatin trials as a matter of fact, across both the primary and secondary primary prevention population and across quite a broad range

of cholesterol levels.

DR. JULIE JOHNSON: So, if I heard it right, the bar is 15 percent?

DR. PARKS: Fifteen percent reduction in LDL cholesterol compared to that of placebo.

DR. JULIE JOHNSON: So, I guess what I'm trying to understand is, I'm getting the impression that you're asking for a higher bar for this product, which does achieve more than 15 percent and probably has more hard outcomes data than a drug like fenofibrate?

DR. PARKS: The application being considered here is actually not of lipid altering per se because this drug is already approved. It already has indication for lipid alteration.

The indication that it is trying to seek here not only in lipid altering, but in a new population as Dr. Orloff had mentioned earlier and in that setting there, the question is whether or not the lipid altering that has already been established and has been approved for, will actually result in any sort of benefit and that question there would be the clinical benefit, the reduction in cardiovascular mortality and morbidity.

So, this drug in itself has already been

granted that indication and has been approved for lipid lowering and certainly the review in the placebo-controlled trial presented and the clinical development program established that or confirmed that.

DR. JULIE JOHNSON: I understand that it's already approved, I guess I'm just trying to understand that every other statin drug, when it was approved, was approved without clinical endpoint data and you are asking for clinical endpoint data in this case.

DR. ORLOFF: Perhaps I could chime in. What you say about the previous drugs is true, and the judgement that a 15 percent lowering ability up from baseline is a clinically significant LDL lowering is, needless to say, somewhat arbitrary.

We have to concede that for the larger group of lipid-altering drugs, notably the statins and the resins, our hypothesis that LDL lowering would be reflected in a clinical cardiovascular benefit turned out to be true. We do know from the epidemiology that there is an apparent diminishing return as you go lower on the total cholesterol or LDL cholesterol scale.

The relative benefit perhaps, and

certainly the absolute benefit of any given degree of cholesterol lowering gets lower as you go down the cholesterol ladder. What we're asking here really is whether for the targeted population, and there is clearly disagreement as to what the risk is in that target population. No one's really been able to say what it is and I don't think anyone's quite clear that the calculations of risk from the AFCAPS placebo population are necessarily reliable.

But the question is whether we're reaching the limits of benefit at which point the risks might outweigh any potential benefits. And as a formal question, we have to ask what, in the way of clinical benefit, has been demonstrated?

CHAIRMAN BRASS: Dr. Temple.

DR. ORLOFF: Is that helpful?

DR. ROBERT TEMPLE: There's another factor. Obviously for physicians, long before there was evidence that lowering cholesterol with statins or anything else was beneficial, were given the opportunity to use those drugs to which they would then apply their wisdom and their ability to read the literature and make complex judgements.

What's proposed here is something that doesn't have the learned intermediary anymore. So

it's not out of the question that one would have a somewhat different standard for the evidence that's involved. I mean that's part of the question we're really asking.

CHAIRMAN BRASS: If I could ask two questions. First, in terms of understanding the risk. Both sponsor and the agency in this presentation referred to higher risk groups or safety concern groups, for example those that are on other drugs, etc.

What I've not seen is an estimate of how much risk is associated with those groups. The sponsor this morning gave a qualitative estimate that there is a large safety margin, but do we know what the risk is in a patient taking a statin and a fibrate, taking erythromycin plus a statin, in terms of the incidence of any serious adverse events? Do we know what that risk is?

DR. PARKS: I'm not aware of any studies that can actually tell us what the absolute risk is and that looking at several publications and addressing the issue of, let's say myopathy and lovastatin, it has been often quoted that the risk is increased in combination therapy, but I'm not sure that that has ever been prospectively studied, that I

actually know what an absolute risk is in the combination with erythromycin or a fibrate.

CHAIRMAN BRASS: So you would consider those risks hypothetical or would you consider them proven, but of unknown magnitude?

DR. PARKS: It think it's proven, but of unknown magnitude. Certainly if we look in the post-marketing data at the drug-drug interaction cases where there is rhabdomyolysis, resulting in rhabdomyolysis, it seems like the cases where there is a drug-drug interaction the severity is greater, the CK elevation is greater, the onset to rhabdomyolysis is sooner than in cases where it's just lovastatin monotherapy.

CHAIRMAN BRASS: I also want to follow up the issue of the HDL subset cohorts. If I understood your presentation, you indicated that in the HDLs over 40, there was actually no decrease in risk in the lovastatin group compared to placebo with an average of 3.6 percent versus 3.1 percent.

That differs both from Dr. Beere's presentation this morning which suggested that there might be a type two error in this cohort and that there was maintained relative benefit, but just unable to show statistical significance, and in the

publication itself, admittedly that's the entire cohort, there was a relative benefit, though not statistically significant, of the drug in the AFCAPS study with HDLs over 40.

Could you just clarify what your bottom line position on that is with respect to any relative, absolute, or risk reduction?

DR. PARKS: Well, I think that answering your question about the HDL and the original AFCAPS cohort, when we reviewed that study, we did look at the reduction in cardiovascular events with the primary and secondary endpoints by HDL also. But the cutoff that we chose was actually 35 and we chose 35 because of the NCEP guidelines primarily.

And we found that actually with a population with HDLs less than 35 or greater than 35, that there was a relative risk reduction that was significant in both population above 35 and below.

What's interesting is that when you take out, you now select out the OTC-eligible population of AFCAPS, HDL did seem to play a role, as I showed in my slide there, and it's not certain if that's because we removed out other individuals with greater risk factors such as diabetes and significant hypertension, such that now the risk that is overriding in the OTC-

eligible population in AFCAPS is that of HDL.

The slide that I placed up there with respect to incidence rates was actually derived from part of the submission that was sent in and as Dr. Beere had mentioned earlier, where they evaluated the HDLs, and it was just striking to us and that's why I evaluated it further.

CHAIRMAN BRASS: But again, those 3.6 and 3.1 estimates are for HDLs greater than 40 in the OTC-eligible cohort of AFCAPS?

DR. PARKS: Yes.

CHAIRMAN BRASS: So there was not even a trend towards benefit, and those rates, incidentally, are much higher because the original publication includes the HDLs greater than 40 for the entire cohort and they have event rates and placebo of only 2 percent.

So your 3 percent in the OTC cohort is higher than the overall cohort and in the overall cohort there was a trend towards benefit in lovastatin.

DR. PARKS: I probably could only speculate in the sense that in the OTC-eligible population it's not the entire cohort at this point. We are talking about a post-hoc analysis.

In some ways it's no longer a randomized population. They have excluded individuals with all the other risk factors and I've mentioned significant hypertension, diabetes, and that in some ways may shift the risk in this now subgroup of an HDL greater than 40 such as it is different from the original cohort.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: First, NCEP guidelines are only guidelines, and we need to remember that. It depends on the patient and the lipid profile and some of the risk factors. And I want to clarify that because they are only guidelines and maybe they need to be reviewed now.

But, I have a few specific questions. In the extension of the 076, do we know how many patients chose to continue the extension study?

DR. PARKS: For 076, I'll try to remember off the top of my head. Thirty percent discontinued in the first phase I believe. I know that by 18 months there was about 50 percent still, so somewhere between 70 percent down to 50 percent. And I'm sure that the sponsor can confirm that.

DR. DAVIDSON: Thank you. They are small questions, they are specific, but there are few. In

076, if they didn't speak English, they were excluded. Was that true for all the studies, or just for 076?

DR. PARKS: I believe it was for only 076. Dr. Segal, was that for 079 also? For 075 that wasn't the case because that was actually a placebo-controlled trial with physician involvement, not an actual use study.

DR. SEGAL: The inability to speak English was an exclusion criteria for all three of these trials. There was advertising for people in Spanish, but they had to be able to understand the informed consent in the study and that requirement was an English requirement.

DR. DAVIDSON: That means the informed consent was never translated to Spanish?

DR. SEGAL: I do not know if there was a translation in Spanish.

DR. DAVIDSON: Okay, thank you. In 081, when you say 8 percent of the patients were allergic, were allergic to the drug or were allergic? Because it seems that 8 percent allergic to lovastatin is a very high percentage and I wonder if that is part of the problem, that they didn't understand the question?

DR. SEGAL: There were eight people that were allergic in 081.

DR. DAVIDSON: Not 8 percent?

DR. SEGAL: No, no, not 8 percent, it was eight people and one of them turned out to self-select incorrectly. The group that was allergic to lovastatin in 081, allergy in fact seemed to be the area that they did best self-selecting in compared to the other groups as far as I could discern. There were eight people and one of them. So it was 13 percent, one person.

DR. DAVIDSON: What was the most common problem with the self-selecting errors? What was the most common problem in the self-selecting mistakes? Do you know?

DR. SEGAL: The most common? I think that the most common was actually people not understanding what their cholesterol was, because those values were actually somewhere in the 40 percent range, I think it was 46 percent. I could go back and check my slide, but people did not have a good idea what their cholesterol was in these trials. They thought it was one thing. When it was measured, it turned out to be something else.

But the concern that I had when I was reading these trials with regard to absolute cholesterol level was that I was concerned about the

way it was being measured because the fasting was really, I mean two hours in 076, I'm not sure that's a fast. I mean, that's not a fast for me. And six hours in the other trials, so they are short fasts and that was one of the questions that I put up.

How long do people need to fast before they can do a good reliable measurement, and do they need more than one blood test? So it's not clear.

The question I had in mind I guess was maybe this was a number they somehow really had had or been told by their physician, but then they were tested in a way that this kind of testing could either overestimate or underestimate a true cholesterol, so I wasn't quite sure.

But it was cholesterol that was the big self-selection, the major one. The rest of the groups fell in around 30 percent.

DR. DAVIDSON: Thank you. And one final question. And I think that's for you actually. There were 84 cases of low literacy, and you defined low literacy below 9th grade and that is actually a very high grade to low literacy. Could you tell me what really was low literacy? Because 9th and 8th and 7th is for me, not low literacy.

Then if you define low literacy below

nine, I would like to know how many were below six. Do you have any idea?

DR. LECHTER: I don't have information on the distribution within that group. It's standard for all of these studies to use 8th grade or below as low literate and I don't know the distribution within that group.

DR. DAVIDSON: My recommendation will be, we need to get up to date. There is a report called Literacy in America. It was published six years ago and I think that not only the agency, but the pharmaceutical companies that sponsor should read that to really be aware of where we are, because 9th grade is actually way too high for the comprehension that we saw in that report in 1993.

CHAIRMAN BRASS: In fact, testimony relative to that report has been presented to the Nonprescription Drugs Advisory Committee and it is in complete concord with what you've said.

DR. DAVIDSON: Thank you.

DR. TAMBORLANE: I'd like to revisit the HDL issue again for Dr. Parks.

If the target OTC population was redefined to include HDL less than 40, would you, from the data that you presented to us, suggest that we do have a

good surrogate marker, we could just look at the changes in cholesterol as a reasonable outcome? Would you change your risk-benefit assessment?

DR. PARKS: I think that HDL was not only the difference in these populations, as I've mentioned. It also had to do with the dose proposed and the degree of LDL lowering with each of those doses. And also keeping in mind that in the AFCAPS study they required a dose titration at 18 months to get further reduction to a particular goal.

So that's one issue that would still need to be addressed, whether the 10-milligram dose itself would be able to provide a clinical benefit.

And the other issue really is that of adherence to therapy. Even if at the 10-milligram dose you have some people who could achieve the same reduction as a 20-milligram dose individual. The question is whether or not there would be enough individuals who would stay on therapy long term in order to realize the benefit.

DR. TAMBORLANE: But that's a separate question. The question is if you were able to achieve a 17 to 22 percent lowering with 10 milligrams in the target population, redefined with an HDL of under 40, would you be willing to accept the idea that in the

long term, if that was sustained, that you could expect a significant improvement in the cardiovascular outcome?

DR. PARKS: It sounds like your raising, if a clinical trial was actually conducted and demonstrated benefit?

DR. TAMBORLANE: Well, you're using the AFCAPS to show that in the over 40 you don't see much of a benefit and if you show that it's under 40, there did appear to be a benefit.

DR. PARKS: Again, that is a, technically it's a post-hoc analysis and it is hypothesis generating and I think that many of us here would say that that might warrant further study.

DR. ORLOFF: Let me pipe in for just a second. I made a point in my introduction and I just want to make sure you do understand this.

The prescription lovastatin now carries an indication for the treatment of the AFCAPS type population. That submission was reviewed and approved and amendments were made to the labeling to specifically indicate the treatment of those patients. They do actually, by the numbers, fall outside of the NCEP guidelines. Those are just guidelines. We have data that speaks to an expected benefit in that

population.

The problem that we're dealing with here, just to clarify a little bit, is that there is some definable risk to the use of this drug.

Likewise, in prescription use, there is an intrinsic risk to the drug. There is also some different profile, if you will, of risks and perhaps benefits that accrue in the over-the-counter population relative to the Rx population.

We don't really have a very good handle on that and when we discussed this issue of being able to extrapolate an expectation of benefit out of the AFCAPS population, what we're saying is that we really don't have a handle on benefit. And so we are in a quandary as to how to evaluate the risk versus benefit.

CHAIRMAN BRASS: I think at this point, because of the hour, we are going to shortly take a break, but some of the sponsor's consultants need to leave very shortly and I'd like to grant them five minutes to make a couple of comments before we take a very short break to move onto the question section. So you have five minutes.

DR. HEMWALL: Thank you Dr. Brass. I'd like to introduce first Dr. Jeffrey Anderson.

DR. ANDERSON: Thank you. I think this has been, from my point of view a very interesting, worthwhile discussion. I would just reemphasize four points.

First, cardiovascular disease is a major problem. That is a fact that can't be disputed. This was mentioned as the number one cause of mortality and morbidity and primary prevention has stalled in the '90s. Things aren't getting better, they are tending to get worse.

So we really do need from a public health point of view to move ahead in reasonable responsible ways.

Second point is that I think that there is clear data now from so many sources that there is a continuum of risk for increasing cholesterol and a benefit of reducing that and the FDA has already stated that they've used that as a criterion for labeling for prescription drugs to I think imply a different higher standard to an intrinsically somewhat lower risk population and require primary endpoint trials really should be very carefully considered. That's an enormous burden and I think probably an unwarranted one.

I think the third point is safety and the

point I would emphasize is 24 million patient-years. I think that should carry a lot more weight than theoretical considerations which of course were much more important 13 years ago for this particular drug. So in terms of benefit-risk, I would emphasize those points.

And just finally in terms of who would benefit, I think this is a question at this point of choice, of reasonable choice among motivated people that want to reduce their risk.

It's true that half will drop out, but it seems to me the glass is half full, not half empty. That those who are motivated to, will I think carefully consider the labeling if they are there for the long term, will interact with healthcare personnel, will achieve benefit, and it shouldn't be just five-year benefit, it may be ten- or 20-year benefit, and that is substantial and accounts in fact for one-third of the events that occur in the U.S. Thank you.

DR. HEMWALL: And finally, Dr. John Farquhar from Stanford University.

DR. FARQUHAR: I'll make two points, one on HDL and the other on public education and it's affect on compliance.

I think the HDL discussion has been taken out of context. First I want to say that our center, incidentally doctors Wood, Haskell, and I were the first to show that exercise raised HDL. We've been very interested in it over the past few decades from an epidemiologic as well as an interventional point of view.

It looks to me as if, and I think we have an agreement from Dr. Willerson and Dr. Anderson, that we have to look at HDL as that the relative benefit of lowering total cholesterol is independent of the HDL level. And if one looks at all of the statin trials and all of the intervention studies, if you just divided it into cortiles, the top cortile in HDL will relatively speaking have the same reduction in events as the bottom cortile, but the absolute level that they start with is much lower. In other words, HDL is independent of the degree of change of LDL.

The second point that I wanted to make is the experience that our group has had in community-base health education leads us to have confidence in the American people to make the right decisions if they are given the adequate information.

We've had experience for example in Hispanic populations in our three-community study and

with appropriate education, they had proportionately a greater increase in their knowledge and a greater reduction in risk factors following a community-based health education program.

Given that point of view, if Merck apparently has the willingness to provide supplemental education through their education and support program, I would anticipate that they could target minorities and other underserved groups in that manner.

So I believe, as I understand, their education and support program to be really quite a good one and I think there's a challenge here that given that the traditional medical care system is doing such a lousy job, and that compliance is only 65 percent in prescription statins, that I would think that they would probably be able to do better job than that and increase the total number of people in this country who are at need who will have access to some degree of risk reduction. Thank you.

CHAIRMAN BRASS: At this point -- Dr. Orloff.

DR. ORLOFF: Just because I know that we're going to break and then come back to questions, I just want to make some clarifying points. I think one of the things that gets confusing here is that

there is perhaps a sense from the stated rationale that this is a drinking water approach.

That is to say, the estimates of benefit are based upon the idea that if we sprinkle lovastatin 10 milligrams across an at-risk population, there will accrue some population benefit. And yet the problem with doing that obviously, that we've been talking about, is that you'll wind up treating a lot of people who are not at risk and therefore do not stand to benefit.

And so what needs to be accomplished here is precisely the ideal that is accomplished or is the ideal to be accomplished in the Rx use of these drugs and it's treatment of this disease and that is along the model of whatever treatment guidelines you look at.

It's an individual risk assessment-based approach where you target therapy to those people who are at the greatest risk and who therefore stand to have the greatest benefit.

And what we have to make a judgement about here, at least in part, is whether that can be accomplished by the consumer in a safe and effective manner. Thank you.

CHAIRMAN BRASS: Okay. We will break and

reconvene at 3:32 promptly. Thank you.

(Whereupon, the foregoing matter went off the record at 3:23 p.m. and went back on the record at 3:33 p.m.)

CHAIRMAN BRASS: At this point, I will be turning the floor over to Dr. Katz to give the charge to the Committee and begin the discussion.

Before I do so, there will be issues that will require a vote of the Joint Committee and I just want to remind, identify those people who will not be able to vote today because of their status and that's Doctors Clark, Blewitt, and Molitch will not be voting, but I want to emphasize they are more than welcome to participate in the discussion.

After we hear the charge from Dr. Katz, we'll be going through the individual questions and discussing them one at a time. During that discussion, I encourage the Committee members to express their own opinion and address any residual questions relevant to those points to either sponsor or the FDA for further discussion. Dr. Katz.

DR. KATZ: Good afternoon Dr. Brass, Advisory Committee Members, and ladies and gentleman in the audience.

We are now at the time of meeting for the

deliberations for the Committee to begin. However, prior to asking the Committee to sit down and start to answer the questions, what I'd like to do this afternoon in a few brief moments, and I'll use brief as an operative word, is to go through some of the issues that we've heard today to highlight some of the points we'd like you to consider while answering the questions that are before you.

The topic of OTC treatment of elevated cholesterol is not a new one to this Advisory Committee. As Dr. Orloff mentioned earlier in his introductory remarks, this topic has been presented on at least three occasions to the Advisory Committee before.

The issues, however, being discussed today are somewhat different from the issues when we've heard this topic in the past. Merck is proposing a new indication or treatment of individuals with milder cholesterol levels in elevations that are currently approved for Rx indications.

In addition, this is not a true switch. This is a lower dose for a new indication as opposed to a dose that already Rx for an Rx indication switching OTC. And I'm just making that as a brief distinction and the reason why I'm doing that is

because it's important as you go back to look at some of the questions that we're asking, for you to be able to go back and assess to make sure that efficacy has been demonstrated by the data that we've heard today, presented both by Merck and by the FDA.

The next slide actually I hope will help to identify some decision-making processes and issues that we'd like you to consider as you go through your deliberations.

The first is the benefit-risk and we've heard a good deal about benefit-risk and particularly we want you to target in for the benefit for the targeted population that's proposed in this application.

In addition, we need to also remember the consumers and the consumer's ability to be able to self-diagnose and self-recognize and treat an asymptomatic chronic condition without the advantage of a third party intermediary.

Since many of these individuals, as we've heard before, may not have access to physicians and may not have access to the healthcare system, that they will be out there picking up the product on their own.

Thus, the other issue that comes in are

the consumer's ability to understand the labeling instructions which would include monitoring, both being able to identify how to do a fasting cholesterol level, how frequently to do it, and how frequently they need to monitor their cholesterol level as well as any other laboratory testing that might need to be done to look for toxicity and adverse events.

Also, the ability of the consumer to have appropriate follow-up care and treatment should a problem arise or they not be able to attain a specific goal.

Also, one needs to consider the consumer's ability to recognize the attainment of that goal and just what that goal should be for a consumer, and their ability to recognize toxicity since some toxicity presents really initial as laboratory data which may be asymptomatic.

It's also important consumers again understand what toxicity would be and where they should go should a problem arise.

In your questions today that we have before you, they are divided actually into three sections. Efficacy and safety in the proposed targeted population. OTC considerations for lovastatin 10 milligrams. And finally the

approvability.

So it's important again, and I want to just emphasize that this application or the indication is a new one, that's not currently been seen in our Rx products.

Thus, in your deliberation, it is important for you to address whether or not the data presented is sufficient to support the efficacy for the indication in the targeted population as well as to address what the appropriate target population should be, to make sure that safety is also obtained.

Thus, at this point in time, what I'd like to do is turn the microphone back over to Dr. Brass so that you can begin the deliberation of the questions. Rather than reading the questions for you, I will just kind of refer you now to your packages where the questions are listed. Thank you.

CHAIRMAN BRASS: Thank you. I'm not going to read the question either. Everybody has them in front of them and hopefully has read them and thought about them before, and so I'm just going to begin with question one and beginning with the bottom line.

Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit of lovastatin 10 milligrams in the target

population?

That point open now for discussion. I do call on people. Dr. Blewitt.

DR. BLEWITT: Well, I suggest that they have and my basis, as I tried to think this through, was that when I was following skiing I used to follow the World Cup and would notice that people would compete, but not necessarily win individual events such as the slalom or giant slalom or something like that, but that they could win it on total points.

And my assessment of approvability is based on the sum total of the data that have been presented here. I don't say that there isn't a little more work that could be done in certain areas, but I think that the basic core issue as to whether this would potentially provide benefit in the target population has been answered adequately.

CHAIRMAN BRASS: Dr. Johnson.

DR. JULIE JOHNSON: I would say that I agree that they've shown clinical benefit and there is really two questions here. Have they shown that it can produce a significant reduction in LDL cholesterol? And there is no question that's the case and as has been stated, they meet this prespecified bar of 15 percent.

The second question is an issue of clinical outcomes data and I guess my interpretation of this literature, and I have a knowledge of this literature that started well before yesterday or when I read these materials, is one where I would disagree with Dr. Orloff's interpretation and that is that irrespective of the studies, if you take the high-risk populations that were studied for example in 4S which is secondary prevention or in WOSCOPS which was primary prevention, down to the lower-risk populations, CARE which was secondary prevention, or AFCAPS/TexCAPS in the primary prevention, those have consistently shown similar relative risk reductions.

Now obviously the absolute risk reduction is greater the higher at risk they are, but the relative risk reductions are consistent. So I think to say well we don't have absolute data in this very, very specific population, but to somehow say every time we take the bar lower and we study a lower risk population, there's been benefit shown, but if we take that next slightly smaller step below AFCAPS, there's not going to be any benefit, I just don't think that the wealth of the literature right now suggests that.

CHAIRMAN BRASS: Can I just ask you, if, since I imply by your comments that you're answering

in the affirmative, for you to define the quote "clinical benefit" that you're affirming?

DR. JULIE JOHNSON: Well, that was part of my original question to Dr. Parks is what is defined as clinical benefit?

Whether you define clinical benefit as lowering LDL cholesterol, which is clear they do show that benefit, my answer is yes, but even if you say clinical benefit as in cardiovascular endpoints, I think that the wealth of the literature would suggest that even if there is not very, very specific literature in this population, the wealth of the literature would imply that there is very, very likely to be clinical benefit in this population.

CHAIRMAN BRASS: If I could just beat this dead horse about HDL just for a minute, because I remain confused about the discrepancy and the interpretation of the HDL data between what was presented by Dr. Parks and the sponsor's interpretation of consistent relative benefit regardless of HDL.

Dr. Parks, my understanding is you showed that the event rate was 3.6 percent in the OTC population with HDLs above 40 on lovastatin versus 3.1 in the placebo group, which I don't see as relative

benefit in the lovastatin group. Could somebody clarify why I'm confused about this?

And I make this point because the average HDL in the target population is over 40 and so that as long as you're defining the target population and extrapolating endpoints into that, I think clarification of that would be very helpful.

If you could go to a microphone and identify yourself please.

DR. HOBERMAN: David Hoberman, Biostatistics, FDA. I certainly disagree with the statements that were made by Dr. Beere.

She referred to a statistical test which did not show an interaction, that the trial was not designed to show that, and she referred I believe to a consistent benefit in the tertiles and your eyes did not deceive you.

Whether or not people who have HDLs over 40 will benefit from this drug if it goes OTC is a question to be answered by a clinical trial, but it's not AFCAPS and it's not the other things that were referred to.

But based on AFCAPS, it's clear that you cannot say that there is a benefit in patients with HDLs over 40. If you want to go to other literature

and make the argument, that's something else. I'm only referring to the statements made by Dr. Beere concerning AFCAPS.

DR. COOK: If I might say something. My name is John Cook, a statistician at Merck. I think we need to be careful about the interpretation of these subgroup analyses that were done here.

The AFCAPS study was not designed to really look at the issue of benefit across the range of HDL. These individuals were identified based upon their baseline risks.

The next point I want to make is that there was a prespecified analysis with the original AFCAPS study to look at HDL and that was done as HDL in a continuum and not in terms of tertiles or potential cuts at either 35 or 40, but looking at the continuum of HDL to see if there was a difference in the relative risk as a function of their baseline HDL.

And that test did not show that there was a significant difference. There was no interaction that was detected between baseline HDL as a continuum and treatment effect.

I think what we need to look at here in terms of the tertiles is one to be very cautious with those types of analyses. They depend a little bit

upon the time horizon that one picks. The analysis, the percentages that they showed were Kaplan-Meier estimates at five years.

If you look at the accrued event rates, it's actually a little bit higher in the placebo group, not significantly different, but if you look at six years, the Kaplan-Meier estimate there shows that there is an increasing risk in the placebo group and there were no more additional events in the fifth year for patients who were treated with lovastatin.

So, we can kind of sit here and chop up the data in many ways. It really wasn't designed to look at those things. That's, I think, one reason why we need to look at other studies, other evidence that shows that this relationship relative risk is very consistent.

CHAIRMAN BRASS: Okay. Let's go to some other data then. Both sponsor and the FDA showed the MR FIT data showing the continuum of risk with LDL over the complete range including 200 to 240, the target population.

The sponsor also alluded to the Framingham data which indicated no loss of LDL predictive value or total cholesterol predictive value until the HDL got over 60. But that was for the full dynamic range

of values.

My question would be in the range between 180 and 240, for HDLs over 40 or 50, are there just epidemiologic data that confirm in that range that LDL remains an independent predictor in that range of average total cholesterols, but above average HDLs?

DR. COOK: I don't know if there's direct evidence. I might turn that to somebody else. We did look at within AFCAPS, the relative risk, the relationship between changes in lipids and changes in risk and we saw a very consistent result regardless of whether their HDLs were over 40 or not.

CHAIRMAN BRASS: But that was biased because you enriched the low end of the HDL range in AFCAPS. So I'm agreeing with you, let's stop talking about that and let's look at the other data, if there is, that's relevant to this issue.

DR. HEMWALL: We could really hang up on this for a while and maybe I can put this in a different perspective in that of the consumer and of our label. We are asking consumers to recognize obviously that they have to check and know their cholesterol levels and most test now given HDL levels.

What we're saying on the label for sake of simplicity, have your cholesterol between 200 and 240,

have your LDL over 130. In practical terms that leaves a few number of consumers that are going to have high HDLs. About 15 percent of our population actually had high HDLs over 50 I believe.

CHAIRMAN BRASS: But the mean in your actual use population was over 40, wasn't it?

DR. HEMWALL: Yes. Let's not hang up on the numbers though. We are willing to put something in our label, based on consensus, on what is a good cut point. In the materials, if your HDL is over that point, this product may not provide benefit for you and you should check with your doctor before you use it.

CHAIRMAN BRASS: Yes, Dr. Grady.

DR. GRADY: I find this kind of hard to think about because of the kind of imprecision of our estimates. We're making a lot of judgements here.

For example, based on changes in LDL cholesterol, and actually the four studies that the sponsor presented us, two of them were unblinded, and therefore susceptible to co-intervention and so forth.

The two blinded studies, the decrease in LDL was only 15 percent and 17.5 percent, so that's kind of borderline. And the other thing I think is we need to look at the bigger picture.

We are now talking about making drug treatment available to millions of totally healthy people and so the benefit, and in this case I mean the absolute benefit, has to outweigh the absolute risk.

CHAIRMAN BRASS: We're only on the benefit side of the equation right now though.

DR. GRADY: Okay. But I mean the benefit really depends on its absoluteness in my mind and that is what's the likely absolute benefit in this population, and so that does come back to their HDL levels and so forth, the higher their HDL, the lower their risk.

So it's very hard to get an estimate of the absolute benefit here given we don't know what compliance will be and we have only sort of LDL changes to estimate that from.

CHAIRMAN BRASS: Yes, Dr. Davidson.

DR. DAVIDSON: Well, this drug is approved. And it's approved because it's affective. The question here is different. There are some questions that I still have.

The measurement of lipids in the study makes me still wonder what I'm seeing, if I'm seeing apples to oranges or I'm seeing a combination.

But the question that you have here is

based on the data. Is this drug effective in lowering lipids? It is effective in lowering lipids.

CHAIRMAN BRASS: Let me just make clear that it actually says clinical benefit and you're interpreting --

DR. DAVIDSON: That's right. That I cannot answer. I don't think it has been demonstrated.

The second part of the question is do we need to go to NCEP guidelines and I think that's clearly not necessary. They are just guidelines and there is no data that everybody shows, if we lower total cholesterol to target, if we lower LDL, with benefit. None of the statins actually will decrease events 100 percent, because then for sure we'll be taking statins all the time.

There are other factors, other than cholesterol that are playing a role. There are other drugs that are very effective in lowering MIs as well. The first question is, the drug lowers cholesterol, the clinical benefit of lovastatin, I didn't hear it today.

CHAIRMAN BRASS: Okay. Dr. Elashoff.

DR. ORLOFF: Excuse me Dr. Brass. I just want to bring this back a little bit to make sure that

we're addressing the right question. This is the question, just to make sure everyone understand, we're not taking about OTC, we're talking about the indication. Is the indication merited?

And let me just remind you that I think we all agree that this is a low-risk population and without trying to put a number on it, it's a lower risk population than the 5.5 percent placebo event rate seen in the AFCAPS cohort. Let's say it's less than 1 percent per year.

The question is, should we be blindly treating all such patients, and is 10 milligrams of lovastatin the correct dose to affect benefit?

DR. ELASHOFF: There are no studies reported of this dose in this population talking about clinical benefit.

Therefore, all the discussion about potential clinical benefit is based on extrapolation from other studies, extrapolation from models fit to epidemiological data which may or may not be applicable to these. I understand it's mostly Framingham and MR FIT, and MR FIT is all male, isn't that right?

So data from preceding time points models, when you get into exactly where a model bends and how

much it bends, you have to be really careful about how you're fitting that model because it may not work really well across the whole range.

Exactly what's predictive in different ranges may vary. It seems to me that there is a lot of extrapolation involved in basing any clinical benefit decisions on the data we have had presented.

CHAIRMAN BRASS: Yes.

DR. MOLITCH: I apologize for not being here this morning and perhaps I missed this in the discussion by the sponsor, but we have a population where they have a certain beginning cholesterol range that we're recommending that these people take the drug over the counter, but I didn't hear or read in the materials what the goal of therapy would be once the person took the 10 milligrams of Mevacor and then in addition, once they do in fact monitor their cholesterol at six or eight weeks later, depending upon what that level was, are the persons supposed to adjust that dose of medication at that point or what are they supposed to do with the information once they get the information at six or eight weeks?

CHAIRMAN BRASS: Some of that was discussed. I don't know if you want to summarize a response or --

DR. SLATER: In answer to your question, roughly 75 percent of people get below the 130 LDL which is considered for most the goal. In this particular paradigm, if the level is not reduced, then the patient is instructed to call their physician.

DR. MOLITCH: Thank you.

CHAIRMAN BRASS: Yes.

DR. TAMBORLANE: Slight disagreement Dr. Orloff, in the question of it's clinical benefit, the OTC issue becomes important because it's not just the initial lowering over the first four to eight weeks, it's the maintenance of this improvement in lipid. I'm willing to accept the lowering the cholesterol as a surrogate marker for cardiovascular risk.

The question is, can you maintain that? And the study that's not been done is to look at compliance with a prescription regimen with good medical follow up versus over-the-counter sort of approach.

CHAIRMAN BRASS: Yes, because I would also disagree a little bit because you were putting a lot of other adjectives into the question that aren't there, including things like optimal therapy.

We discussed this morning, and sponsor acknowledged, that these patients would be better

treated by a physician with appropriate monitoring and dose titration.

So I don't interpret the question to be as broad at this point in our discussion, but simply a question of clinical benefit of 10 milligrams yes or no, not as compared to 40 milligrams.

DR. ORLOFF: That's what I'm driving at. We want the Committee to give us some feedback on whether this new indication is merited. Forget over the counter. Does this patient population warrant treatment across the board, because that's what an indication means.

If you have a total cholesterol between 200 and 240, and an LDL of greater than 130, take 10 milligrams of lova, and you're the right age and sex, and etc.

CHAIRMAN BRASS: Again. I think that is a question, and we're happy to discuss that question, but it's subtlety different than what's posed here.

Because for example, whether or not that population would benefit from primary prevention in any form with a statin is a different issue than whether 10 milligrams has clinical benefit in that population.

And so, I think the point you're raising

will come out with the subsequent questions and try to do it one step at the time. And so I'm going to -- I'm sorry, yes sir, down at the end.

DR. GRADY: I just want to say that compliance does become an issue because you don't see any real clinical benefit with any of the statins for six months to 12 months, so --

CHAIRMAN BRASS: I understand.

DR. GRADY: I think over-the-counter use, trying to estimate the magnitude of the benefit depends to some extent on compliance as well.

CHAIRMAN BRASS: And those points will come out in subsequent questions.

DR. CLARK: Yes. I think there is some specific aspects of these questions, but in terms of number, it says indications based on an expectation of cardiovascular benefit.

I think what has been shown is that this dose does lower the LDL and one would expect a benefit that may not have yet been demonstrated and whether or not the population that's proposed is going to appropriate becomes a slightly different question.

So the reduction of LDL has been shown, so the expectation of a cardiovascular event should be there, but if the requirements have been demonstrated

then I think that's another issue, which it is not.

CHAIRMAN BRASS: Dr. Temple.

DR. ROBERT TEMPLE: Well, the question says that you would propose the indication based on an expectation, but it then goes on to ask, has the sponsor adequately demonstrated a clinical benefit, which in theory could be either because they have a direct study of it or because you're prepared to extrapolate from other data. I mean, there's two ways to learn things.

CHAIRMAN BRASS: So, with those points in mind, I'm going to split the question into two questions for a vote right now. And I want to first, if it's helpful to you, feel free to tell me not to. But I'd first like to answer the question with clinical benefit simply defined as a lowering of LDL cholesterol. And establish whether or not there is consensus on that point and then immediately vote on whether the effect has been shown to affect cardiovascular events.

And I think that will clearly separate out that differentiation in everybody's mind. So, yes.

DR. EDWARD KRENZELOK: Can you clarify that, the second part, because does that reflect just a lowering of LDL or a lowering of LDL as presented by

the sponsor?

CHAIRMAN BRASS: I will phrase this specifically just before we vote on it, because if I phrase it now, I'll phrase it differently when we vote and everybody will get confused.

So the first question that we'll be voting is yes or no, has the data submitted in the NDA by sponsor, demonstrated that lovastatin 10 milligrams in the target population is associated with a lowering of LDL cholesterol?

You want to do it by show of hands or do you want to go around the room? Okay, so show of hands. All who say yes, that that proposition is true, please raise your hands.

(Hand vote taken, 13-0)

CHAIRMAN BRASS: Any noes?

Any abstentions?

Okay. So the second question is. Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit in reducing cardiovascular events by lovastatin 10 milligrams in the target population?

All those in favor who agree with that proposition please raise your hand and vote yes.

All those who disagree, please raise your

hand and vote no.

Any abstentions?

DR. ORLOFF: Excuse me Dr. Brass, could you give the vote tally verbally for the record.

CHAIRMAN BRASS: On the first question, the vote was 13 yes, 0 no. And on the second it was 1 yes and 12 noes.

Then the next question is, since we at least got a partial no, what additional data are needed to demonstrate a cardiovascular benefit in the target population?

And I don't know if we need to discuss this a lot further, clearly a placebo-controlled trial in that population with cardiovascular endpoints would do it.

Are there other things that the Committee feels would be either equivalent to or other ways to answer that question by as much?

DR. SLATER: Before you go down that path, a hypothetical endpoint trial --

CHAIRMAN BRASS: Please use the microphone.

DR. SLATER: To properly power an endpoint trial in this population, one would have to exclude the AFCAPS eligible patients because it would be

unethical to repeat the trial in those patients.

So our calculation is that it would require tens of thousands of patients for an extraordinarily long period of time to absolutely defer this decision to a point when it would be likely irrelevant.

CHAIRMAN BRASS: I understand and that is exactly why I'm posing the question I am, in terms of well everybody --

DR. SLATER: I wasn't sure that that had been thoroughly appreciated by the --

CHAIRMAN BRASS: Where given that situation, are there other data or other information that could be provided to the Committee that would give it greater confidence in the association between the LDL reduction in this population and risk reduction?

DR. DAVIDSON: Well, my concern is that we really need to decide when and how to collect lipids and for how long, which is not something that was done during this OTC trial. And it would not be bad.

I heard the idea of looking and seeing if we can compare, even though it is not a trial that is easily done, to trial the way we do trials for medications like with physicians and monitoring the

patients.

CHAIRMAN BRASS: Are there other thoughts on this point? And let me just emphasize that we're not saying there's not a benefit, we're just basing it on what's been presented to us.

DR. EDWARD KRENZELOK: I was a little bit surprised there really wasn't very much emphasis on any of the studies on the effect of diet and exercise and I just wonder what impact diet and exercise might have had and there was conflicting data at least as we looked at, I think it was 075 and 076 in terms of the ultimate data.

And I just wonder if it might be possible to reanalyze the data looking at those variables and see what impact those things have on LDL and HDL and that may help resolve some issues, at least in my mind.

CHAIRMAN BRASS: I think with that information, I doubt it would fundamentally address this. And let me just emphasize a part of the reason this issue is important is because the data in the prescription world, with titrated dose and physician supervision, has documented the efficacy of primary prevention in a cohort that includes many of these same patients.

So then again, now the issue of the 10 milligrams versus a proven therapy, the burden of proof on the 10-milligram dose paradoxically becomes more difficult because now there is, in fact. Doctor, comment?

DR. TAMBORLANE: Well, I was thinking a little out loud, but it seems to me it's going to be difficult to do a long-term cardiovascular risk factor, but some study that actually would compare again the prescription use of an optimized dose versus the standard 10-milligram dose over a relatively short term, a year or something like that. If you had comparable lipid-lowering effects, it might be of some benefit.

DR. DAVIDSON: Well Bill, actually if you look at some of the studies, in 12 months you start seeing in the treated and untreated a different curve. Maybe not power enough to look at many events, but you start seeing events at one year. Then I think that's possible.

CHAIRMAN BRASS: Dr. Temple.

DR. ROBERT TEMPLE: I just want to be sure we understand. The last suggestion was for example you might take a population say like the AFCAPS population and randomize them to aggressive monitoring

by physician titration and alternatively to just give them 10 milligrams and ignore them. I don't mean to be facetious, but that's the sort of thing one might look at.

Of course that would be for that population, but still.

CHAIRMAN BRASS: And at either cardiovascular endpoint on that study, you'll still need a tremendous number.

DR. ROBERT TEMPLE: No, no, I didn't mean that. That would not be a cardiovascular endpoint obviously, it would be a, how do I do with my lipids?

CHAIRMAN BRASS: Right, and that would be a comparison of the LDL as was suggested.

DR. GRADY: And I think that's then reassuring, particularly if there was a persistent equal effect on lipids over time and it's still one of the things that concerns me is that this is not going to persist for a year or two.

CHAIRMAN BRASS: Dr. Johnson.

DR. JULIE JOHNSON: I guess that there are two questions that I sort of have and one is what would a trial that shows that it lowers LDL provide us when we voted unanimously that they've already documented that it lowers LDL?

My second question is this issue about persistence and compliance with therapy long term. Clearly if people are not compliant with their therapy they're not going to derive a benefit and I guess sort of being the devil's advocate, why should we penalize those who are compliant and will persist with their therapy for many years, just because there is a high percent of the population that is noncompliant?

And that's certainly not something that's going to be confined to the OTC world. There's plenty of that for prescription drugs.

DR. TAMBORLANE: I would respond to that by saying the sort of borderline swing person might be more compliant if properly monitored by a medical team, and that if you're going to make it available over the counter, that might discourage those individuals from seeking that kind of advice and support, and end up with less compliance.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Well, we talk about the well-informed, well-motivated patients. Those patients go to see us and they comply, and they actually request from the physician to the lipids and they are interested in doing the lipids and they know what a normal LDL is and they read all the magazines.

Those are not the ones I'm worried about.

CHAIRMAN BRASS: Have we covered the issues for question one adequately from your prospective? Then we will move on to question two, and again I will take the liberty of just reading the punch line.

Taking into account these and other safety issues, has the sponsor presented adequate data to support the safety of lovastatin 10 milligrams in the target population?

Dr. Neill.

DR. NEILL: Yes.

CHAIRMAN BRASS: And again, in our initial answering to this question, we are taking it globally and not simply in the OTC context, but that simply is 10 milligrams safe in this target population?

Any other points that would be raised?

Then we will take a quick vote on this one as well. All those who feel that the safety of 10 milligrams in the target population has been demonstrated, please raise your hand.

(Hand vote taken)

DR. TITUS: Thirteen yeses.

CHAIRMAN BRASS: Noes?

Abstentions?

Need for further discussion on two?

Question three. Taking into consideration the balance of risk and benefit, has the sponsor presented data that are adequate to support the use of lovastatin 10 milligrams in the low-risk population with total cholesterol 200 to 400, LDL greater than 130, regardless of the HDL-C level without coronary heart disease or diabetes?

And I think we discussed a lot of this in our discussion of the first point. Are there any issues that anybody would like to bring out that wasn't?

Yes, Dr. Davidson.

DR. DAVIDSON: I'm going back to the studies were exclusive and noninclusive. Really with the way the studies were done, it's hard to tell if all the populations that are at risk could benefit from.

CHAIRMAN BRASS: I think some of the issues that we had with the HDL in particular in defining subpopulations were brought out and I think some of even the epidemiologic data that would lend further support to the hypothesis that in this range the LDL remains independent of relatively high HDLs I think would be important in helping understand that

relationship better.

Are there other points that people would like to bring out? I'm going to ask, if you don't mind, we won't bother to vote on that one separately because it's so much like number one or do you want a separate vote?

Now we get to the multipart questions.

Okay, question four. These now begin to focus specifically on the issues related to OTC use.

Assuming an indication for the use of lovastatin 10 milligrams in the proposed target population could be justified based on an expectation of clinical benefit, has the sponsor adequately demonstrated that consumers can achieve such a clinical benefit in an OTC setting?

In responding to this question, please consider the following: The ability of consumers to self-select/deselect, the ability of consumers to evaluate response to treatment, ability to adhere to chronic therapy, the need for the physician or the healthcare professional in the effect of treatment, and the capacity of the label to direct consumers in the effective use of lovastatin 10 milligrams OTC.

So I think I'll just open this up for discussion. Dr. Neill.

DR. NEILL: I have a question about the actual use study that relates to subparts A and B, whether consumers can appropriately self-select and deselect and whether they can evaluate response to treatment. And it might be best to actually focus specifically on the actual use unblinded trial.

My understanding of that trial is that patients were recruited, they came into a storefront-like place, were asked to self-select, they were assessed whether or not they appropriately self-selected, and for those patients who ended up on medication regardless of the selection process, their lipids were periodically checked for a period that extended past eight weeks.

It's unclear to me whether or not the fact that their lipids -- let me say this differently. We're asking consumers to check their cholesterol or check with their physician after eight weeks and to have their cholesterol checked.

I didn't hear any data that informs me about how those consumers knew their initial cholesterol, although I've been told that pharmacy and out-of-physician-office testing is very common, I haven't heard any data about that and I'm curious about whether that was collected.

And then I guess I'm also curious because I believe, in these studies, their lipids were checked by the study personnel and it's not the case that you simply followed them along to see would they visit their doctor? Would they have their cholesterol lipids checked? And see whether they did and see how they did that, did they do it appropriately using any of these other methods which are now so prevalent?

And I'm being a little facetious because I'm not sure that that's the case, that they're that prevalent. And if this were really an actual use study I think it would be important to design it in a way that you monitored what they did from as far a distance as possible rather than drawing their lipids for them, telling them to fast for two or six or some number of hours, and having them see a study physician as opposed to their physician.

So if somebody could inform me about whether any of those things happened in a natural environment or natural experiment rather than with study personnel, I'd be happy to hear it.

DR. LAROUCHE: Your description of our trials mixed together two of the different trials, so the one where we have the longest data on the lipid reductions was actually from the pharmacy study and