We have been reminded the press has asked the people asking the questions to please identify yourself when you do ask a question.

Dr. Parker.

DR. PARKER: I just was wondering when we look at the data that is going to give us a little more information about gender and age to help us sort of look at the issue related to either pregnancy or eligible for childbearing, do we also have information that we could include on that about how many in the study had asymptomatic liver disease. That is one question.

The other relates to our thinking. I believe one of the things we will respond to relates to this idea about the hierarchy of information in label comprehension. I am getting lost, I will be honest. You know, I get lost so easily, and I am flipping through papers and I am getting my piles mixed up.

Is there any way to take the proposed hierarchy that we have been presented with--I already forgot that term--the deal breakers, I believe was the term that was used, some sort of ranking of these, and take whatever information we have from the studies to help us be able to

look at that very specifically.

You know, what do we know about people's ability to make judgments based on a proposed hierarchy, if there is any way to sort of make that more concise than sort of piecemealing it. Maybe you have already tried to do that or maybe you are asking us to help drive that. Thanks.

DR. LEONARD-SEGAL: We have the same complicated confusion problem on this, so what we have done, because there was nothing pre-defined here because these studies were in progress, is we actually decided to offer you some different ideas about hierarchies.

We are not sure that any of the hierarchies that we have presented to you today contain all the deal breakers. Maybe they contain more than what ought to be deal breakers. So, we are asking you to help us brainstorm this today.

We have had other applications for other kinds of drugs, other indications where we have found this to be an easier kind of job to do. But for this one, for this day, we are asking you to help us with this.

DR. TINETTI: We can definitely add to your confusion.

Yes. Identify yourself also.

DR. GLASSER: Steve Glasser.

I am particularly concerned, while we are talking about deal breakers I guess, about the 1 in 3, 30 percent of patients who are on lipids, who would have added lovastatin to existing lipids.

I know it is going to be a small number in the studies, larger number in real life, but do we have any more information on doses of their statin, and things like that, so it is sort of estimate what kind of problem that could really be?

DR. HEMWALL: Yes. Again keeping in mind that there is probably an enhanced number of people that were under these circumstances because of the nature of the clinical study. In fact, the label turned away 80 percent of the people that actually were taking the other lipid-lowering medications.

But when you look at the medications they were taking, they pretty much reflected how the marketplace is divided up with most of them taking statins, and the more common ones were atorvastatin 10 mg and 20 mg, and simvastatin 20 to 40 mg.

So, what you are concerned about is something that we believe we can do much better with, with better labeling and, of course, with the support program in place.

But if one were to add the 20 mg of lovastatin to the lipid-lowering that is already seen, say, with these products of greater potency, where we may be seeing a 40 to 45 percent reduction, adding lovastatin to that will only marginally increase the reduction in lipid lowering.

There is a rule of thumb that you get about a 4 to 6 percent reduction when you double the dose with the statin that they are on, so adding 20 mg of lovastatin will give a very marginal increase.

Now, what that means is two things. One, the consumer will recognize it is not doing anything for them when they get their lipids checked, and that they are spending the extra money. When they have the support system, they will also realize they are not doing the correct thing.

The other thing, though, it is a very minor increase in what would be of concern about increased adverse events, which are already low for all the statins in their dose ranges, but adding this on would not add an additional

large concern, something we want to avoid.

The other thing to keep in mind--

DR. TINETTI: Thank you. I think that answered your question. This is just a clarification time.

DR. GLASSER: Could I just add one clarification of that, though? Were they aware that they were on a statin and would have added this, or were they not aware they were on a statin?

DR. HEMWALL: What we have is their self-reported information of what they were taking when we asked them what are you taking in those interviews afterwards.

DR. TINETTI: Thank you.

Dr. Taylor.

DR. TAYLOR: Yes. As a follow-on to that question--

DR. TINETTI: Identify yourself.

DR. TAYLOR: Dr. Taylor.

[Laughter.]

DR. TINETTI: Just following the rules.

DR. TAYLOR: As a follow-on to that question, is there any relationship to the decision to add to their medication in relationship to the literacy or the income

level?

DR. HEMWALL: No. We analyzed that data very carefully, and there were no differences in almost any of the different areas you would want to look at in the SELECT results relating to literacy or income level.

DR. PICKERING: I would like to ask Captain Shay, I think it was, you referred to the risk of hemorrhagic stroke or somebody did.

Could you amplify that?

CAPT SHAY: That wasn't me.

DR. CRAIG: I think we bring that up mainly because it was brought to us as a concern from outside of the Agency, as well. I think it is probably more of a concern in high-dose statins and people who are at high risk, but we do present it as something that is ongoing, under review in the Agency, about things that are seen in epidemiology studies.

Some statins actually have things in their label currently regarding possible risk of hemorrhagic stroke, so in the sense of you being clear, that is why we are bringing it up.

DR. TINETTI: I was actually one of the people

that asked that there be more information provided. I was a little surprised there wasn't a little bit more.

I think that is probably something we want to have a discussion a bit more this afternoon, because not all showed that it was associated only with high-risk statins, so if there is any information that would be available for the panel this afternoon, that would be terrific. Otherwise, I brought some with me, as well. It is an important point.

DR. PARKER: I just wanted to ask whether or not the phrase "do you have the heart for it," was used at all to recruit people for the SELECT study, and whether or not you have any information on what that phrase means to the people in the study.

DR. HEMWALL: No, I want to be clear that there was no promotional information, and by that I also mean the education and support information that goes along with this program once it would be in the marketplace, none of that was included in the SELECT study, and that phrase has not been tested with consumers.

Mr. Quesnelle was giving you some examples of the types of promotional messages that would be used for a

product like this.

DR. TINETTI: I have one more question for Dr. Colman clarifying with the ALS. You said in the randomized controlled trials there were 18 episodes of ALS, which I think would be in 400,000 person years of follow-up.

Do you know what would be expected in this age population in background, do we have that to do a comparison? Obviously, sometimes a randomized controlled trial, subjects are all healthier than the general population.

DR. MOSHOLDER: Andy Mosholder, Division of Drug Risk Evaluation. I will try to address that.

We don't have exact age and gender breakdown for the clinical trial data, but in terms of sort of a ballpark, it's a little higher than the general population rate of about 2 per million per year or, I am sorry, 2 per 100,000 per year. So, this is about 4.5 per 100,000 per year, and since the incidence increases with age, that is sort of in the ballpark, but it is hard to be precise.

DR. TINETTI: Thank you. I think it is time to break for lunch, and I have one statement I have to read to you before we do that.

We will reconvene again in one hour from now, so it will be just around 1:30. Take any possessions with you that you want. The ballroom will be secured by the FDA staff, and you will not be allowed back in until we reconvene.

I just want to remind the members of the panel not to discuss anything about the meeting during lunch.

Thank you.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

[1:30 p.m.]

Open Public Hearing

DR. TINETTI: I am going to start the open public hearing component.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement, to advise the committee if you do not have

any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their considerations of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for consideration.

I just want to remind the speakers that you are limited to five minutes and the microphone does go off at five minutes, so make sure that you say what you want to say at least ahead of time, at the front.

We can start.

DR. LEWIS: Good afternoon. I am Dr. Sandra Lewis, Director of Research and Prevention at the Northwest

Cardiovascular Institute in Portland, Oregon. I am also a member of the American Heart Association Women in Cardiology Committee, and I was recently recognized by Good Housekeeping magazine as one of the top 44 cardiologists and cardiology programs for women.

My conflicts include clinical investigation and consulting for the major statin-producing pharmaceutical company.

As a practicing cardiologist for nearly 25 years, I strongly believe a nonprescription statin will address the unmet and urgent need for safe, effective, and accessible treatment options to lower cholesterol and reduce coronary heart disease.

My initial reaction to an over-the-counter statin was frankly skeptical. Like many physicians, I felt statins should remain under direct physician management. I still believe this in regard to high-risk patients who need to reach more challenging lipid targets, but for those at moderate risk, with elevated cholesterol, who have not yet had an event, I have come to view a nonprescription statin as not only an opportunity, but a necessity, because the current system is just not working.

About 20 million Americans have moderately high LDL cholesterol, but only one-third of these are being treated. They are at risk for that first cardiovascular event which often comes without warning and may be fatal.

Why this treatment gap? Well, many people have a mind-set that prescription medications treat disease. They feel they should be able to control cholesterol with diet and exercise. Taking a prescription medication means failure.

In fact, the Institute of Medicine, in their Quality Chasm report, has mandated self-directed healthcare. The OTC Mevacor program represents an ideal opportunity to implement this mandate in a group motivated toward health promotion. This is creative and this is new.

I hear concerns that lower risk people may take over-the-counter Mevacor, however, although atherosclerotic events increase at age 45 or 55, atherosclerosis itself is a life-long process. Fatty cholesterol streaks have been seen in autopsy studies of young soldiers since the Korean War, and intravascular ultrasound shows plaque in young heart transplant donors.

Although the absolute number of events is lower in

lower risk groups, the relative risk reduction with statins is equal in all groups. Lower is better at any level of risk. In other words, strict label cutoffs appear to be precise, but atherosclerosis is not.

Statins have been available for nearly 20 years. We have more research on statins than perhaps any other class of medicines. They are effective and safe, particularly at the 20 mg dose that is being proposed today.

Furthermore, nonprescription statins have an important role in reducing risk in women. Heart disease and stroke are the number one cause of death for women. Despite national campaigns, red dresses on our lapels and improved awareness, women remain unaware of this.

Ask a woman her major health risk, and she will tell you cancer, breast cancer. Recognizing that current approaches including Framingham risk assessment underestimate risk for women, this year the American Heart Association issued new guidelines for women, which urge physicians to take into account lifetime risks.

In an editorial in the journal Circulation, which accompanied the publication of these new guidelines, the study authors wrote, and I quote, "Even the presence of a

single risk factor at 50 years of age is associated with substantially increased lifetime absolute risk of CVD and shorter duration of survival."

Today, you have an opportunity to safely change behaviors for so many at risk. I urge the panel to give men and women an added tool in battling heart disease by voting to recommend the Mevacor program for nonprescription status.

Thank you.

MS. HUGHES: I represent the Board of Directors of the Preventive Cardiovascular Nurses Association, PCNA. We receive support for our educational initiative from members of the food and pharmaceutical industry. However, we have received no support from the sponsor today.

PCNA is a national organization of 2000-plus nurses dedicated to the primary and secondary prevention of cardiovascular disease. We achieve our mission through public and professional education, through increasing consumer awareness of the importance of reducing CVD risk, and through advocacy regarding nursing's role in the care of persons and families at risk for CVD and stroke.

The nurses on our board who authored this statement with me average well over 30 years experience each

in the field of cardiovascular nursing. We remember when the care of the acute MI patient was reactive rather than proactive, and when available strategies for the treatment of dyslipidemia included many agents, often poorly tolerated, that were given in multiple daily doses and which only modestly reduced cholesterol levels and only modestly reduced cardiovascular event rates.

The approval of lovastatin, the first statin in 1987 and the agents in the class that followed, effectively revolutionized pharmacologic treatment of dyslipidemia. In a larger sense, the approval of that first statin really led to the genesis of the whole field of preventive cardiology.

In numerous well-designed clinical trials of hundreds of thousands of adults, cholesterol lowering through the use of statins has been found to be remarkably safe and effective.

The results of these trials have demonstrated substantial reduction in morbidity and mortality. But of millions of Americans eligible for treatment with cholesterol-lowering medicine, only a fraction receive these.

Many who begin taking them fail to continue

therapy over time. Barriers to the initiation of, and persistence with, treatment are complex and multifactorial. Making a low-dose statin available without a prescription is one strategy to close the undertreatment gap for those at moderate risk.

We have a vantage point allowing us to see the gap between the evidence-based treatments that are available to prevent first and subsequent events and what actually happens in day-to-day practice.

Today, we are gathered to discuss the possibility of a new mode of access to statin therapy, one that would provide part of the solution to the current undertreatment gap.

The Board of Directors of PCNA acknowledges the potential public health benefit of the OTC availability of low-dose statins. We support the concept of the switch if the research demonstrates that the population that uses this product is comprised of appropriate candidates for OTC therapy with regard to age, level of risk, medical history, and baseline lipids, and that those who elect to use the product follow the instructions on the label with regard to dosage and frequency, and the promotion of this product must

be accompanied by a responsible marketing and public education campaign.

In closing, we believe that the OTC availability of a statin will be associated with other important public health benefits. More than just a box on a shelf, this new option would allow Americans to take a more active role in their own health and well-being.

The associated marketing effort and media response will raise awareness of the importance of treating dyslipidemia as a strategy to reduce overall CVD risk. We believe that this increased awareness will stimulate important dialogue between the public and the healthcare community.

In response, we should all embrace the opportunity to educate our patients and the public, not only with regard to the use of pharmacologic lipid-lowering agents, but about the central role of nutrition and physical activity on cardiovascular health.

The Preventive Cardiovascular Nurses Association is committed to participating in this important campaign that has clear potential to save lives.

Thank you.

MR. LEVY: Good afternoon. My name is Stewart Levy. I am the Senior Vice President of Sales and Marketing for Impact Health. I have not been paid by any of the sponsors here today, however, our company has done project work with the various sponsors on a one-time basis.

For over 20 years, our organization has provided nationwide and community-based biometric screening and consumer health education programs. As a member of the health promotion industry, it is our opinion that the technology, professional staff, and infrastructure exists to support consumers' interest in obtaining cholesterol awareness.

Furthermore, the access to these biometric testing services is not a barrier due to the strategic interest of employers, retailers, and advocacy groups to provide venues for these program. Most importantly, consumers themselves are willing to pay out of pocket for cholesterol testing services and cardiovascular education.

There are many different approaches available for consumers to check their cholesterol levels. One way is certainly through the services offered by organizations, such as Impact Health. Our company typically partners with

various healthcare organizations, pharmaceutical manufacturers, retail chains, and employer groups to conduct health fairs on an event and also on an ongoing basis. These venues can be quite varied and may include NASCAR races, state fairs, churches, community centers, malls, and retail settings.

We can readily partner with GSK to deploy staff and to conduct such screening and cholesterol awareness campaigns in a multitude of settings that are convenient and appropriate for cardiovascular education.

We have clear certification and our company is also licensed as a moderately complex laboratory available to perform field-based lipid screening. In fact, the technologies that are utilized are the same instruments used in physician practices settings with the added benefit of results in just a few minutes

These instruments are calibrated and are extremely accurate as compared to reference labs, are highly portable, and require only a fingerstick with a few drops of blood to provide an accurate full lipid profile.

Our health education screening process always includes an upfront consent, collection of personal health

information, identification of other risk factors, and also current therapeutic regimens.

Our staff is trained to provide consumers with education on established clinical guidelines, such as NCEP cholesterol guidelines and Framingham risk. We will also counsel consumers on modifiable risk factors, such as healthy diet and exercise habit to help them manage their elevated cholesterol.

Moreover, our staff follows Federal and State regulations involving bloodborne pathogens requiring OSHA and personal health information, which is managed according to HIPAA regulation.

It is our position that there currently exists organizations, such as ours, that can be activated to conduct lipid screening educational programs and identification of venues which would help support the provision of these services on an ongoing basis.

This certainly can be one of various components of education awareness and support program for an OTC statin product.

As an executive in the health promotion industry, and as a pharmacist myself, I believe that the approval of

an OTC statin product would dramatically enhance public health through increased understanding and knowledge of cardiovascular risk factors, as well as promoting heart healthy behaviors through better diet and exercise habits.

Thank you.

DR. NASH: Good afternoon. My name is David Nash. I am the Grandon Professor of Medicine and Health Policy at Jefferson Medical College in Philadelphia. I am the editor in chief of Pharmacy and Therapeutics, Disease Management, and the American Journal of Medical Quality.

Merck has sponsored research over the last decade in our department at Jefferson Medical School.

Why am I here today? I am here today, ladies and gentlemen, to advocate for policies that will improve the health of the public. I would like to make three very brief points, one regarding the context in which we find ourselves today, the drug itself, and our failed healthcare system.

First, the context. Elizabeth McGlynn and an army of researchers over the last decade have proven Americans get the appropriate care when they visit their doctor about 50 percent of the time. You might as well roll the dice when you come to the doctor or come to the hospital. Our

system does not work.

Heart disease remains our number one killer. Ladies and gentlemen, we ought to be able to do a better job. Every doctor, nurse, and pharmacist has two jobs when she comes to work every day. Job one, do a good job; job two, figure out how to do it better.

My second point about the drug is very brief. Mevacor and other drugs in that class have a 15-year research history that demonstrates beyond any doubt from a reasonable person's perspective that this is an active and appropriate primary-prevention strategy for coronary heart disease.

My third and final point regards the system in which we find ourselves and my experience and published evidence regarding how our British colleagues have handled behind-the-counter Mevacor. Behind the counter won't work. We need to put this drug right in front of the consumer.

The folks who have spoken prior to me have emphasized how important it is from a public policy perspective to make this drug readily available. We have three reports from a very respected consulting company over the last seven years that confirms this drug will not

disrupt the payment process. Managed care organizations would welcome this change, as would the major national pharmaceutical benefit management companies that manage most of the prescriptions in the United States.

So, the context, the drug itself, and the system in which we find ourselves leads me to the following conclusion. You should not approve this drug for over-the-counter use, colleagues. You should put this drug in the drinking water.

Thank you very much.

DR. HOWARD: Good afternoon. I am Dr. Jim Howard. I am a clinical lipidologist from the Washington, D.C. area and I am here representing the National Lipid Association.

I wish to read into the record a statement that was crafted by our president, Dr. Ann Goldberg, and approved by the Board of Directors of the NLA, which is composed of some of the most prominent lipidologists in the country today.

The National Lipid Association is a nonprofit organization that serves physicians, nurses, physician assistants, pharmacists and dieticians who help manage patients with lipid disorders. These include patients with

cardiovascular disease and those at high risk.

The NLA represents more than 2,700 lipid specialists in the United States and provides continuing medical education for physicians and other healthcare providers to advance their professional development and prepare them for certification in clinical lipidology. I failed to state we have received support from all of the major pharmaceutical companies making hyperlipidemic drugs in those efforts.

The NLA's mission is to enhance the practice of lipid management in clinical medicine and thereby help reduce related deaths and disabilities in this regard. The NLA recognizes the social responsibility related to its mission to review and analyze the pending consumer issues and national medical policy.

The issue of OTC statins has been studied and previously published by the NLA. You should have received a copy of this monograph, which is called "Should Consumers be Given an OTC Statin Option to Help Reduce their CHD Risk: Exploring the Evidence." This was given in December 2004 and a copy has been provided to the members of this Committee.

This document provides a review of the data, key survey findings of consumers, physicians and other allied health professionals, and formalizes public comments received by the NLA from other organizations with relevant input regarding issues of OTC statin therapy.

In 2005, the NLA submitted a statement to the FDA recognizing the safety and the efficacy of OTC statins and the likelihood of proper self-selection.

Since that time, the NLA has completed work on a comprehensive meta-analysis that examined the safety of prescription statins across the range of approved dosing. This work, published in April 2006 in the American Journal of Cardiology, showed the prescription statins were very safe and effective. Again, you should have received a copy of this publication in the American Journal of Cardiology.

All of this has been done in light of the fact that coronary heart disease remains our biggest killer. While we have made progress in treating patients with high cholesterol, huge treatment gaps still remain for those at moderate risk.

All agree that diet and lifestyle changes are and should be the cornerstone of therapy for such patients and

the NLA has endorsed and promoted this approach. However, while many people have succeeded in making such changes, many more have not tried, and those that have tried have not been successful and thereby remain above the target goals.

It is known that many in this group used dietary supplements and nonprescription remedies that are of unproven safety and efficacy, such as garlic or selenium to lower cholesterol, and surveys have shown that these consumers, while consulting with their healthcare professional, would prefer an OTC product to a prescription product.

It is clear, therefore, that options with proven efficacy and safety are highly desirable for this target population. In 2005, the then constituted FDA Advisory Committee voted unanimously that low-dose statin therapy is safe and effective in an OTC setting for lowering blood cholesterol and those with a specific moderate risk target population could benefit.

The NLA is in agreement with these findings and supports the concept that the benefit-risk ratios of OTC statins' availability in the specified target moderate risk population is favorable and would help close this treatment

gap.

The NLA believes that if found favorably by the FDA, the product should be sold at retail locations where pharmacists are physically present. We also feel that the product should emphasize that patients should obtain a lipid test to find out about their individual cholesterol profile and urge them to discuss all their options, including OTC statins, with their healthcare provider.

We would also suggest that postmarketing analysis and review at one and two years would be desirable in evaluating the benefits and negatives of this policy.

DR. KRIS-ETHERTON: I am Penny Kris-Etherton, Distinguished Professor of Nutrition at Penn State University. I have no financial relationships to disclose.

The focus of my statement is on how nutrition and lifestyle and OTC statins can all work together to decrease cardiovascular disease risk.

As you heard from Dr. Howard, diet is a key lifestyle practice that continues to be the cornerstone of cardiovascular disease risk management. A large evidence base convincingly demonstrates beneficial effects of a healthy dietary pattern on major cardiovascular risk factors

including an elevated LDL cholesterol and high blood pressure.

There are two important outcomes of over-the-counter statin therapy that will help individuals achieve their LDL cholesterol treatment goals and facilitate achieving the greatest benefit attainable in response to following a healthy diet that I would like to share with you today, and there are two additional benefits of the Mevacor OTC program that I will also mention.

First, it is a fact of long standing that diet can markedly reduce LDL cholesterol levels. Well controlled diet studies demonstrate a 20 to 30 percent reduction in LDL cholesterol with multiple diet interventions, and that is similar to the response that is observed for first generation statin drugs.

However, longer term studies with free-living individuals on self-selected diets consistently demonstrate a response that is approximately half that which is achievable by maximal adherence to cholesterol-lowering diet.

Unfortunately, the reality in practice is that many individuals do not achieve the maximal benefit of diet

for LDL cholesterol lowering. Thus, an OTC statin in combination with a blood cholesterol lowering diet offers great potential for markedly lowering LDL cholesterol levels. Numerous studies have shown that the effects of diet and statin drugs are additive.

Beyond their LDL cholesterol lowering effect, statins reduce inflammation. This is very important because new evidence shows that elevated C-reactive protein levels are associated with a blunted cholesterol-lowering response to a heart healthy diet, and a major NIH-funded study recently reported this.

Thus, another important clinical benefit of statins is decreasing inflammation and facilitating maximal cholesterol-lowering response to diet.

So, in summary, approving OTC statin therapy will help individuals achieve LDL cholesterol goal together with healthy diet and lifestyle practices. Importantly, other health benefits beyond cardiovascular disease could be realized by the adoption of healthy diet and lifestyle practices that would be promoted by the OTC education materials.

Thus, the potential of a healthy diet and

lifestyle ripple effect due to the OTC program to dramatically affect public health is very exciting.

Finally, there are two additional benefits of Mevacor OTC program that I think are worth mentioning. OTC program can serve as a tool for nutritional professionals in clinical practice who are helping patients, clients achieve their LDL treatment goals.

The availability of this tool or OTC Mevacor program as we know it now will strengthen the counseling relationship between a dietitian and client, and would be expected to improve adherence to a healthy diet and lifestyle behaviors, and adherence to a healthy diet and lifestyle practices would be expected to reduce risk of many chronic diseases beyond cardiovascular disease.

Then, too, seeing your LDL cholesterol decrease is very motivating to individuals. They see the benefits of their efforts. Patients realize that they can follow healthy lifestyle behaviors, so as self-efficacy increases, so, too, does adherence to healthy lifestyle behaviors.

So, in closing, as an academic nutritionist who has spent my career understanding what the most effective diet is to lower LDL cholesterol as well as other CVD risk

factors, and how we can get people to follow our lifestyle recommendations. I find the Mevacor OTC program an exciting strategy for helping to make this happen.

Thank you very much.

MS. REILLY: Hello. Good afternoon. My name is Cindy Reilly and I am the Director of Clinical Standards and Quality at the American Society of Health-System Pharmacists.

ASHP does receive unrestricted educational grants for a small percentage of their educational programs from various manufacturers including the sponsor of today's NDA.

ASHP is a professional association with over 30,000 members and represents pharmacists who practice in hospitals and organized health systems. I appreciate the opportunity to present the views of ASHP on the proposed OTC use of lovastatin.

The effectiveness of statins in reducing LDL-C has prompted calls for more widespread use of these therapies including suggestions for their reclassification to OTC status.

ASHP does not support the three classification because the society does not believe that current

nonprescription dispensing models provide the safeguards required to ensure the safe and effective use of these therapies. However, the society does believe that alternative models for dispensing these valuable medications should be explored and I will address the proposed model at the conclusion of my comments today.

ASHP believes that statins are most effective and should be used only as part of a multimodal approach to reducing the morbidity and mortality associated with CHD. This multi-pronged approach includes drug therapy in conjunction with diet and exercise interventions. ASHP also believes that evaluation and management of lipid disorders should be guided by the recommendations of the ATP III Guidelines.

Those guidelines do identify statins as the drug of choice for most patients who require a lipid-lowering therapy, and numerous studies have shown that statins are effective for both primary and secondary prevention in CHD. Therefore, interest in enhancing consumer access to these therapies is not without merit.

However, to approve reclassification of lovastatin to OTC status, FDA must find that the proposed product meets

the criteria outlined by the Durham-Humphrey Amendment to the FTC Act.

Consistent with those criteria, ASHP believes that any dispensing model for statins should identify appropriate candidates for therapy based on cholesterol levels and other risk factors, allow for monitoring of response to treatment including the occurrence of adverse drug events, and maximize the effectiveness of treatment by encouraging adherence to drug and other therapies.

It is important to note that higher CHD risk is present when individuals have two or more risk factors. Therefore, ASHP believes that before statin therapy begins, a cardiac risk assessment should be performed by a competent healthcare professional who can work with the patient to develop the optimal treatment plan based on treatment guidelines and the patient assessment.

Although the proposed LDL-C labeling attempts to ensure appropriate use according to the ATP III Guidelines, ASHP believes that statins are not suitable for OTC status because the anticipated real use conditions under that model do not provide for the circumstances I have just outlined.

While the earlier CUSTOM study and the new label

comprehension studies do demonstrate some positive results, it is important to note that those studies were not designed to demonstrate effectiveness of therapy in the nonprescription model and were conducted in small populations under controlled conditions.

After statin therapy starts, ongoing evaluation is needed to assess the patient's response and to monitor for adverse drug events, such as myopathy. Although adverse drug events from statins are rare at the low dose proposed for the nonprescription formulation, they can occur.

The wider use encouraged by OTC status will include statin use by individuals with multiple disease states and those taking potentially interacting medications.

Because statins are a chronic therapy, new risks may develop as the patient's health status changes. For these reasons, use of statins requires ongoing vigilance. The existing model for OTC medications would place the entire burden for performing these functions on the patient and would likely result in increased adverse drug reactions.

For these reasons, ASHP believes that reclassifications of statins to OTC status is not advisable.

At the November 14th FDA public meeting, ASHP expressed

support for the behind-the-counter availability of certain drug products.

The society believes that BTC availability of statins would provide a significant health benefit to consumers who would be able to draw upon the education, training and experience of pharmacists to help them assess their need for the medication and its appropriate use.

MR. RANDALL: Thank you for the opportunity to testify today at the FDA's Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee hearing in the pending application submitted by Merck and their product Mevacor.

My name is David Randall. I serve as Executive Director at the Consumer Driven Health Care Institute based here in Washington.

CDHCI is an educational and research organization dedicated to promoting consumerism and market-based mechanisms in health care. Our members include the innovators and consumer driven health care and are represented by fiduciaries, technology and solution providers, retail-based health care organizations, and third-party administrators.

Our mission, in short, is as follows. Consumers will work with their physicians and healthcare providers to create a better healthcare outcome for themselves and their families.

Healthcare usage is more cost efficient with empowered and knowledgeable consumers who use information tools. Price and quality transparency about healthcare professionals is a key method for effective consumer health choices.

A few brief facts have emerged as a result of consumerism in healthcare. Currently, by estimates from the Treasury Department, there are over 5 million health savings accounts in use. This number is expected to grow to over 15 million in the next five years.

HSAs have spawned a wave of product innovation and technologies that allow consumers to choose products and services for themselves and to control the accounts for their own benefit and use.

Corporations large and small are using these accounts along with HRAs, health reimbursement accounts, and FSAs, flexible spending accounts, in creative ways to empower individuals to shop for routine services.

I must take this opportunity to also quote two noted economists since I believe they are relevant to the idea consumerism and healthcare. Specifically, Gordon Telik and Milton Friedman. Both of these men warned against the dangers of a third-party payment effect in healthcare services. Friedman said it best when he said, "Why worry about what you are spending when someone else is paying the bill."

Consumerism in healthcare services and especially routine services helps to address the admonitions of Friedman and Telik. I make this statement as a means of provoking thought about the potential issues that this application raises.

I am here today to speak to the broader issue of healthcare consumerism and making products available to consumers that they can use. I am not here today to discuss the efficacy of the drug submitted by Merck or to discuss any clinical nor pharmaceutical issues that this panel is required to deal with.

Most importantly, I urge this panel and the FDA, in your role as guardian of consumer safety and protection, to look beyond your statutory and regulatory duties and

examine the potential benefits of allowing consumers to have direct access to products that have the potential to be beneficial and accessible as with other nonprescription drugs and medications.

In the interest of brevity and this panel's time, I will conclude my remarks and reiterate that CDHCI would urge this panel to look beyond your required obligations under Federal law and examine products and services that promote healthcare consumerism to allow individuals to make informed decisions for themselves.

Finally, I would note that CDHCI does not have any financial conflicts with the applicant.

Thank you.

MS. EAPEN: Good afternoon. My name is Ria Eapen and I am the Health Policy Associate for the National Consumers League.

Today, I will be presenting some key findings from the research we recently conducted to explore consumer perceptions and attitude about an over-the-counter cholesterol-lowering drug as an option for those with moderately high cholesterol.

Given the time constraints of this presentation,

please refer to the two supplemental documents that have been submitted for additional information.

NCL is a private nonprofit advocacy group that uses education, research, advocacy, and public/private collaboration to accomplish its mission of representing consumer interests on marketplace and workplace issues.

While my presence at this meeting is independent of the sponsor, NCL does receive funding from a variety of sources including government grants and pharmaceutical companies.

For more than a century, NCL has provided government, businesses, and other organizations with a consumers' perspective on numerous special concerns including drug safety.

NCL commissioned this study as a follow-up to a similar study conducted in 2004 to explore consumers' attitudes towards the possibility of an OTC statin and the relative benefits of OTC versus prescription treatment.

In exploring this topic, NCL is not lending support to the approval of an OTC statin. We look to the FDA to consider all of the clinical and consumer use data and offer these consumers' survey data to help inform that

discussion.

To achieve our research goal, NCL commissioned Harris Interactive to conduct a national on-line survey between October 25th and November 5th, 2007. Included in the survey were 710 U.S. residents, age 35 and older who were at known moderate risk for developing high cholesterol--that is, a total cholesterol level of between 180 and 240.

None of the survey respondents were using medical management to treat their cholesterol. African-Americans and Hispanics were oversampled and the results were weighted as needed.

Near the beginning of the survey, respondents were asked to read a description of the proposed OTC statin product in the OTC prescription comparison sections of the survey. Respondents were instructed to consider a similar low dose cholesterol-lowering medication that is available only by prescription from a doctor.

Overall, the survey data indicate that people are interested in an OTC statin option. 82 percent responded that an OTC statin would be preferable to a prescription statin, and respondents reported being much more likely, 64 percent to 36 percent, to discuss OTC products than the

prescription products with their doctor.

Since 2004, there has been a decrease in the percentage of people who are most likely to use the OTC statin after reading a description of the product. This number dropped from 20 percent in 2004 to 11 percent in 2007.

African-Americans report the lowest likelihood of using an OTC statin compared with white and Hispanic respondents, and women are less likely than men to report they are very or extremely likely to use an OTC statin.

Survey respondents most inclined to use OTC statin include those with greater levels of concern about cholesterol, those with higher cholesterol levels, and those who take vitamins or supplements daily.

Ninety-eight percent of those who reported being most concerned about their cholesterol said that the OTC products would be appropriate for someone with healthcare needs much like their own, and 94 percent reported that the OTC products would be appropriate for someone who takes charge of his or her health.

Those who say they are more likely to consider taking the OTC product than the prescription products report

that an OTC is more appealing largely because of convenience factors

OTC statins are viewed as safer, more natural, more suitable for someone who takes charge of his or her health and less likely to cause side effects than prescription statins.

Those who prefer their prescription option have a greater trust in the product and the fact that a doctor prescribed it. The prescription version is viewed as more effective, more reliable, more trustworthy, and more suitable for someone who is in poor health than is the OTC statin.

Since 2004, respondents reported being more health conscious, less concerned about cholesterol, and less comfortable relying on medications to handle health concerns.

To learn more about the findings of the survey, please review the supplemental documents that have been submitted.

Thank you for your time and consideration of this information.

DR. BOUGH: Good afternoon. My name is Marcie

Bough. I am a pharmacist and APhA's Director of Federal Regulatory Affairs.

Thank you for allowing the American Pharmacists Association to provide our views.

At this time I have no conflict to state, but will acknowledge that we receive unrestricted educational grants from manufacturers to develop educational materials for pharmacists.

APhA represents over 60,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in advancing the profession of pharmacy. APhA members provide care in all practice settings such as community pharmacies, hospitals, long-term care facilities, managed care organizations, hospice settings, and the military.

In each of these settings, pharmacists help consumers manage and improve their medication use including the appropriate selection and monitoring of prescription and over-the-counter products. Ensuring the public's health and safety, especially with respect to medication use, is the APhA's and pharmacist's highest priority.

APhA supports the transition of suitable

prescription drug products to nonprescription or OTC status when supported by studies assessing the safety, efficacy, and appropriateness of such drug products for OTC use.

We rarely take positions on specific product switches, and we do not have a specific recommendation on that question today. However, we do have opinions and information to share and request that you consider these comments in your deliberations.

As we have heard today, the public health issue of high cholesterol has been well documented and highlighted. What I would like to further highlight is the pharmacists can play a key role in helping identify patients for therapy and in managing their medication if this product is available OTC.

Pharmacists are the most accessible healthcare providers and the only providers available to interact with patients at the point-of-sale for both prescription and OTS medications. It is important to note that a large variety of OTC products are available in locations without pharmacies.

In these environments, consumers make OTC decisions without the option to talk to a pharmacist. APhA

applauds the manufacturer's proposal to make this product available only at pharmacies.

Recent studies have shown that pharmacists can and should play a role in helping patients manage their medication. Specific to the treatment of hyperlipidemia, the APhA Foundation's Project ImPACT Hyperlipidemia demonstrates that through pharmacist-patient interactions, patient medication persistence and compliance rates improved from the national average of 40 percent to an improved 90 percent.

In addition, more than 60 percent of those patients received patient care from a pharmacist in their community and achieved their target NCEP therapeutic goals.

Again, pharmacists are in an excellent position to work with interested consumers to help at the point of decision-making and purchase of Mevacor if made available OTC.

A recent APhA survey of nearly 1,700 consumers found that consumers frequently turn to their pharmacist for advice on both prescription and OTC medications. Forty-three percent of respondents reported asking a pharmacist a question about health needs or concerns in the past year and

45 percent are likely to have asked for advice before purchasing an OTC product for the first time.

Their survey also found that when consumers initiate a conversation with a pharmacist, it is often to ask whether a medication will interfere with other medications (52 percent), should they expect side effects (39 percent), how to take the medication (26 percent), or to ask what the medication is supposed to do (26 percent).

The survey results emphasize that consumers view their pharmacist as a source of information for their healthcare needs.

If Mevacor is approved for OTC use, pharmacists will continue to serve as a resource for consumers with health concerns. Pharmacists can help if requested to ensure that patients are appropriate self-treatment candidates and can assist patients with appropriate product selection.

In addition, many pharmacists offer point-of-care testing services for cholesterol levels that can help inform patients in their decision. When necessary, pharmacists may also refer patients to a physician for appropriate care.

Pharmacists can also work with patients to ensure

that they understand when to use the product, how to use the product, and can suggest lifestyle modifications that will help with lowering cholesterol levels.

Pharmacists can also monitor for interactions with OTC products and other medications that the patient is taking.

Thank you for the opportunity to present the view of the nation's pharmacists.

DR. POLANSKY: Good afternoon. My name is Dr. Jesse Polansky. I am a public health physician with over 20 years of experience translating evidence in a practice including several years with Pfizer in their Outcomes Research Department.

I would like to talk a little about the uncertainty and the efficacy in primary prevention. In reviewing at least the historical proposal by Merck, in reading through at least the statistical review memo, that certainly noted that this was a post-hoc analysis of a primary prevention trial, and the population had a low HDL population.

So, for me, that creates a translation problem over the over-the-counter population that is being targeted.

It did hearten me that in the previous advisory panel, they certainly made reference to thinking about the difference between absolute and relative risk reduction.

I guess I would also say I am not sure everyone in the community at this point believes lower is better especially in our low and moderate risk populations where we certainly don't have very rich clinical trial data.

I would say it is disappointing in that regard that the NIH canceled their trial to actually evaluate that.

Now, in terms of safety, it was also heartening to hear at least some comments earlier today that there is potentially a hemorrhagic stroke signal, and I guess I noted that first when I read the 4D trial, which was obviously not for Mevacor but for atorvastatin.

But in that population of diabetics on dialysis, it was actually a clinically significant finding of a very elevated risk of hemorrhagic stroke in that population, which we certainly haven't heard too much about.

In addition, I guess it was heartening that it was a post-hoc analysis for SPARCL by FDA that actually led to a label change. So, I am hoping the Advisory Committee explores things beyond the GI and muscle side effect

profiles of these drugs.

I would also say we have certainly seen in clinical trial data, which is not exactly epidemiologic, it's a little stronger, some signal for GI and more recently I think in a rosuvastatin trial, perhaps a finding about prostate cancer.

I guess most notably what I haven't heard too much about in the documents or today's discussion to date, is there is an NIH-funded trial out at UCSD where they are beginning to produce publications where we are seeing issues in terms of cognitive, behavioral, and other certainly important from a patient's perspective side effects.

I think there was even some fairly high profile recent press about the gross underreporting of statin side effects in one of the findings from that study.

So, I certainly hope the panel makes that body of information available to them as they are sort of thinking about balancing risks and benefits.

Then, I guess we certain heard a little about the potential ALS signal, and that is good, too, as we sort of think through these complex decisions.

Now, obviously, my understanding is we are using

to some degree the NCEP ATP III Guidelines as a framework to sort of think about these things, but it hasn't been exactly clear to me in reading the documents that we are actually implementing the full spirit in terms of not only goals, as well as cut points.

To that regard, I put on the screen here sort of the distribution that was published several years ago about how we think about the patient populations who need total lifestyle change versus those who actually need drug therapy, and there are some very compelling numbers there that I am concerned that if we see this unbridled use in an over-the-counter setting, we will see all sorts of these folks who could certainly benefit from TLC migrating quickly over to the drug therapy side.

I haven't heard too much about the UK experience. That certainly was a bigger part of the last proposal or discussion at least, and I think controversy remains there.

I would just make a few comments. Certainly, I am concerned about undertreatment in patients with favorable risk-benefit profiles, we are certainly talking about that, and finally, that we are marginalizing the total lifestyle change imperative.

MS. NELSON: Hi. My name is Susan Nelson. I am here as a consumer with no affiliations. I am from Bainbridge Island, Washington, and above, on the screen, will be my late son Jacob.

It is my very strong opinion that Mevacor not be approved for over-the-counter status. It is, as all statins are, a very strong medicine whose potential side effects have not been made public to prescribing physicians or the consumers.

My late husband was prescribed Mevacor when it was first approved in the 1980s. His cholesterol was reduced to 133, however, in the four years he was on it, he also lost his mind, he became so depressed that he lost the business he created, lost his ability to be a parent to his kids, and virtually, his whole life.

My late son Jacob was prescribed another statin and lost his ability to focus and concentrate. He also had such violent nightmares he jumped out of a hotel window. After being on a 20 mg daily dose of a statin for over two years, Jake stopped taking it for six weeks.

During this time, he was able to again read, concentrate, and focus. Upon resuming his statin, he

quickly began to have the same violent nightmares, only this time he bought a gun and shot himself.

Two important factors. Jake had no previous psychological problems and statins are quickly absorbed into the system. By the way, we consulted five doctors about his confusion and nightmares, and none of them made the association with the statin, which was the only med Jake was taking at the time, not even the head of the Northwest Lipid Clinic in Seattle. I was assured that statins were safe and did not cross into the central nervous system.

I have done a lot of research with well-known doctors who have confirmed my belief that there is a direct correlation with statins and the mind--depression, aggression, suicide, confusion, as well as other debilitating muscle related problems.

These wonder drugs are being prescribed to more people than any other and, therefore, more people are being affected by the side effects than ever. Doctors do not have the knowledge to recognize side effects, because they have not been educated about them.

Patients are complaining about aches and pains and depression and confusion, and are being sent to other

doctors for the ailments that may be caused by statins. You simply cannot sell a drug over the counter without having properly warned the physicians and public about this powerful medicine.

The information is there, but the statistics have all been altered and the public deceived. When there are billions of dollars involved, of course, the drug companies don't want people to know how potentially deadly their biggest money makers are.

I have lost two too many in my little family to let this deadly drug proliferate without letting the public know the risks. If we had known about them, I know my husband's suffering and my son's death would have been prevented.

Please pay close attention to the independent statin research done by Dr. Beatrice Golomb at the University of California/San Diego, her statin studies, and also the important information by Dr. Duane Graveline.

Thank you.

DR. WOLFE: I do not have a conflict of interest.

This morning's Chicago Tribune has a story, interviewing someone from Merck saying that their studies

show, quote, "overwhelmingly favorable results that consumers can self-assess and make appropriate decision to purchase over-the-counter Mevacor."

On the contrary, in the company's own new SELECT study, the overwhelming majority of patients who, after reading the product label made a decision on their own to purchase Mevacor, made the wrong decision. The overall figure was 75 percent of them made the wrong decision. In some groups where there were men, women, or the LDL or the total cholesterol, the range went from 65 percent wrong decision, as high as 93 percent wrong decision.

The FDA medical officer who made this analysis--this is all from the briefing documents--the medical officer who made this analysis commented that these results were "sobering."

Among the reasons why the decisions in the SELECT study to purchase were wrong and potentially dangerous for such a large proportion of the population were:

One, 21.5 percent of people deciding on their own to purchase OTC Mevacor had a less risky cardiovascular risk profile than the threshold of 5 percent or higher risk of coronary heart disease in 10 years, for which there is

evidence that the drug would be of any benefit to them.

This large proportion of purchasers would therefore be exposed to the risks of Mevacor--liver damage, muscle damage, and other adverse effects without any evidence of a benefit.

Two, others who decided on their own to purchase OTC Mevacor did not qualify for primary prevention, which is the only proposed indication, because they had already had heart attacks, stroke, or other evidence of cardiovascular disease.

On the average, about 30 percent of these participants with CHD, diabetes or stroke wanted to purchase the product. Amongst these were a number of people who were already on cholesterol or lipid-lowering drugs who said they would stop their current therapy and switch to the clearly weaker Mevacor. Others said they would double up on what they were already doing, risking, according to the FDA, increased risk of rhabdomyolysis.

The third category of wrong choice; many women of childbearing age who were too young, namely, lower than 55 to qualify for the drug, nevertheless made decisions to use the drug. If they should become pregnant, they would expose

the fetus to the only pregnancy Category X drug that would be approved for FDA use. The definition here is "Human/animal fetal risk outweighs the clinical benefit."

The company unsuccessfully tried to convince the FDA to take it out of Category X because it would sort of look bad to have an over-the-counter drug in this way, but this attempt was rejected. The label, therefore, for the prescription version says Category X.

NIH has recently reviewed a lot of data on this, human data, and concluded that, "While a small case series is unable to test the hypothesis of statin teratogenicity"--there is animal evidence--"the patterns of defects seem sufficiently provocative to indicate that this hypothesis be pursued fully."

In the UK, where one statin, simvastatin, was made available behind the counter with pharmacist intervention in 2004, there were serious concerns by the pharmacists who were surveyed including their idea that there needed to be full cardiovascular risk assessment of patients before deciding on the use of the statin, and access to full clinical information.

Dr. Frank Davidoff, formerly of this committee,

and formerly Editor of the Annals, has written about this, objecting to it saying, amongst other things, that the increasing use of over-the-counter aspirin might even further lessen the evidence that this works at such a low dose.

I called him to see if he still maintains this view, and he said yes. He also said doing this, in his article that was published, might be akin to having an experiment on people with unknown evidence of benefits or risk. The benefits again have not been tested in the OTC setting, benefits meaning prevention of cardiovascular disease.

In summary, the contrast between rational and successful OTC use of analgesics and antihistamines versus a statin such as lovastatin could not be sharper. For pain and allergies, the ability for people to make an accurate assessment of these symptoms, to quickly be able to measure the success of the treatment on the symptoms and to adjust the dose accordingly is quite clear.

For statins, none of these criteria are met. In addition to the necessary measurement of total and/or LDL cholesterol in such asymptomatic people, the need to

consider a myriad of additional risk factors makes an accurate assessment of whether someone is or is not a candidate very, very difficult, and the same is true for adjusting the dose.

In earlier testimony in 2000 and 2005, we opposed strongly the switch. We continue to oppose it more. The evidence is even more convincing against it.

Thank you.

DR. TINETTI: Thank you. The open public hearing of this meeting is now concluded and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments.

Before we get to the questions, I think probably it would be good to have a half hour or so general discussion. I am sure there is further questions that the panel have for both the FDA and Merck.

So, this will be the time for questions you have, either clarifications or further information that you would find helpful. Again, if you could remember just to identify yourself.

Discussion

DR. BURMAN: I just want a clarification from the sponsor, as well as from Dr. Hu from the FDA, regarding the mitigating factors regarding the study. That was on Slide 29 and 30 of Dr. Hu's presentation, the mitigating factors including talking to a physician is one aspect.

I would like more clarification of those. How does saying that they would talk to a physician mitigate the responses that they had?

DR. HEMWALL: In certain parts of the label, there are clear directions to check with your doctor. As we talked about earlier, there are certain parts of the label where even talking to your doctor does not mitigate your decision if it is wrong or indication to talk to your doctor.

But in these areas where the label has been worked out with FDA, talk to your doctor is a recommendation that is made, and that is one of the areas where consumers said they wanted to check with their doctor. And, of course, in the SELECT study, they didn't have the chance to do that like they did in CUSTOM, so they wanted to do that before they went forward with their decision.

DR. HU: I also think that the sponsor thought that if someone spoke with their doctor, that they would get the proper advice. In some of the cases they had, they were following the label, and some of the cases they just wanted further information.

In some instances, they didn't quite understand what was going on, but I think the sponsor felt if they consulted with their doctor, their doctor would make the right decision for them. So, in that way they would be mitigated.

DR. ROSEN: For the sponsor, I think you mentioned the cost. It's a two-part question. Can you just reiterate what you are estimating the cost per pill is for over the counter?

DR. HEMWALL: Well, final cost has not been decided, but it would probably be in the range of a dollar to $1.50 a day.

DR. ROSEN: The second part of the question is when you do your surveys or in SELECT, did you query the participants about what would happen if the OTC was not covered by their insurance versus if they had that knowledge of whether their managed care plan or their health insurance

covered it when it was not OTC, but what would happen when it was OTC?

DR. HEMWALL: This was not something we asked participants in SELECT.

DR. ROSEN: Do you have any information on cost in respect to their decision-making for OTC?

DR. HEMWALL: I will ask Mr. Hansen to respond to that.

MR. HANSEN: It should have a lot of information on how consumers are viewing cost in the OTC. For the most part, a lot of our research, the way we pose it to the consumer is, here is a concept of an OTC Mevacor 20 mg for a dollar to $1.50 a day. We have compared that to an Rx prescription from what they would normally pay either for a co-pay or out of pocket.

Many of the data that you heard even during the open public forum confirms what we have heard, is that the moderate risk population really would prefer to have the OTC even though it may be more economic to get the prescription.

DR. ROSEN: But you don't have any direct information about querying them if they are presented with those choices direct, right? You don't say would you prefer

that it may be over the counter even though you are managed care or your insurance covers it?

MR. HANSEN: Yes, our studies absolutely asked that same question. We say OTC a dollar, a $1.50, a day versus a prescription for your normal co-pay if it was covered.

DR. ROSEN: And what do the numbers run?

MR. HANSEN: Three out of four consistently in this moderate-risk population prefer the OTC option than the prescription option. This goes back to again the mind-set that these consumers view themselves as well, not sick.

DR. GLASSER: Well, I guess of my many questions--and I don't think the healthcare system is ideal particularly as it applies to control of cholesterol--but if we believe that it is as broken as some do, then, I guess my question is what good is it going to do to talk to their doctor.

I don't suppose that is a question that could be answered, so it may be--

DR. TINETTI: We will let that one linger in the air.

DR. PICKERING: I have a question that is really

addressed to FDA. If this is approved, what assurance do we have or what control do you have over what happens with the educational program after approval?

DR. LEONARD-SEGAL: It is a complicated question. We have control over what is considered labeling, and what is considered labeling is what is on the box, what is in the box.

Then, there are some indefinites right now that we couldn't answer as to whether information that is next to the box on the shelf or information that is in the box or next to the box that might refer to a web site could be considered labeling, but what we can control is labeling.

So, we don't have a precise answer for you on that, but the labeling is what the consumer would need to be able to use to achieve effective and safe dosing and use of this product over the counter.

Does that help you? I wish I could be more precise. I really can't be.

DR. HEMWALL: I would just like to add that we have formally requested the FDA in our NDA, in writing, to make the commitments that we talked about this morning to be part of the terms of approval, and we are willing to follow

up on that.

I think you have already seen the track record that GSK has--even without having written into the terms of approval that their intentions that they give and that they make in front of this committee, they follow through on.

DR. NELSON: Could I ask the sponsor to maybe go over again the hierarchy in the SELECT trial? I think there was some confusion. We had some discussion of that before lunch. Just give us an idea of how those went down again, if you could, please.

DR. TINETTI: Before you have a hierarchy, I guess I want to ask the FDA. That is something that they are particularly interested in us addressing, and I think we all have a lot of confusion about that.

I am wondering if that might be more efficient if we could just have the hierarchies all in one place and have a general discussion, because I think the hierarchies are going to be a point of confusion for all of us.

I am just wondering what might be the most efficient way to approach the hierarchy issue, if you really want us to address that.

DR. LEONARD-SEGAL: Linda, I don't think we have

slides that actually list them all in one place, but you do actually all have copies of the slides in your handout that list all of the different hierarchies that were looked at. Perhaps the best thing is just to refer by number on the page, and maybe we could flip up the slides as we go one by one, if you want to do it that way.

DR. TINETTI: I am open to anything. I just don't want to sort of do it piecemeal kind of approach to the hierarchies, because I think it is confusing enough.

DR. HEMWALL: Would it be helpful if we kind of explained the philosophy behind the hierarchies that FDA--

DR. TINETTI: I guess I would rather have FDA tell us first what their philosophy is of the hierarchies and what they want us to address, and then you can comment upon it, if that would be all right, because I presume it came from the FDA's interest in the hierarchies.

DR. LEONARD-SEGAL: Well, I think that what we would like to hear from you is what you think are the critical labeling elements, the pieces of information that are critical for appropriate use of lovastatin if it were to be an over-the-counter product, such that we would be able to take those elements and then understand self-selection by

those elements to be able to determine success.

There isn't any information that is on the label that isn't important, but the concept behind these hierarchies was that there might be some information that is more important on the label than other information that is on the label.

So, it is a complicated topic and it is one that we have been chewing over and over, and so we would like to hear the views, even if you can't provide us with a specific hierarchy that you think would be best, or if you feel that every element on this label would be of the same importance.

These are the things that we would like I think to hear from you today.

DR. TINETTI: So, what I am hearing you saying is rather than choosing among the seven hierarchies, which I am sure if you have seven different labels, and you do it, seven factorial could be an infinite number.

What you are asking us, are there really clear characteristics that clearly have to drive the decision and need to be part of the decision? Okay. I think that is a more manageable question.

DR. LEONARD-SEGAL: I mean we don't believe that

the hierarchies that we have provided are necessarily the best or the most perfect. Some are analyses that Merck provided to us. We tried to think, in addition to those, what we might have been interested in.

As Dr. Hu indicated in the presentations, these discussions for this application did not occur ahead of time.

DR. TINETTI: I guess the question is did you want to respond to Dr. Nelson in the context of the FDA's statement that they are now more interested in the specific characteristics that drive the decision rather than any one hierarchy.

DR. HEMWALL: Yes. Maybe it would be helpful if I showed Slide 69, and this is one I showed earlier in my presentation. I tried to get across the concept, but it is indeed a new one for thinking about labels with multiple criteria.

When we looked at the hierarchy, the thing that you want to think about is what are the consequences of not heeding the label on that particular element. So, we first put, at the very top, the absolute safety warning. We want to have the best possible behavior in the absolute safety

warning.

Second, the relative safety warnings where again we did show very good behavior, and at the very top of all the hierarchies that you see, are the safety areas where people have done well. Then, I think where people are now starting to decide and deliberate which of these other benefit guidelines are the most important to adhere to in order to best use the product.

Again, we think about what are the consequences of not heeding, and in the cases of all the benefit guidelines, if you are following the safety warnings, then, the consequences are going to be that you may not get optimal benefit. You will still get lipid lowering.

Then, of course, the elements that consumers were most often wrong on was, in fact, not knowing or not being within the exact range on their cholesterols, and it is not that surprising. We may not all know our exact cholesterol number. We know the range it is in. But I get my cholesterol tested annually and I couldn't tell you right now what exactly my LDL is, but when we ask these consumers, their ranges that they said were pretty good.

This is what I think FDA is asking us to look at

is of the errors that are made, what are the consequences, and there is no safety consequence or very little, minimal safety risk we have seen with the 20 mg dose and the behavior that goes along with it.

So what does the Committee think are the other important elements of the benefit guidelines to adhere to, and if we have the general adherence, they are always going to get the benefit of lipid lowering as long as they keep the safety criteria, which they did.

We could look at a sample criteria if that would help.

DR. TINETTI: I don't think so. What I am hearing is we are not necessarily interested in particular hierarchies. It was more I think the way you displayed it here nicely, of all of these characteristics, which ones are really key and which ones are essential, and are there some that perhaps are not as important.

So, I think the way you have presented it here is fine. Thank you.

DR. PROSCHAN: I was wondering, the Kaiser Permanente study seemed to indicate that the lovastatin decreased the risk of liver disease, and I am wondering does

Merck believe that is real.

I mean it has been suggested that that is, you know, because of these biases, and I am wondering, given that it drives up certain liver measurements, why would it be the case that it would lower liver disease.

In other words, I guess I am asking is there really any plausible explanation other than biases that would explain why it is lower liver risk.

DR. HEMWALL: I am going to introduce one of our experts here, Dr. Paul Watkins, who is an internationally recognized liver expert and has studied the statins and liver and a number of different drugs that are associated with liver metabolism.

DR. WATKINS: Yes, I mean I think that is an intriguing finding that in the Kaiser study it actually appeared that lovastatin improved liver dysfunction, at least measured by liver chemistries.

Why that might be the case is unclear. It could be, I suppose, channeling bias. On the other hand, there are some data that statins actually improve, non-alcoholic fatty liver disease, for example. There is a publication that showed in rat liver that some statins actually up-

regulate fatty acid binding protein through transcriptional activation, and that might be one mechanism of moving fat out of the liver.

We could speculate other things, such as anti-inflammatory properties, but I don't believe--I mean I think that is an interesting observation that deserves further study, but I think the important point is that there is complete agreement that lovastatin is remarkably safe for the liver and what the Kaiser study shows, and I certainly agree with, the FDA conclusions that this was a well-performed study and that the results are consistent with the results of other studies and other observations that there is no increased risk in patients with pre-existing liver disease.

DR. FLATAU: I had several questions about the benefit to consumers of the switched over the counter status. The first is back to the cost.

How does the cost, the dollar, the $1.50 a tablet, compare to the cost of prescription generic lovastatin now?

MR. HANSEN: First of all, we are certainly not advocating that people switch from prescription to over the counter, but the prices vary. It depends upon what type of

plan you have. Co-pays can be on average for a generic product between $15.00 and $20.00 a month. Again, the OTC that we are proposing, some will be the range of $1.00 to $1.50 a day.

DR. FLATAU: The retail price without insurance coverage.

MR. HANSEN: The retail price again varies. For the 20 mg Mevacor, it can be available at fairly low co-pays at certain organizations, such as Wal-Mart. It could be as high as $60.00 a month at others, so that is the range that you would get for generic lovastatin 20 mg.

DR. FLATAU: Is that the Mevacor or the generic?

MR. HANSEN: I am sorry, lovastatin generic.

DR. FLATAU: I mean I went to my Walgreens where I get my prescriptions filled, and it was 29.99 for 30 tables 20 mg. So, you are proposing a higher price.

MR. HANSEN: Possibly. But, again, that is just the price of the medicine itself, and we have very good insights for the consumer, cost is not the most important issue. Access is important and taking charge of their own health is important.

DR. FLATAU: Cost is important to me.

MR. HANSEN: But those costs are available today, and those people are not being treated.

DR. FLATAU: A further question is what are the other benefits to the consumer from over the counter versus the current situation where they have to go to prescription?

I mean other than the price, which we have said already, it is not clear to me what the benefits would be. Clearly, this target population, most of them should be treated with statins. That is not really controversial. But what is the benefit of it being over the counter versus the current situation.

MR. HANSEN: The first benefit is being over the counter provides overall greater access and awareness. And we have seen that with many medications, such as nicotine replacement. We have seen it with alli. And we have clear data that shows making a product over the counter increases awareness and increases use.

DR. FLATAU: So, it seems to me that the awareness of this has largely to do with the educational and support program that you propose, and which is a great thing to have, but has really nothing to do with over-the-counter status, and just to do with the greater awareness, and if

what we need is an educational program, then, we should go get an educational program, and not switch to over-the-counter status.

MR. HANSEN: Well, the issue with greater education and prescription statins is that in this target population, the moderate risk population is not being treated. Their awareness of prescription statins today is over 90 percent. Statins are one of the most advertised and most promoted, and all kinds of educational programs are out there for prescription statins. That is not working.

What we have seen with OTC is the consumers taking charge themselves. Even though it may cost more, they are going to still continue to see their doctor. But, because they are doing it themselves, are more likely to use it and stay with it.

DR. PARKER: I have a few questions. One is what goes in the box? It's kind of big. I am just curious. I understand that the FDA has control of the labeling and the materials that are in the box. So, one question is what is in the box? Forty-five pills plus what?

MR. HANSEN: I will show you that. I just have to find the slide and that will be the easiest way to

demonstrate. We have actually joked that you need backpack straps for that box.

If you can show slide, please.

[Slide.]

MR. HANSEN: Here is just an example of what is inside the package. First of all, to the left and on the top is the Heart Healthy Living Guide, and that primarily focuses on the disease of high cholesterol, how high cholesterol occurs in your body, how diet and exercise works, and the importance of taking the pill every day, so that is more of non-branded educational diet and exercise information.

In the middle is what is called the Quick Start Guide. It is a six-panel brochure that literally takes the consumer stepwise through all the key elements of the label starting first with should you take it and then, if you do take it, did you make it. What that means is did the consumer get to goal. So it really emphasizes the importance of the six-week cholesterol test and getting to goal, and we saw that work very effectively in the CUSTOM trial.

The other items that you see here are the patient

package insert. Not shown here is we actually have a doctor and a pharmacist card which proved to be successful in CUSTOM. This way, the consumer fills out the card, tells their doctor and pharmacist when they started taking Mevacor so that the pharmacist can put it in the medication record, and the physician can put it into their medication chart or into their patient chart.

Then, last, that we talked about earlier, is the new edition of the refrigerator magnet that says if you get unexplained muscle pain you should stop taking the drug immediately and talk to your physician.

DR. TINETTI: It is just muscle pain?

MR. HANSEN: No, actually, on the label it says unexplained muscle pain, weakness, or--I am missing one--tenderness.

DR. TINETTI: And the magnet also says--

MR. HANSEN: Yes, it does.

DR. TINETTI: Thank you.

MR. HANSEN: It is even a more full explanation than the label itself.

DR. PARKER: I had another question. If somebody didn't kind of orient me to this thing, and I see it on the

shelf, I go pick it up, I start trying to sort of--I would like to know what happens when someone just picks this thing up and really starts trying to go through this and figure out, you know--it says that you have to read the entire Drug Facts label inside, but actually, part of it is on the bottom. You know, it's not inside, it's on the bottom depending on how you orient it.

Then, when you open it up, I am sort of wondering about some of the human factors stuff that goes into this. That is sort of what I am getting at. Then, it says you have to read the whole Drug Facts label inside. So you open it up and you have got one line of the Drug Facts here, and you have got the panel of it here, and then down here you get some more of the Drug Facts--you know, the Drug Facts as they go.

The first thing, I usually think some of the most important stuff is going to be at the top, right, boom. It was on your hit list of the relative--what do we call those things--the deal-maker, the breaker-maker, list, okay.

So, warning;"Do not use if you know you are allergic to lovastatin." That is the only thing written at the top besides do not use. But, if you go on down about, I

don't know, 25 lines, it says, "If pregnant or breast-feeding or think you may become pregnant, do not use."

But that is not up there with the do not use up at the top. But yet it was over on the other side here, you know, where you had to go through the algorithm, and that is not in the same box as the drug labels where it says the Drug Facts where you have to read it.

I am just thinking of how long it would actually take and then I lose my own train of thought when I sort of go through this.

I mean I appreciate the details and the intricacies of this, but it seems to me for safe and effective self-selection by a consumer, this whole thing about if we really are concerned about women of childbearing age who might be pregnant taking this, we are trying to absolutely--because of this product X labeling by the FDA, because of what we understand about it in use in pregnant women, or don't understand, and the fact that it falls in that category, I can't help but sort of ask myself, so if you gave this to 10,000 pregnant women, what am I supposed to think about that if people have that much trouble sort of wading their way through this and understanding given what

we have seen.

MR. HANSEN: That is a good question because, as you mentioned, there is a lot of information on the label and we made sure that we started with focus groups and then we went into pilot testing, and then went into the pivotal label comprehension study.

Importantly, to your question of how did they do just with the box and not the internal materials, the FDA posed the same question and that is exactly what was tested in the label comprehension study for SELECT and the SELECT study. That is all they had was the package box.

So, all the results you see today from the pivotal label comprehension study and the SELECT use study were the label only.

Now, specifically, your question about pregnancy and did they find the warning, a lot of the reasons for the placement are not necessarily the sponsor's. They are to abide with the Drug Facts format.

So, if this committee feels like there are certain ways that we could change that or highlight that, we are certainly open to those options, but we did have to abide by those Drug Facts, and that is the way those lay out in a

normal way.

We do have data, if you are interested, from the pivotal label comprehension on how well people did specifically with the pregnancy warning that you raised, and I can show that.

DR. PARKER: One other question just was whether or not--maybe it is here and I missed it--is it clear from reading any of this that the way you test your cholesterol is you get a blood test?

I mean it says cholesterol level, test your cholesterol, is it clear that that comes in your blood?

MR. HANSEN: I am not sure.

DR. PARKER: And just whether or not people know that from what they are presented.

MR. HANSEN: For the most part, what we found is that people interested in this, 70 to 80 percent of them have had a blood cholesterol test in the past year. That is part of the reason for their interest.

So, my assumption is that they do understand that, but we have not specifically asked that question.

DR. TINETTI: The press has reminded us again to please give your name when you ask the question.

MR. LEVIN: Very quickly, just to go back to the cost and then I think maybe to go back to the hierarchy and to sort of try to get through that one.

On the cost side, I would argue that your response is a little unfair, because most tiered drug plans are in the $5.00 to $15.00 co-pay range for generics. To get up to $20.00 or $25.00, you have got to be in the older branded drug category, number one.

Number two, many drug plans encourage the use of mail order for 90-day scripts, where the co-pay, you pay once for a 90-day supply. So, I think there is no question in my mind that when you have a generic drug, and with recent events with the Wal-Marts of the world, this drug, it is going to be like claritin, it is going to be a very expensive over-the-counter drug.

So, in terms of the public benefit, in terms of the cost to our healthcare system, frankly, it doesn't make any sense to me at all, but that is not what we are here to discuss.

To go back to your slide on the hierarchy, I would suggest that 20 years' experience in trying to deal with the risk to pregnant women of Accutane tells us that simply

stating don't take this drug if you are pregnant or if you think you are going to get pregnant is not very much protection.

The FDA, the maker and then the makers when the drug went generic, and those of us who sat on advisory committees, over and over again, struggled with how to reduce the risk in women who said to their physician, I won't get pregnant, but did get pregnant.

So, we have ended up with a no test/no drug kind of situation, because of the seriousness of this. If this is the first time that an X drug is going OTC, I don't think this is sufficient based on what we know with Accutane, for example.

I am not comparing drug to drug, but I am comparing the difficulty in reducing the risk of someone getting pregnant while on the drug even though they have been told not to get pregnant, they have been asked if they are using birth control, and that doesn't work very well, we have found that out over time.

So, I just suggest that if you want to reduce the risk of women getting pregnant while on this drug, you have to do a lot more than this based on our experience with

Accutane.

DR. HEMWALL: Those are important comments and I would like to introduce Dr. Anthony Scialli, who is an expert in this area, to put some of this in perspective because I think we have lost the perspective around the overall concern about potential risk for the fetus.

MR. LEVIN: Could I just sort of finish through that? Can we go back to your slide where you sort of broke it down into the must know, should know?

DR. HEMWALL: Yes, but we would like to respond to that particular issue.

MR. LEVIN: Okay. I mean it seems to me that there are some things missing here. Is it true there is no risk to putting people on life-long therapy who don't need the therapy? That is, the people outside the sweet spot on the low end, and is it true that there is absolutely no risk to people self-managing who are at the high risk?

I don't think so, but what I keep hearing from you is it is good to be on a statin, it is good to be on a statin, it is good to be on a statin, even though we know from the studies that a substantial percent of people who don't need to be on a statin would say I want to take a

statin, and a substantial number of people who should be on prescription dosage therapy and under a physician's management say no, I will take the over-the-counter version.

DR. TINETTI: Mr. Levin, if there is a specific question, can you pose a specific question that they can answer?

MR. LEVIN: The question is don't you think those are risk factors that people should be aware of, that they may misdiagnose themselves in a sense and be at high risk, and end up on inadequate therapy, or they might misdiagnose themselves and put themselves on lifetime therapy when there is absolutely no need for that therapy.

DR. HEMWALL: Well, first off, we don't advocate lifetime therapy with this product, and the labeling and the materials that go with it clearly recommend reestablishing your qualifications to use it on an annual basis.

In fact, that is exactly what the right side of this list here is, is to make sure consumers understand if they already have heart disease, stroke, or diabetes, they should be under a doctor's care, and we really want them to go get on a prescription statin.

DR. TINETTI: Where does it say that they need to

yearly reevaluate their appropriateness for this drug?

DR. HEMWALL: It is in the inside materials, and all the interactive material that goes with it continues to remind the individual. So yes, this is something that we think there may be a net benefit, because there are people out there that have these conditions and our studies show aren't on any therapy. So, at least they will get some lowering, and that will be helpful.

But as we saw in the CUSTOM study, over 75 percent of the people at high risk, once they became aware of their situation, through the use of the materials in the package and the support program, went to see their physician and over half were put on statin therapy. So, that is the benefit side on the upper end.

So, we are saying that at least those people are getting into the system, and the ones that aren't are getting some lipid lowering.

On the lower end, these are people that already have additional risk factors. They have the age requirement, and they may be close, and they have stated they have a family history, and there are people with good reasons that want to take this product.

In those cases, if they haven't created a problem with any of the safety warnings, which they don't, then, it is a matter of the degree of benefit, and not additional risks.

So, are they getting optimal benefit or suboptimal benefit? That is how we are approaching it, but the whole program is meant to focus people into that center range, and it does that quite well. But we do--in order to get the full benefit for everybody, you have to accept some outliers on both sides.

I think the concern about pregnancy has been raised and in some cases--although the committee voted favorably last time, I really want Dr. Scialli to be able to explain some of this so people understand on the women under 55 is meant to be a risk factor, women over 55 are at higher risk. It is not about pregnancy. It helps reduce those women that would take it at the lower age range, but it is not really a big concern.

I want Dr. Scialli to respond to that.

DR. SCIALLI: Thank you. I direct a reproductive toxicology center which operates REPROTOX, which is one of the two reproductive toxicology databases in the world as

far as I am aware. Both of the databases, both REPROTOX and TERIS, consider the risk of adverse pregnancy outcome from lovastatin to be unlikely, and there are good reasons for that.

We are delighted in reproductive toxicology if we have good experimental animal data, and we are delighted if we have human reports, but we are absolutely ecstatic if we have both, which in the case of lovastatin we do.

The experimental animal studies are very clear that there is no increase in birth defects absent significant maternal toxicity. For the human reports, there are more than 700 reported cases of first trimester exposure to statins in the literature and there is no pattern of abnormalities.

In those studies that have been sufficiently large to do some comparison of rates, there is no suggestion of an increase in total birth defects or any individual pattern of abnormalities.

So, we are very comfortable that lovastatin is not Accutane and we do not believe that we are going to anticipate any increase in risk to pregnancies from inadvertent exposures to this medication.

Thank you.

DR. TINETTI: It is almost time for a break. Maybe before we do break, we will have time for a few more questions afterwards.

I guess one of the questions I would like to ask Merck is, as the first drug who is going over the counter for an asymptomatic chronic condition, as you well pointed out, people want to be informed consumers and make the decision, and I guess my question has to do with how informed the present approach is to helping people make an informed decision.

For these chronic asymptomatic conditions it seems to me the issues are how long before they are going to get benefit, what kind of benefit they are going to get, and the likelihood they are going to have benefit.

So, if you could walk through us with that a bit, can you tell us--first of all, let's take probably your mid-range person is at 10 percent. Let's take somebody who has a 10 percent risk of a cardiovascular event in the next 10 years. How long are they going to have to take this medication before they see a benefit?

DR. HEMWALL: Well, if we just look at the AFCAPS

data, the curves begin to separate after one year.

DR. TINETTI: So about a year.

DR. HEMWALL: Yes.

DR. TINETTI: That is fair enough. Can you tell us what type of benefit? Are we talking about mortality? Are we talking about a major heart attack, that they are going to be incapacitated. We are going to be talking about an asymptomatic heart attack. Can you give us the spectrum of the types of events that you are likely to prevent with this 10 percent risk people?

DR. HEMWALL: Yes. I am going to introduce Dr. Antonio Gotto from Cornell Medical Center, who was actually one of the lead investigators in the AFCAP study.

DR. TINETTI: While you are walking up there, one other question I would ask is that you saw the benefit, could you tell us how many of the people stayed on the 20 mg versus had to go up to the 40 mg?

DR. GOTTO: Yes. I am Antonio Gotto. I was the chair of the Steering Committee of AFCAPS/TexCAPS.

The average risk of an event in the placebo population of a major cardiac event was about 1.3 percent per year, so it is probably about as close as you will get

to the population that we are talking about.

The major endpoints were fatal and non-fatal myocardial infarction and admission to the hospital with unstable angina documented by angiography or an exercise test.

There was no difference in the relative benefit in the groups on 20 versus 40 mg. The goal at that time or the approved target for NCEP at that time was 130. We were trying to titrate down, as close as we could get to 100, and got down to about 110.

There was some increase. We started at 20 mg and wound up with about an equal number in the trial on 20 mg and 40 mg.

DR. TINETTI: So, about half were on 20, half on 40.

DR. GOTTO: About half.

DR. TINETTI: Of those events, how many were fatal? Of the endpoints, how many were fatal MIs?

DR. GOTTO: The fatal MIs were relatively small, I don't remember the number. The study wasn't powered for mortality.

DR. TINETTI: I understand that. I am just trying

to get a relative idea of the benefit.

DR. GOTTO: Right. I don't remember the exact number of fatals.

DR. TINETTI: So, some of these people could have been fairly minor events, but they could have still met the criteria.

DR. GOTTO: They weren't minor events. They had to have a definitely defined myocardial infarction by enzyme and EKG changes.

DR. TINETTI: What about long-term sequelae? At six months, do we have--I am trying to get a sense of what the events were.

DR. GOTTO: Yes. We followed them for two years after the study was over, and the benefit was maintained at that period of time.

DR. TINETTI: That is not my question. My question was of the people who had an event. I am still not quite sure what that event was. I see a lot of people that come in and have an MI, have enzymes, and three months later they are quite fine, others are incapacitated.

I am just trying to get a sense, again because if people are going to have to have an informed consent

decision-making, they need to know what it is that they are preventing, and I am trying to get a sense from you what are the events that they are going to be able to prevent.

DR. GOTTO: What was prevented were fatal MIs, non-fatal myocardial infarctions with hard criteria, admissions for unstable angina with documentation and revascularization. There was a statistically significant reduction in bypass surgery and angioplasty and stenting.

DR. TINETTI: Thank you. My last question has to do again, because we are now putting it onto the people themselves to make the decision about whether or not this is a medication they want to take for whatever reason.

We have heard a lot about the relative risk reduction, but in this population it may be the absolute risk reduction. I guess I would like to take, if somebody could sort of walk us through that.

If we take 100 people who are in this 10 percent category, how many of them would have an event over the next 10 years with the statin and how many would have an event without the statin. I want to get an idea.

DR. GOTTO: These calculations are subject to quite wide variations, but roughly, you would need to treat

45 patients over a 10-year period in order to prevent an event.

DR. TINETTI: So, you have 100 people. If they don't take a statin, how many of them--these are your 10 percent risk people--if they don't take a statin over 10 years, how many of them are going to have an event? That is pretty simple.

DR. GOTTO: Right. It's one.

DR. TINETTI: This one does not take a statistician.

DR. GOTTO: The reduction was 37 percent. So, if the event rate was 1.3 percent in the year in the control group, it is 37 percent less if you are on a statin.

DR. TINETTI: I understand your relative risk. I am talking absolute risk. You have 100 people, and if they have a 10 percent risk, 10 of them will have an event and 90 will not. I think that is correct from my first grade math.

If you now give those people, if they all take the statin as prescribed for at least a year, because it takes that long to get the benefit, and they take it religiously, and you have your 37 percent reduction, how many of those 10 people who would have had an event, will now have an event?

DR. GOTTO: Who would have had an event, will not have an event?

DR. TINETTI: Right.

DR. GOTTO: Thirty-seven percent.

DR. TINETTI: So, three.

DR. GOTTO: Right.

DR. TINETTI: So, basically what we have done is gone from three to four. We will give you the benefit, we will go up to four. So, now you are having--out of 100 people, there will now be 6 people who have an event rather than 10 people.

DR. GOTTO: Right.

DR. TINETTI: And you get the sense with the marketing and the packaging, the discussion you have had with the public, that they are going to understand that?

DR. GOTTO: The public--doctors have a hard time understanding relative versus actual risk.

DR. TINETTI: But we have already agreed that doctors aren't able to do this, that is why we are having the population do it. I think you are having a little hard time doing it.

But again I mean it seems to me this is an

informed decision if people really have to understand the extent of their benefit.

DR. GOTTO: Yes, but--

DR. TINETTI: And how are you going to help them to do that?

DR. HEMWALL: I think Jerry Hansen is best to handle the question about how we communicate to consumers and what we understand about how consumers view these questions.

DR. TINETTI: I don't think it is a matter of questions, it is a matter of are you communicating the actual data to them in a way that they can make the decision.

MR. HANSEN: Yes, that is what I am ready to address.

First of all, as we just saw in this debate, the argument of relative versus absolute risk is hard for physicians and healthcare professionals to understand, and obviously, that cannot be communicated on an OTC label. We actually looked at trying to do the Framingham risk on the package.

We had two approaches. One was more NCEP driven,

which was age plus cholesterol value plus a risk factor. Another approach we looked at was the Framingham risk score and having consumers calculate that on the box. Like we saw with BMI with alli, that was a disaster. Consumers had a hard time understanding that.

So, we consulted with FDA, and based on their input, went after the LDL plus 2 label, which was more consumer-friendly.

What we can do, however, is we can provide within our program where we have more time to describe it, and have calculators and interactive items, go through the concept of absolute risk with the patient. And we are prepared to do that and we know there is interest in that.

DR. TINETTI: Dr. Taylor had one question and then we will go to break.

DR. TAYLOR: The question I have is before you get to the kind of numbers that you are describing, of risk, intervention, and so forth, most over-the-counter preparations are for acute illnesses, and that is a mentality that people have.

Is there anything in your studies that you collected data on compliance? If the effect is only seen

after a year, how sure are you going to be that folks are going to take it for a year given that the mentality of over the counter is short term?

MR. HANSEN: We actually have some excellent data from two of our use trials on how consumers will persist with OTC therapy. But first I wanted to make the point, because a lot of people say that chronic asymptomatic conditions is a new OTC condition. But I will remind you that consumers every day take these products. Calcium for osteoporosis is a chronic asymptomatic condition, low-dose aspirin for heart disease, preventing heart disease. There are approximately 30 to 40 million consumers doing that every day.

So, this is an extension of that, not a whole new mind-set or whole new paradigm.

Now, specifically, your question, if you can show the slide please.

[Slide.]

The first data that we have is from the CUSTOM trial, and if you look at the middle bar, you have the CUSTOM results that 62 percent of the consumers in CUSTOM were still persisting on therapy after 6 months of therapy.

What is interesting is that if you look at appropriate persistence--that is, the people who should still be taking the drug--we had 17 percent of the people appropriately stop taking the drug because the program informed them it wasn't right for them. So, appropriate persistence was really 79 percent, which as you can see is this high, if not a little higher than what you would see in the prescription setting.

We also have further data that supports the 6-month data, but takes it all the way out to 18 months, and if you can show me that slide.

[Slide.]

This was Study 076 and 722 people. We actually extended this trial beyond 6 months, out to 18 months. If you were to overlay the CUSTOM results, the 6-month results are almost identical, and what you see typically in prescription trials, as well, that most of the drop-off is in the first 3 to 6 months, but if you get somebody to stay on therapy and persist, they usually do it for the long term.

So, here is 18 months. Again, if you overlay this with benchmark studies in prescription, it is almost

identical.

DR. TINETTI: Thank you. I think we are going to take a 10-minute break. We are a little bit behind schedule here, and I know people need to get out, so a 10-minute break and we will go to the questions.

[Break.]

DR. TINETTI: We want to make sure, this is such an important topic, that everything does get discussed, and Merck has asked for 4 minutes to clarify further response to one of the questions. So they have 4 minutes.

DR. HEMWALL: I will introduce Dr. Adamsons to provide that information.

DR. ADAMSONS: Just prior to the break, the question came up what benefit would people realize with Mevacor Daily. I want to start by reminding people that Mevacor Daily is intended for people at moderate risk, so that means appropriate age plus at least one additional risk factor, and this was a label that was developed with the input of the FDA, and it is accepted that this is a group that will benefit from statin therapy.

Now, whenever you put something out there, you get people on either end of the intended target population who