rigorous evaluation, but I think that as I view the benefit-to-risk ratio with these conservative estimates, I believe in this society in the year 2000, that this particular drug qualifies, so thank you.

CHAIRMAN BRASS: Dr. Johnson, you had a question.

DR. JOHNSON: I'm sort of going back to some of the questions that were being answered before this statement. And that is these people who shifted, did you interview them to try to gain some understanding in terms of why they shifted from Rx to OTC? I mean especially people who have prescription coverage. It's a little hard for me to understand why they would go from something that is, you know, a co-pay of five to 15 dollars or something like that, to have to pay for something out of pocket. So I'm wondering if you gained any insight that might be useful in your advertising to minimize that Rx-to-OTC movement.

DR. FRIEDMAN: I agree with you. That would be very helpful. Unfortunately, we don't have that information. I think that that attitudinal research would be very important and certainly we would want to be sure that the messages for OTC and the messages for prescription were very distinct and

very careful. But unfortunately I don't have that information for you today.

DR. JOHNSON: On sort of a related question, and this has to do with what I think is the current label and is on page 70 of the documents that you provide to us. One of the statements it says, "Ask a doctor or pharmacist before use if you are already taking prescription medications to lower your cholesterol". I'm a little curious about the wording of that and why it doesn't say, "Do not use if you are taking—", because the way that statement is worded somehow implies that it's okay to take this. And I'm just not understanding what situation they would ever use this is they were on a prescription cholesterol-lowering drug.

DR. FRIEDMAN: I think that's a good point. You know, I think that would be something--, that's a very good suggestion.

DR. JOHNSON: Okay. And my other question, again, sort of related to why it's not under the "do not use" category, is "if pregnant or breastfeeding ask a health professional before use". Again this implies that it's okay to use in a pregnancy and I think it's been described yesterday and today that there's really no reason to ever use

this drug during pregnancy. It may be safe if it's inadvertently used, but there would be no situation where someone would recommend its use, and this statement suggests, to me at least, that it may be acceptable to use during pregnancy.

DR. FRIEDMAN: There is certainly no intent that a pregnant woman would use OTC Pravachol 10. This is the standard pregnancy warning for an OTC package. Certainly we could change that language to make it stronger because the OTC product would never be intended for a pregnant woman to use.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: To follow-up on that a little bit, then switching from an Rx drug makes me wonder if they really understood what medications they were taking and what their medications are for and if you had any feel for asking them about their medications and what they were for.

DR. FRIEDMAN: We did know a little bit because there were some people that we considered trading down from the prescription to the OTC who in fact shifted, they were either on 10 mg. prescription and they took the OTC option, so we do know that. And some people who were, say, on 20 mg. doubled up on the OTC. So I think that they did know that they were

taking the medicine. Why they exhibited this behavior, I'm not exactly sure.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Three short questions. We ask that question and we haven't actually had an answer. From those that were actually treated and you were able to get lipids, you know, how many were able to reach the goals?

DR. FRIEDMAN: Just bear with me for a moment. From what you can see here is, this is in PREDICT. Everybody who qualified, whether or not they took medication, and then this is the people who qualified and actually took medication. You can see that 80 percent of people, of everyone who qualified whether or not they took medication reached their NCEP goal. If they took medication it was, in fact, 88 percent. If you used a more stringent criteria, which was not what the study doctors were instructed to do, it's about three-quarters. I mean two-thirds, I'm sorry.

DR. DAVIDSON: That's combining both studies?

DR. FRIEDMAN: This is PREDICT.

DR. DAVIDSON: Right. Give me just OTC.

DR. FRIEDMAN: It's actually a little

better in OTC, but it's certainly not different. Do you want to give me a minute to find that slide?

DR. DAVIDSON: Yes. And maybe somebody else can answer my next question. Because my next question is something that is important for all of us. You interviewed 200 people about OTC preference, you know. And they were really, you know, interested in OTC prescription. Who were those 200 people? How do you choose them? You know, could you give me a little background on those people?

MS. KRIGER: This was a classic consumer research study conducted amongst a random sample of adults 35 plus who are concerned about cholesterol.

DR. DAVIDSON: Okay. You don't have any demographics?

MS. KRIGER: I don't have those with me, but it was just, it was a random adult population 35 plus. I don't have those, the demographic breakouts with me.

DR. DAVIDSON: Thank you. And my final question is, from the patients that, you know, you interview, obviously you had a nice ethnic population, but how many really were treated? You know, because you only told us how many actually came in for the studies, but how many were really entering the study

we do not know. And that's very important for you and for us because if you have a nice way to reach them, but you don't have a way to retain them, we have a problem.

DR. FRIEDMAN: And you're absolutely right about that. I do have the demographics at each of the levels, and what we do see is sort of at each step, minority populations tend to fall off. There is less interest in purchasing and, once people purchase and take they stay on it. But there is less of an interest in purchasing the product and I think that that is exactly what is seen in the current healthcare system and something that we need to address in a program like this, and again may be, you know, another way of trying to address this. I do have the lipid data.

DR. DAVIDSON: Okay. Let's go to the lipid data and we'll come back to that point.

DR. FRIEDMAN: It's a very busy slide. This is the way we have it. Let me just try to go over for you. This is the qualified and treated population in PREDICT, OTC and the prescription confidence intervals between the two. You look at the overall baseline LDL which is about 160, no different, change in the percent reaching the NCEP goal is here,

and the percent reaching LDL less than 130 is here. So there's really no difference. We then broke it up by people whose CHD some physicians did for people with CHD and very few people without CHD in moderate risk, and without CHD in lower risk. And you can see basically that the numbers are, the numbers per group.

CHAIRMAN BRASS: Again, this is part of the data that confused me as well. And I realize now, if you put that back on? I realize those are means and not medians, but it suggests in both populations, large numbers had LDL less than 160 and therefore in terms of indication for therapy and in terms of their ability to reach the goal.

DR. FRIEDMAN: Yeah, now don't forget in this group right here, this is the moderate-risk group. The mean baseline was 155, so their goal was 130 and 80 percent reached that goal. Here, which is the lower-risk group and again, the guidelines, and this one for initiation was 160. Again, 95 percent reached the NCEP goal.

CHAIRMAN BRASS: Reached the goal of less than 130?

DR. FRIEDMAN: No, that's not 130. I have that only for the top here. I don't know why that's, I'm sorry that's not on this slide.

CHAIRMAN BRASS: So for that group that we say 95 percent reached their NCEP goal, what goal was that?

DR. FRIEDMAN: 160.

CHAIRMAN BRASS: Yeah, so most of them were 160. Half of them were there when they started.

DR. FRIEDMAN: No, they were above 160 to get in.

CHAIRMAN BRASS: Now, they couldn't have been with 166 plus or minus 17.

DR. FRIEDMAN: I'll have to look at that.

CHAIRMAN BRASS: Yeah, okay. I'm sorry, I interrupted you.

DR. DAVIDSON: That was my point. You know, and it's important data for us to know.

DR. FRIEDMAN: Yeah, It think that the overall impression is that the group was split about half and half moderate and lower-risk and the mean LDL was 165 for the lower-risk, 145 for the moderate-risk and 65 percent of people achieved an LDL of less than 130 in this environment. And again that was not with a physician doing anything to get that lower-risk group down to 130.

DR. DAVIDSON: Going back to my question. We need to learn why we're not successful in

maintaining or getting special populations to these clinical trials for the treatment. You know, you mentioned that one of the reasons was because they didn't want to buy the drug? Is that the main reason? Do you have, did you do any analysis of why you could retain it, or was it that, you know, your material was not friendly or designed to those special populations?

DR. FRIEDMAN: Again, we recruited into the study robust samples, as you saw, of minority populations. We did see that there was less interest about, in some minority populations about ten percent less interest in purchasing the product.

DR. DAVIDSON: Do you know why there was less interest?

DR. FRIEDMAN: No we don't. And we know that we placed sites in communities. We had people from the communities in the sites, but I don't have any further information. I agree with you that that's an extremely important issue in all healthcare related aspects and certainly something we would want to work with groups to-- I mean the whole goal of this is to improve access. And that's what we'd like to do.

DR. DAVIDSON: Did you field test your material for sensitivity for this population before you embark on the trial?

DR. FRIEDMAN: No we did not.

DR. DAVIDSON: Thank you.

CHAIRMAN BRASS: Dr. Grady.

DR. GRADY: One of the things we're being asked to do is to try and estimate whether the benefit outweighs the risk, so to get an idea that benefit, the absolute risk is important, but also the relative risk. So maybe you could help me think about the relative risk. In the trials that have already been done using 40 of Pravachol, the lipid LDL reduction was about 30 percent, is that correct?

DR. COHEN: Yes.

DR. GRADY: And the relative risk on the average was about, the relative risk reduction was about 25 percent. So in the 10 mg. dose, we're seeing about, let's say an 18 percent reduction in risk of, I mean in LDL cholesterol. But that's also occurring in people whose cholesterols to begin with are at a lower level in whom the relative risk reduction might be smaller. So when I try to think about the relative risk reduction might be in the population we're aiming at, I'm coming out with a relatively small number like, I don't know, ten percent. Do you think that's fair?

DR. COHEN: Mr. Chairman, may I? I thank

you for that question. This is the clinical trial we did at lunchtime. And so if you'll bear with me I'm going to show a slide I haven't seen.

(Laughter)

DR. COHEN: These data are from the Framingham data set, but it's looking at the population group at risk, and that's what we wanted to find. So we're looking at, in this case, men and women at, the men in two age groups, 40 and 35, the ages of interest, because we know that this is the lower-risk end in terms of absolute risk. And then we're looking at women age 50. And at the top we're looking at those whose LDL is 130, total cholesterol of 240, and the second panel, at the lower panel, we're looking at LDL cholesterol of 140, total cholesterol 240. Same stratification with regard to, thank you, male/female and age. And you can see what impact the increase in cholesterol has in risk just straight away, 11 versus 13, 10 versus 12, and seven versus nine. And you can see what the absolute risk here is with respect to the observations from these Framingham data.

DR. GRADY: What relative risk are you using to get that absolute risk reduction?

DR. COHEN: This is based, it says it

right here. Absolute risk reduction for 18 percent reduction in LDL and total cholesterol. And that, I think, is fair because what we're talking about is an OTC user population who uses the drug, who uses it with compliance, who takes it in accordance with directions, who is following, whatever percentage that is. Maybe it's half of those who initially try it, maybe it's somewhat more or less. But less us say whatever that number is, put a figure on it. Then that group will reduce their cholesterol and average LDL by 18 percent and based on the Framingham data we would come back to the risk estimate reduction. Can't show you clinical trial data that would be in order of this magnitude, 2.7, 2.0 and 0.9 percent. This is ten year risk of a cardiovascular event and I can tell you the endpoints if you wish. It's a composite endpoints of coronary deaths, myocardial infarction, angina, and hospitalization for unstable angina, coronary insufficiency. So that kind of puts it into a risk respective to allow the committee, I think, to make a judgment about this cost benefit ratio, recognizing what the potential benefits are when you look at it across the population base and considering it relative to the risk in this population.

DR. ELASHOFF: Excuse me. I don't get any

sense of how you could have gotten risk reduction data out of the Framingham data.

DR. COHEN: Ma'am, this is projected or estimated risk reduction.

DR. ELASHOFF: How is it estimated? How is it projected? From what?

DR. COHEN: It's projected at, looking at rates relative to those whose LDL is at that 18 percent lower level. This is an epidemiologic approach in the absence of clinical trials. Now we do have clinical trial data all the way down to AFCAPS/TexCAPS range, and in that range we saw exactly what we predicted from the epidemiologic model. As you heard yesterday there was a 37 percent reduction in events.

CHAIRMAN BRASS: Let a statistician talk to a statistician.

DR. KOCH: Okay, first, I don't know exactly what they did to get these numbers.

(Laughter)

DR. KOCH: My understanding of how they might get the numbers is that they access the Framingham database and they used a regression equation for which the inputs would be gender, age, LDL and total cholesterol. And then they then, in the

control group without Pravachol 10, they used what that would be projected at directly, and then they basically hypothetically considered how the patients who would have an 18 percent reduction of LDL and total cholesterol would do while still keeping age and gender fixed but then correspondingly reducing the two cholesterol measures. And they excluded diabetics and heart disease, et cetera. But they were using prediction equations from Framingham with and without the anticipated reduction in cholesterol that was demonstrated in the studies. So it's basically a simulation or a projection using the Framingham database and prediction equations that came from Framingham, or at least that's my understanding of what was done.

DR. BROWN: That's a successful tactic that they use. That's a successful tactic that has been used to predict the outcome of clinical trials. So it's not an illegitimate effort that they've done here.

DR. ELASHOFF: I didn't say that. I said that I just didn't understand what they had done.

DR. BROWN: I just noticed your eyebrows going up high.

DR. ELASHOFF: I mean, in essence,

although it's a little more complicated model, you've taken some standard curve and slipped down the 18 percent on it, but you've put other things into the model and whether or not there are interactions in there that we should be worried about or not, or other factors, I don't know. But in essence you've taken one of those curves and slipped down that amount. Okay.

CHAIRMAN BRASS: The only other thing I would add is it's important to recognize those are ten year risk rates.

DR. GRADY: One other question. It is important that they are ten year risks, but the other question is, are these cardiovascular events, does this include chest pain or is this, what are the events? Is it angina?

DR. CARO: Hi, Jaime Caro from Boston. The running of Framingham risk equations for these kinds of models is now a fairly standard way of calculating the risk reductions, and yes, there are other things in there. Blood pressure is in there, diabetics status, gender, age and so on. Interactions are in there. Is there published equations from the Framingham heart study? Your question was?

DR. GRADY: What are the cardiovascular

outcomes?

DR. CARO: What are the events. Yes, there's several risk equations that have been published. The one that was used for this is the more comprehensive one that includes stroke, TIA, MI, coronary insufficiency, death and angina.

DR. GRADY: Thank you. It's also interesting if you look at what the relative risk is there, it's about a 25 percent risk reduction in the 50 year old females, about 20 percent in the 40 year old males, and only about 12 percent in the younger men.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: Are we to conclude from this that you're changing your ages from 35 to 45, to 40 and 50?

(Laughter)

DR. FRIEDMAN: I think that's a compelling argument.

(Laughter)

CHAIRMAN BRASS: Dr. Krenzelok.

DR. KRENZELOK: Along the lines of age, and certainly a much more mundane observation than what we've been discussing for the last half hour or so, I had an opportunity to really take a look at the

PravaCare program newsletters which I think are very informative and so on, but depending upon what age is ultimately the bottom age, it probably would be really good to have consistency between the indications and the newsletter, for example. I was reading one and it just struck me that, sort of suggestive that young people should begin to take this. On the front page of one of them it said, if you're over the age of 20 chances are you need to begin to manage your cholesterol level now. So maybe it would be a good idea to introduce some consistency and raise that to 35 or 40, or somehow incorporate some other issues into it.

DR. FRIEDMAN: I agree with you. I think, I'm sorry, I don't remember the exact language in all the newsletters, but certainly the intent of the newsletters is to have people manage cardiovascular risks. And actually the first step is lifestyle modification. So I think we need to make it clearer that you should start, or anyone in their family, should start modifying the risk at a young age. But certainly the time for intervention with drugs would be different. Very good point.

CHAIRMAN BRASS: Are there any other general questions before we go on to the FDA

questions?

DR. UDEN: Just one general question about that which you've just talked about. In your, when you did the prelude to the PREDICT and the other study, you said that all of these people-- the comment was made many times-- had followed diet and exercise prior to entry. What data do we have that they actually followed diet and had exercised and to what diet and what exercise?

DR. FRIEDMAN: Yes. To assess diet, we were very interested in assessing diet very carefully, but yet, as would be done in a clinical setting, to not superimpose a true clinical trial environment. So we chose the MEDFICTS tool, which is a validated tool, used and proposed by the NCEP—it's in the NCEP ATP II treatment guidelines-- when what it does is it's a questionnaire that clinicians should use in their office to categorize people into an AHA STEP I and STEP II, or no AHA diet. We administered this diet to people, everyone who came in, and at any time they would have a physician contact, and also at the end of six months. The people, the participants were not aware of their score, so they didn't, we didn't want to have a training effect of how they would answer it. And that is how we assessed their dietary adherence

throughout the course of the study. According to the MEDFICTS tool, 80 percent of people in this population were following an AHA STEP I or STEP II diet. The majority of them maintained that diet. It was about ten percent improved, is what I showed you. In terms of exercise and smoking, we also looked at that in the studies. But again, we thought diet would be the most important thing to look at in a validated way. So we looked qualitatively at exercise and smoking. We didn't have very detailed exercise questionnaire. And we, in response to that questionnaire, again, about half the people said that they were exercising as defined as three times a week or more, and again that statement was maintained constant, but that was very soft data. We did ask about smoking and the smoking, we saw that there were ten percent of people who came into the trial were smokers, which is about half the national rate. And at the end of the trial it was the same.

CHAIRMAN BRASS: Dr. Blewitt. Dr. Jenkins.

DR. JENKINS: I would just like to go back to the slide you showed of your controlled clinical trial you did during lunch. There was something Dr. Grady pointed out that I was wondering if you could

clarify for me that I don't quite understand either, and we're interpreting a lot of numbers on to equations quickly. And that's why the relative risk reduction was 25 percent, 20 percent, and 12 percent in the three different groups. Just how does the math work out that way?

DR. CARO: It has to do with the interactions and the equations. Age interacts very heavily with gender, with the presence of hypertension, and so on. And because it interacts, a risk does not change linearly with age, and therefore, nor with cholesterol values. And so as you run the equations, you have two curves which are not parallel to each other.

CHAIRMAN BRASS: I think that point's very important because I think it got confused in some of the earlier implications in that the relative risk reduction is not, to my understanding, constant across the population and at the lower the risk, the lower the relative risk reduction as well as the absolute reduction. I think it's very important.

DR. CARO: Not necessarily. It depends on what's leading to the risk.

CHAIRMAN BRASS: I agree. I apologize. I genuinely.

(Laughter)

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: Two questions. Did you measure in either of your two consumer-use studies, especially the OPTIONS where you had access to the patient chart, the extent to which patients monitored, evaluated their response to treatment outside the physician's office? I asked this yesterday, so I felt compelled to ask it today. In other words, using a drugstore or another of these prevalent means to measure cholesterol outside of a physician's office.

DR. FRIEDMAN: We didn't monitor that systematically. In PREDICT, the only information we had was people who brought in laboratories from their personal physician's offices, but we did not monitor the use of outside services.

DR. NEILL: Last question. Did you monitor in any of the trials the extent to which patients may have taken more than the recommended dose? And if so, how did you monitor it and what were the results?

DR. FRIEDMAN: No we didn't. People were asked, the only way that we looked at it was to see how many cartons people purchased, which give us an estimate. There was a comment made earlier from the

FDA reviewer about compliance. Just as we don't in our regular clinical practices ask people to bring in their medicines and count their pills, we didn't ask them to do that here. So a pill count of compliance seemed to be very unreliable and in fact, when we looked at compliance and tried to correlate it with LDL reduction, there was absolutely no correlation. So people didn't bring in all their unused pills. So what we did look at, though, to try to see if people were buying a lot more than they should, is the expected number of cartons that should be purchased. And there we found that people were buying, for the most part, the expected number of cartons.

DR. NEILL: What's for the least part?

DR. FRIEDMAN: Well, that's a little hard to say and I don't have the data completely broken up because, again, there were the people who stopped taking therapy, so you would expect that they would have bought one or two cartons. We do need, I don't have that data to correlate exactly, but I think what I can say is that people were not buying or taking two or three cartons when they should have been taking one.

CHAIRMAN BRASS: Dr. Katz, would you like to reintroduce the charge?

DR. GRADY: Could I ask just one more question? And I don't, I mean, of the pharmacologist, I think, in the room. You know, if the rate of adverse effects, and the worst one is potentially rhabdomyolysis, if there were to be interactions, if there were to be a higher rate of outcomes in an OTC population, how much might that be? Are we thinking, you know, twofold, tenfold, a hundredfold? Does anybody have any estimates of, you know, what that might be?

DR. FRIEDMAN: I'd like to ask Dr. White who has looked at our cases of rhabdomyolysis very carefully to answer that.

DR. WHITE: Michael White, University of Connecticut, School of Pharmacy, Hartford Hospital. I think when you look at drug interactions as a specific subsa as we've already seen, we're looking at increases in plasma levels with a 10 mg. dose of twofold, 1.5 to twofold, which would give you the same risk as you had if you were going from a 10 mg. dose up to a 20 mg. dose, which there's substantial information to show overall safety. Now overall if we take the 57 people who had cases of rhabdomyolysis that met the FDA's criteria of greater than 10,000, and that conservatively if you take the 17 people in

the study who also had unknown levels, but the doctor had said that they had rhabdomyolysis, we put them all in together and what you saw for an overall risk was 0.3 for 100,000 patient years or about, an over threefold less than what we had heard yesterday. And at some point you have to think that you're approaching what the underlying background information is, especially when you look at confounders. And we did go and I looked through personally each one of the individually reported cases, looking at potential confounders, and there were a number of them. Twenty-four patients that had critical confounders, and I'm looking at E-4-1. But anyway, there were a number of cases that had critical confounders that led you to believe that those cases couldn't have really have been due to pravastatin based on the time course average of over two years that they were ended up being on pravastatin. And then the very consistent time course that they had of other factors that they know are much more commonly related to rhabdomyolysis. And then there were other ones that had important confounders, leaving about one-third of those overall cases without any known confounders. So I think that when you put all those things in together based on the very low incidents and the fact that idiopathic

poliomycitis that people know can cause rhabdomyolysis happens from five to a hundred cases per 100,000 patients and that it's known that that can cause rhabdomyolysis. How close are we getting to the underlying background information? And then also looking at the pharmacologic effects, knowing that active uptake in the liver, passive uptake into other cells and that you'd need very, very high concentrations to be able to penetrate those cells and potentially have those effects. Thank you.

CHAIRMAN BRASS: Dr. Katz.

DR. KATZ: Good afternoon. I'm Linda Katz, Deputy Director from the Division of Over-the-Counter Drug Products. For those of you who were here yesterday, I will not go through the charge in the same way that I did yesterday, because we spent a good deal of time at this meeting in discussion going over the critical issues. What I would like to do is to focus you on the next slide to the areas for deliberation, and just to identify a few key issues and points again that we'd like for you to take into consideration as you answer the questions that are covered under efficacy and safety, OTC considerations, and approvability. We've heard a lot about who is the target population. And in going ahead and looking at

the efficacy and safety, it's important to see if the data that we have in this application does support the efficacy and safety for the targeted population for the indication, which is a new one. And I make this point again, that this is a new indication and this is not a switch. We are looking at individuals with milder elevations of cholesterol levels that what we currently have approved for Rx. And therefore, when we go ahead and we've looked to answer the questions of benefit risk, we need to make sure that we have the data to support the treatment in that particular population. In addition, when we go through OTC considerations, we need to make sure we understand how consumers will utilize these products. We need to again make sure that the consumers can understand how to use them and to understand how to monitor their laboratory data, both in terms of efficacy as well as monitoring for any adverse effects. We also need to look into taking in to consideration what exactly is the goal for the consumer, and has that goal been clearly identified for the consumer? The paradigm that's been identified today is different from that from yesterday, because as we see it set in today's studies, that there's been more of a physician involvement. But that's something also we need to

take in to consideration, just how the physician should be involved for the consumer in the OTC market place. The additional point that I'd like to make is we are talking about a consumer and not a patient. If someone goes into a drugstore to buy a product, that they are out there, and one hopes that they will follow the labels and can comply with things as instructed. But again, individuals are perfectly free to buy a product and they don't necessarily have to go and follow through. And when you, again, in your deliberations, when we finally get to the last question will be approvability. And approvability, again, will be based on the benefit risk that has been demonstrated for this particular population. With that I'd like to turn over the meeting to Dr. Brass so that you can begin the final portion and the deliberations of the questions. Thank you.

CHAIRMAN BRASS: Thank you. The questions that have been distributed look eerily familiar to those of you who were here yesterday and I'll remind, just a couple of general points said to hopefully maintain focus. The first several questions are not OTC-specific questions, but are in fact general questions. But that in answering all of these questions, the answers should be rooted in the data

that has been presented in the context of the NDA today and not an extrapolation to what you think might be true or might become available. We will save that to the end where the final question gives us an opportunity to add additional information as to what would swayed you in either direction. I'm going to break question one up the same way I did yesterday and read it paraphrased as somebody interpreted it yesterday, to be based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit defined as lowering of LDL with lovastatin 10 mg. in the target population, but we'll change it pravastatin.

(Laughter)

CHAIRMAN BRASS: Didn't think I caught it, did you?

(Laughter)

CHAIRMAN BRASS: So that question is now open for discussion. Seeing no discussion, oh, I'm sorry.

DR. ELASHOFF: The question being did they demonstrate that LDL was lowered?

CHAIRMAN BRASS: That's correct.

DR. GRADY: Well, actually the way the question's stated in the page here, it says the

expectation of a cardiovascular benefit.

CHAIRMAN BRASS: That's why I didn't read that question. That's not, we're going to do it like we did yesterday and split it up and first do the LDL part. Okay, is that clear? No, it's not, Dr. Grady? Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit defined as lowering of LDL with pravastatin 10 mg. in the target population? Okay. All who agree with that statement, please raise your hand and indicate yes.

(Hand vote taken)

DR. TITUS: Thirteen yesses.

CHAIRMAN BRASS: Opposed? Abstained?

DR. UDEN: Yes.

(Laughter)

CHAIRMAN BRASS: Fourteen yes, no noes, no abstentions. The second part of the first question: Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit defined as outcome-based cardiovascular benefit with pravastatin 10 mg. in the target population? So now has the benefit been demonstrated with respect to cardiovascular risk? And that is open to discussion. Since I want there to be discussion on this point, I will ask Dr. Grady to express her opinion.

DR. GRADY: Well, obviously, I think all of us would be much more comfortable if there were a trial with real clinical outcomes because what we're doing here is using a surrogate outcome which is changing LDL cholesterol as a predictor of real clinical benefit. And I'm always leery of surrogate outcomes. On the other hand, this is one of the best surrogate outcomes that we have studied over the past ten years. I would say that if we believe that this magnitude of change in LDL is a predictor of real clinical benefits in this low-risk population, whatever their HDL cholesterols happen to be, then we can probably expect that the magnitude of that benefit is something on the order of one in a 100 to one in 250 or something like that over a five year period, which again brings up the importance of people sticking with this therapy over a five year period. Because I don't think any clinical benefit can be expected over six months to a year. You don't ever see that even in trials. So there are a lot of steps I think and that's my worry, is there are a lot of steps we have to make assumptions that everything is going to go well. If everything went well, I think there is the expectation of clinical benefit.

CHAIRMAN BRASS: And the agency can

correct my reinterpretation but the question specifically says demonstrated, as I have now phrased it, as opposed to an expectation of. And I think there'll be the opportunity to discuss the expectation when we talk about risk-to-benefit and other potential interpretations of the LDL, so that I would put a relatively personally high threshold on that syntax, demonstrated a clinical benefit. Including, though, if you were confident that the surrogate extrapolated to this population, then I think you could consider it having been demonstrated. Is that fair or am I?

DR. KATZ: You're correct. What we're looking for is demonstrated.

CHAIRMAN BRASS: Dr. Molitch?

DR. MOLITCH: It certainly is not directly demonstrated. It can be extrapolated from other data as probably a very small thing. I think this discussion about HDL was not a totally meaningless discussion. I think that when we looked at the absolute risk reductions, in fact, they probably did get smaller with higher HDLs, so that the AFCAPS/TexCAPS data really doesn't quite reflect the population that might be using this. And again, I will editorialize as I did yesterday that if we were actually looking at a cost benefit ratio as opposed to

a risk benefit ratio, then I would love to see some of those costs expended in patients with higher lipid levels that weren't ever receiving these drugs.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Well, there's no evidence based on what they presented. And number two, you know, the intended population that I saw was not really what I feel is the intended population for over-the-counter. Therefore, you know, the answer is to that question, you know, as far as I'm concerned is, the intended population was not there and we don't have evidence-based medicine because they didn't measure the outcomes.

CHAIRMAN BRASS: Dr. Elashoff.

DR. ELASHOFF: Yeah, I wanted to emphasize that it's not just that it has to be estimated from other data, but that it does have to be extrapolated from other data. That is, that you're going on many cases out beyond the range of the other data, and extrapolation validity is heavily dependent on exact details of the model you're fitting. And whether that fits well everywhere in details as where as sort of reasonably well in the middle.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: I have a question for Dr.

Davidson. And that is, I guess, what you think the intended population is. I guess my impression is the intended population is a well-motivated population and my suspicion is your concern is the under-served population wasn't well-represented in the study, and I think the problem there is really one of a lack of knowledge in that population to make them motivated and so, I guess I would contend that they probably did hit the population that's likely to use this product. That may not be from a public health perspective, the optimal, not include all of the population we want, but it probably is the population that will actually use the product.

CHAIRMAN BRASS: I will just remind that in the context of this question, it's not necessarily the OTC population. It's the general. And the target population referred to is specifically the target population as defined by the sponsor, so it's that intended population defined based on the criteria set up by sponsor for age, LDL, total cholesterol, et cetera.

DR. DAVIDSON: Well, the problem is that, you know, they can define, but it is an over-the-counter product. You know, and therefore, they made the wrong definition.

DR. TAMBORLANE: I also would be interested in your being a little more specific, Jaime. What target population did they miss?

DR. DAVIDSON: Well, you know, many of those patients, you know, were actually seeing physicians, 85 percent of those were seeing physicians but were not treated. Then if I would go to that population then what I will do is, you know, very well, you know, I was told that, you know, at the time the study was done, we didn't know what to do with cholesterols, you know, at certain point. Then if that's where we're going to change, then you know, the target is not the patient. The target is us, the physicians.

DR. TAMBORLANE: Okay. Because it's not under-served populations that some of the stuff we heard about the first day, those kind of.

DR. DAVIDSON: Well, they're different things, you know. I really want to also be sure that we serve everybody, you know. In the United States, we have more than 80 million or 90 million minorities or ethnic differences, you know, and they're at high-risk with this problems. You know, then if we're going to go for an over-the-counter medication, you know, those people also need to be reached. You know,

and we need to consider because over-the-counter will be misused or improperly used or maybe not used for what I feel is the intended population. Intended is everybody in the United States that is at risk.

CHAIRMAN BRASS: I don't want to continue this part of the conversation because it's specifically directed to the OTC issues. And I want to save that to the OTC, so if it's general about cardiovascular benefit, Dr. Silverstein.

DR. SILVERSTEIN: I guess I'm trying to get back to that question, too, because we've digressed a little bit. And the question is whether or not efficacy in reducing cardiovascular risk with an OTC preparation has been demonstrated?

CHAIRMAN BRASS: No, no. It does not say OTC.

DR. SILVERSTEIN: Just the 10 mg.

CHAIRMAN BRASS: That is correct.

DR. SILVERSTEIN: Okay. Okay, I see.

CHAIRMAN BRASS: Any other comments before we vote? I will read the question again. Based on the data submitted in the NDA, has the sponsor adequately demonstrated clinical benefit defined as improved cardiovascular, a decrease in cardiovascular events with pravastatin 10 mg. in the target

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

DR. JOHNSON: What does "is" mean?

(Laughter)

DR. JOHNSON: Okay. You said that demonstrated means demonstrated or it could mean--, I'm a little confused.

CHAIRMAN BRASS: Well, it means demonstrated. I was simply illustrating that things could be demonstrated in other ways other than a placebo-controlled clinical trial. And if, in fact, you feel it has been demonstrated in any way, that the answer to this question is yes. And because I think arguments have been made that in an attempt to demonstrate to you, that the answer to this question is yes in the absence of this trial. So if you feel that it in fact has been demonstrated to you, then you should vote yes. If it has not been demonstrated to you, you should vote no. Okay. All who feel the answer to that question is yes, please raise your hand.

(Hand vote taken)

DR. TITUS: One yes.

CHAIRMAN BRASS: All those who feel the

answer to that question is no, please raise your hand.

(Hand vote taken)

DR. TITUS: Thirteen noes.

CHAIRMAN BRASS: All abstentions, please raise your hand. And once more we add up to the right number. Okay, the second issue again focused on a general context of the 10 mg. dose is, has the sponsor presented adequate data to support the safety of pravastatin 10 mg. in the target population? And again this question is not yet OTC-specific. This is just a general safety question. Are there any comments or discussion? All who feel that the answer to that question is yes, please raise your hand.

(Hand vote taken)

DR. TITUS: Thirteen yes.

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

(Hand vote taken)

DR. TITUS: Zero no.

CHAIRMAN BRASS: All who are abstaining, please raise your hand.

(Hand vote taken)

DR. TITUS: One abstention.

CHAIRMAN BRASS: Question three. Taking into consideration the balance of risk and benefit,

has the sponsor presented data that are adequate to support the use of pravastatin 10 mg. in the low-risk population with total cholesterol 200-240, LDL greater than 130, regardless of HDL level without CHD or diabetes? Yesterday we elected not to discuss this question, feeling that our answers to one and two implied an answer and felt the time would be better spent focusing on those issues specifically in the OTC context. Is there any difficulty in that plan for today?

DR. KATZ: That's fine. When you get down to the last question, obviously, we'll have to modify since it refers back to this question.

CHAIRMAN BRASS: That's correct. Now we focus on the issues related to the efficacy and safety in the OTC context. Assuming an indication for the use of pravastatin 10 mg. in the proposed target population could be justified based on an expectation of clinical benefit, has the sponsor adequately demonstrated that consumers can achieve such a clinical benefit in an OTC setting? In responding to this question, please consider the following: the ability of consumers to self-select, the ability of consumers to evaluate response to treatment, the ability of consumers to adhere to chronic therapy, the

need for the physician or other healthcare professional in the effective treatment, the capacity of the proposed label to direct consumers in the effective use of pravastatin. And I think I will begin the discussion of this point by talking about two issues in specific. One relative to point C - the ability of consumers to adhere to chronic therapy with pravastatin. There's been much discussion about this and I think all of us are disappointed by the long-term compliance. However, I'd like to suggest that that may be a legitimate disappointment, but not a primary consideration in this decision-making. That in fact a subset of appropriate consumers were able to comply for an extended period of time with a favorable benefit and the risk to the overall exposed population was low enough, we would consider that to be not a bad thing. And there is precedent for that. When this committee, or a variation on this committee, discussed the use of nicotine products for smoking cessation, it was in the face of data that said most patients would not complete the therapy with nicotine-containing products for smoking cessation but those that did would derive benefit, and those that didn't would not be exposed to unacceptable risk. So I think that the issue of compliance needs to be done in the context of

the population risk and the patients who do comply, their benefit. And so I think that the context in which we talk about that needs to be focused in that way. The second point I would make is the same one I have made for an extended period of time, including the previously referred to discussions in the historical past. And that is I remain concerned about the ability of an OTC population to exercise appropriate decision-making to derive benefit in the absence of a learned intermediary, whether it's a physician or otherwise. The sponsor indicated in their design of these two actual-use trials that with the presence of a learned intermediary one could achieve benefits in the OTC setting that were comparable to that in the prescription setting, but it was artificial in the sense that all these patients to a very high degree, in fact, were utilizing a learned intermediary to achieve that end. And it related to Dr. Davidson's point. In a general use population, will there be high percentages of patients who attempt to self-medicate in the absence of the learned intermediary with some risk and certainly not optimal benefit? I personally remain concerned about the impact of OTC availability in the absence of a learned intermediary on degrading patient-physician

interactions for those individuals who do as illustrated by the dropout rates even in this kind of setting with populations who are being studied in this kind of controlled setting. And finally, the other point I would derive from the data presented by sponsor in terms of, and again I have to compliment the sponsor for doing the study well enough to provide us this degree of insight, is that the learned intermediary had to make lots of interventions in order to treat the populations who were randomized to the learned intermediary. Some of these might be very low-risk issues - a patient with a cholesterol greater than 250 continuing to take the drug - but I think all represent illustration of limitations to the degree that you've defined a target population for this drug and to the degree adherence to that target population is viewed as important. Two assumptions that I think are worthy of challenge, but to a degree those are assumptions, I think the data indicates that indiscriminate availability will resolve in substantial use outside of the target population. And I open to other committee members. Dr. Blewitt.

DR. BLEWITT: I'm not sure that I actually saw that in the study. It seemed to me that they cast a very wide blanket. They went to numerous sources

and in the process they determined what the population was that's going to take the drug. So when you go out to thousands of people, then you find out who in fact is going to take it.

CHAIRMAN BRASS: No, I'm basing my comments on those people who were randomized to OTC, read the label, started taking the drug, and then subsequently were found not to fit the target population when profiled. So I'm not using the largest denominator. I'm looking at the denominator who self-selected to use. And we saw similar data yesterday as well.

DR. BLEWITT: I understand. And I just am not sure that in you trying to convert actual-use studies to real life, and that's certainly legitimate. But I can't see that, how that differs, if you will, from OTC--, other than chronic use, from OTC drugs in general. You are going to have a certain population who are going to take non-steroidals for arthritis. Or, you know, they'll be self-treating osteoarthritis and things like that. So it's going to happen. And the question is how bad is that going to be if people do that? And my take on it is that it's not going to run you into some terrible problems. If someone decides not to see their physician but to do it on

their own, if they're doing it right, and if they're following up their cholesterol levels on a regular basis, and checking periodically with their physician, I don't see anything personally wrong with that. In fact, I would see that as a potential advantage.

CHAIRMAN BRASS: Yeah, all I would emphasize is two points. One is, I think the long-term use is a nontrivial difference between the example you cited. And the context of this question is, again, not an approvability risk-to-benefit ratio, but the question is whether or not it has been demonstrated that the target population utilizes this drug for the purposes indicated in the OTC setting.

DR. BLEWITT: I understand that and I agree. But I also have to ask what level of proof do you require? Is this a leap of faith or does it just take a little step in logic to take you from one point to the next? And I don't see it as a particular leap. I think there have been enough presentations today from experts to suggest that there is a real population overall to be served. And I'll go back to what I heard Dr. Cohen say earlier because I had said this to myself, it's not the people who aren't going to take it, whether 20 or 30 percent of the people who are eligible take it, it's the 20--, it is the 20 or

30 percent who actually do take it. It's not who decided not to do it. It's not the people who aren't compliant. It's those that are that would tend to be served by this, by this OTC availability of this drug.

CHAIRMAN BRASS: That's the point I was trying to make. I agree with that. Dr. Clark.

DR. CLARK: I think that it's pretty clear that this proposal would move healthcare into a new arena and I think that what has been demonstrated here is that in order for it to be effective, you do need a learned intermediary. But I think that should not come as a surprise because it's new to both the patients, consumers and providers. And I think it may have been Dr. Brown who mentioned he's given 10,000 lectures in 15 years to physicians where it's not a new arena. So I think the expectation that there would need to be ongoing educational programs and other types of supports to make this effective because it is something different should not be taken as a negative but an expectation of moving in this direction.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: Which means that we are relying upon the sponsor and good faith on the sponsor that they will continue to move forward and educate the

population that we're trying to target, and educate physicians about this. And, you know, once the product is OTC, no matter what they say here, we do not have any assurances because they don't have to do it to have those educational programs. That being said, I do believe that with the educational programs that they have, or at least have tried to have presented here, I think they've done a pretty good job. In fact, a very good job in presenting data that would led me to believe that, you know, if this was OTC, that some consumers would be able to greatly benefit from it.

CHAIRMAN BRASS: Dr. Blewitt.

DR. BLEWITT: As regards compliance, my other musings on this, my musing on this is that if I were a drug company and I were now marketing this drug for long-term use, it would be in the company's best interest to want people to comply with this regimen. The more people that take it long-term, the better off you are, so that is your target. I sometimes get the perception that, well, they're talking about this educational program today, but then what happens when it's approved? You know, is it going to just fall by the wayside? And I know that these things don't just happen and that there's every, there is certainly a

push to continue those educational programs. And that without them, I think that there is a population that won't be well served.

CHAIRMAN BRASS: Dr. Johnson.

DR. JOHNSON: I guess my take on it is that there may be some what would be defined as inappropriate or not the target population using this drug. But when I, based on both the data presented yesterday and today, it appears that the true high-risk people are not selecting this therapy. People with ischemic disease, people with diabetes. So those in whom we would be very concerned about them using this therapy, those people aren't selecting and I think that's a good thing. So who does that leave? That leaves people in the primary prevention category really in three groups: less than 200, 200 to 240, and over 240. If the people less than 200 are taking drug, they're probably wasting their money, although we don't know that. It may be that a total cholesterol of 150 as the MRFIT data suggests is the optimal LDL, or the optimal total cholesterol. So they're probably not going to derive much benefit, but I also think these are such safe drugs that they're probably not at much risk. The 200 to 240's our target, so they're okay. And I guess the way I view

the people over 240 is that certainly it would be better if they were on 20 or 40 mg. of pravastatin, but they're on nothing. And if they go from nothing to 10 mg. of pravastatin, they're still gaining more benefit than from nothing. So I guess I don't see even in the inappropriate use categories that those are really bad things in the big picture.

CHAIRMAN BRASS: I'm just going to comment because I think that the risk population as you characterized it for the OTC use is variable. I happen to agree that if a patient with a total cholesterol of 260 took this drug "inappropriately" as opposed to taking nothing, a good would be done, not a horror. But I am more concerned about the risk populations in two ways. One, I come back to the 27 percent of patients who were on a prescription drug, self-selected themselves to take this OTC product. And neither the PREDICT or OPTIONS study was very enriched in patients with coronary artery disease or diabetes to allow the de-selection to be assessed adequately, so I come back to this relatively small cohort, but 27 percent of them did in fact select. And I come back to that if ten percent of patients on optimal therapy with a physician discontinue therapy to switch to the less optimal OTC drug in an

unsupervised situation, that too represents an at-risk population in terms of the decision-making. Dr. Tamborlane.

DR. TAMBORLANE: Yes, to follow up, I mean, a subtle change in the sort of interpretation of the next, these two questions then the OTC setting becomes more of a safety issue rather than an efficacy issue. Is that, because from your earlier statement, that is, if you had poor compliance and, you know, somebody took it, then that's okay. You know, that might be okay for clinical efficacy, but a major concern of safety is not the toxicity of the agent but the fact in the OTC setting that a substantial number of patients would not get optimal therapy, namely proper titration by a learned intermediary.

CHAIRMAN BRASS: I think that's right. The reason I mention in the context of this question which is a benefits question is because this question is structured in a way to include consumer self-selection for the target population. And as I've indicated previously, the assumption that the target population is the right one or the wrong one is something that can be discussed separately. But we're being asked to assess the ability of consumers to self-select based on that target population

definition. And what I'm suggesting is in a variety of ways, some of which would generate little concern, some of which to generate more concern, the ability of consumers to self-select, in my opinion, has not been demonstrated. And to a degree that's part of the benefit assessment is why I answered it that way. Dr. Gelato.

DR. GELATO: Just to sort of get up a question of are these people who are on prescription drugs going to go off of them. And I guess I would view those people as being high-risk people, because if they've been put on a medication, they're high-risk. And what that says to me is if they're on one drug, they're probably on multiple and maybe this isn't a fair thing. But it seems like they would be going back to their physician and I would assume that you would ask them what are you taking? You know, so there would be some fail-safe there, because I think that's a population that's going to be directing, you know interacting pretty heavily with their primary care provider, I would imagine, because they probably have more than one problem, because we're thinking about diabetics and people who have heart disease and so on. So I, I don't know, maybe I just don't feel it's the same concern because I think that they're

going to be monitored in a different way, but maybe that's not right, so.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: I want to say, you know, my concern is we need people to take the medication but we need these people to take the medication correctly and we need to reach those people who have the high-risk, you know, to be treated and treated to target. You know, and I think we're all saying the same is how to get that? Is over-the-counter the way to do it, you know? And that's my concern, you know. I agree. We need to treat them. You know, we already answered question one. The drug is a good drug. It lowers lipids. You know, but how do we get to the real people that need it, you know? And that's part of the problem, you know.

CHAIRMAN BRASS: Dr. Silverstein.

DR. SILVERSTEIN: Question about the ability of consumers to evaluate the response to treatment and to monitor cholesterol levels. Somewhere in these books when I was reviewing it, I noted that the amount of people who had LDL cholesterol follow-up was lower in the OTC group than in the treatment group, which says that they're not getting adequate follow-up of their lipid levels. And

I'm concerned about that. I'm concerned about people who can buy a drug over-the-counter really adequately following up. I really don't think that's been demonstrated in this study. You know, the fact that they had to go to a doctor to get a refill, basically, after two months.

CHAIRMAN BRASS: I will allow sponsor to comment on the data but I would just extrapolate more to your last point, that I think the follow-up rates in the study design employed by sponsor are likely to be much higher than would be in an unlimited access kind of setting. So that again, the demonstration of the consumer's ability to follow-up and interpret has not, in my opinion, been demonstrated even though the follow-up, I think, was actually pretty good.

DR. FRIEDMAN: Yes. Just to clarify a couple of points. First, the follow-up was actually a little better in the OTC versus prescription, 85 versus 83 percent. And I would like to make the point that the OTC participants were unaware that they could not repurchase if they didn't have the follow-up. That was never in the consent and they did not know that they would not be allowed to repurchase if they didn't see the doctor. They only found out about that when they went to that retail site and tried to

repurchase. And we know that of the 720 people that did purchase, only 10 of them were denied the repurchase because they didn't see the doctor.

CHAIRMAN BRASS: Dr. Grady.

DR. GRADY: Yeah, I think that I take a different view on this. I mean, I think there is some danger that people with high-risk won't get appropriate care and follow-up. On the other hand, we don't do appropriate care and follow-up of people at high-risk right now. We don't control their lipids. We do a horrible job at it. And what we're really doing is restricting these drugs from those people. They can't get them unless they go to physicians. The other, I think, problem is that if you start thinking about people at lower-risk, what we've also done for hypercholesterolemia, which is really not a disease. It may be a risk factor, it may be a mechanism, but it's not a disease. We've medicalized it, and we've labeled it. And those are some of the real downsides to treating healthy people with preventive interventions that have, you know, a low potential benefit. So I think if you can avoid that by using over-the-counter medications, the balance here actually may be favorable.

CHAIRMAN BRASS: Do you believe there are

data in the submitted NDA to draw conclusions on issues you raised?

DR. GRADY: I think that the data showed that the treatment and follow-up, I particularly like this proposal because they really do emphasize that patients, that people who have high cholesterol need to go see their physicians. And they did in equal numbers, I think they showed that. And in fact the physicians who were treating the patients who were in the medical care group here were instructed to tell them to treat themselves at levels of cholesterol that most physicians in practice may overlook. So I think, you know, it's an artificial setting here, but both for the OTC as well as for the treatment group, and I think they did a pretty good job in demonstrating that the outcomes, in terms of seeing their physicians, changing their lipids and so forth, were pretty good. And given that this is a difficult study to do, kind of study to do.

CHAIRMAN BRASS: I understand and again, but to the degree to which the 85 percent of the OTC group seeing their physician is integral to your assessment of the success of the OTC program, you could leave the pills out of the box and have them buy the box with a note in it to say go see your doctor

and tell them to start you on monitoring treatment.

DR. GRADY: That's what they're proposing to do.

DR. UDEN: If Dr. Neill has a question related to that, I will hold my question. Mine is a proof.

DR. NEILL: Not a question, but a statement. I think that they have demonstrated the ability to self-monitor, to evaluate their response, and also to adhere to chronic therapy and that their demonstration is that the ability of consumers to do this is poor, and that that is comparable to what happens in the prescription environment. And I don't think that we're discussing whether or not it's been demonstrated, but rather, can't it be done better? And I think I know the answer to that. No, and not even doctors in the office do it better.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: Just a clarification. Again, what population are we talking about here? Each, total cholesterol of 200 to 240, LDL cholesterol of greater than 130, and what age? Greater than 50 for women and 40 for men? What's our population here again?

DR. NEILL: In the NDA, the target--, and

I'm not aware that the NDA can, that we're being asked to consider a different age than is in the NDA. I understand that the labeling may change and that the sponsor may want to resubmit for a different age range, but I've already answered two questions related to the target population. Men greater than 35 years and women greater than 45 years.

DR. JENKINS: That's the sponsor's proposed target populations. I think that's what you should base your answers on. If you think there's a different target population that you would answer differently, you will have the opportunity at the end to suggest things that could be done differently that you might feel more comfortable with.

CHAIRMAN BRASS: Other comments before we vote on this question? Okay. So the question is, has sponsor adequately demonstrated consumers can achieve such a clinical benefit in an OTC setting, including consideration of the following subpoints? All who feel the answer to that question is yes, please raise your hand.

(Hand vote taken)

DR. TITUS: Eight yesses.

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

(Hand vote taken)

DR. TITUS: Six noes.

CHAIRMAN BRASS: Any abstentions? Next is, are issues related to safety in the OTC setting. Assuming that pravastatin 10 mg. is deemed adequately safe when used for the proposed indications target population, has the sponsor presented adequate evidence that consumers will be able to use pravastatin 10 mg. safely in an OTC setting? Consider the following points: ability of consumer to identify adverse reactions, ability of consumers to monitor hepatic safety, need for and ability of the consumer to identify and avoid interacting drugs, likelihood of the use of pravastatin at higher than recommended doses, the ability of women who are pregnant or likely to become pregnant to avoid use, the need of the physician or the healthcare professional in the safe treatment, the capacity of the proposed label to direct consumers in the safe use. I would just open the discussion in addition to my relevant comments earlier to say that I do not believe that the liver toxicity issue is one of concern in this population, and I do not think that the issue of interacting drugs is nearly the issue it was for another drug we considered because the issue of, the route of

elimination for this compound, making inadvertent interactions less likely. I do remain concerned about potential pharmacodynamic interactions that may contribute to the rhabdomyolysis, but admittedly, that would be a relatively rare instance. Other comments or points for discussion? Dr. Johnson.

DR. JOHNSON: I think in general there's a lot of safety here and I think there are a couple of things in the package insert which I've already brought, or in the Drug Facts label which could be done to increase the safety of the use of this product, assuming that sort of at-risk patients use the product, but in general I agree that hepatoxicity is not a problem, drug interactions are not a problem, and rhabdo is probably in reality a very, very small problem.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: I think as far as safety's concerned is a very safe drug and actually the sponsor addressed the issues in the label that are required.

CHAIRMAN BRASS: Other comments? Yes, Dr. Molitch.

DR. MOLITCH: I think one of the concerns that I have is not specifically these aspects, but for the patient who has some great notion that they have

hypercholesterolemia, and will take one tablet a day of this, and will think that everything is hunky-dory about that, and in fact their cholesterol is 280, their LDL is 190, and they then don't seek adequate care for that. So to me, this has a safety aspect to it, too. It's not quite the same as what's listed here.

CHAIRMAN BRASS: No, I agree, and it is included there. The likelihood of use of pravastatin at, I'm sorry, no it says at higher. Yeah. But I agree with the point you've made and it is one that I remain concerned about and as I've indicated, because of the high use of the learned intermediary, I do not think we have the database with this NDA to make that assessment. Dr. Neill.

DR. NEILL: All the caveats about the patient education materials and their alterability after marketing aside, this proposed label does include a slightly different set of "see your doctor if", which includes some big groups that haven't been, smokers, for example. And so I am also more comfortable that the risk of under-treatment in a higher-risk population may be lower.

CHAIRMAN BRASS: Dr. Tamborlane.

DR. TAMBORLANE: I want to get back to

this, I think I tried to make this point before, that if you're concerned about that people aren't going to get proper treatment because they're not getting, you know, they have higher levels and stuff. We really were talking about that under four, not four, but, under four rather than this question. This question is really restricted to risk of the toxicity of the drug. So I just wondered whether everybody considered that when they voted the last vote. That the failure to get proper treatment at the higher values, et cetera, was really what we just voted on before.

CHAIRMAN BRASS: Dr. Molitch.

DR. MOLITCH: I actually just have one question, perhaps for the FDA, or somebody, I'm not sure whom. Do we have data on other drugs that are over-the-counter for what percentage of people who take those drugs actually read the warning labels or the labels that are inserted in these packages? Is it like somebody who reads the manual before trying to work a computer? Is it like one percent, or ten percent or 90 percent? Do we have any understanding of that information?

CHAIRMAN BRASS: This question has come up a lot before and the general answer is no. In my opinion, we do not know that. And similarly for the

package insert. Dr. Blewitt.

DR. BLEWITT: No, that's actually not true. There's been a lot of work done on that. CHPA has given a number of presentations on studies that they have done with regard to patients' ability to read the label and have shown excellent results. I don't have the numbers or anything like that, but I'm sure if you ever wanted that review-- oh, on cue.

CHAIRMAN BRASS: Could we have the back mic on please? Why don't you just come to the table and grab a mic?

DR. SOLLER: My name's Dr. Bill Soller. I'm Senior Vice President of Consumer Healthcare Products Association. There have been a number of studies that have been done over the years that have asked consumers, nationally representative studies, that have asked consumers whether they read the label the first time before using the product. And uniformly, the percentages are above 95 percent. One study 99 percent, the Heller Study. And I only would add to that and what Dr. Blewitt was saying, and that was that there have been many label comprehension studies that have been done on the switches since the Nonprescription Drug Advisory Committee started meeting in '92, and there were issues relating to

whether individuals read warnings before using these products. And uniformly, that was a very high priority issue for the committee. And the label comprehension studies that were done, plus the actual-use studies, were sufficient for the committee to vote in the affirmative for the switch of those products. So I think putting that, the practical experience together along with the Heller Studies and other things that have been done by this association and other associations around the world that show a very high percentage of individuals read the label before using the product the first time, gives a lot of confidence in these kinds of decisions.

CHAIRMAN BRASS: Yes.

DR. ELASHOFF: Apropos of that and the possibility that a number of young women will take it, although you might read it the first time, this is supposed to be taken chronically, you're not likely to read it over again the second and the third time, and by the time the person gets pregnant, they may well have forgotten about that sort of thing. It's an ingrained part of their life and may not look at it. So I'm concerned about the fact that there really isn't any that I would call real information about safety in pregnancy.

DR. DELAP: I'd like to, the reason we're having a little, it's hard to answer that question about the label use and practice in a general sense. I think Dr. Soller gave the best possible general answer to the question. We tend to focus much more on the issue at hand in a deliberation like this. How well does the current label communicate, and then the actual-use studies tend to tell us how well it communicates over time. And the best studies are the ones that Dr. Brass suggested in the conversation yesterday. And perhaps we've seen some of that today. The really wide open kind of study where you just let people use the product and you see who bought it, see how they used it, and you see what happened. That's the best kind of experience. It's not easy to do.

DR. GANLEY: I just want to add something. I'm not sure at the public meeting we had two weeks ago, I can't remember if it was National Consumers League that presented data, and it was actually a little less in a survey that they did of what people actually do in terms of reading the labeling. I think it was greater than 90 percent, and it was even, I think, less for a package insert. But I think more importantly it's not just reading it, but following the directions. And there is some data on the vaginal

antifungals where it asks people not to use it until they've at least been diagnosed with this condition previously by a physician. Yet I think approximately 40 percent of people who used them had never had it, or had not sought a physician's diagnosis before. So it's not just reading the label, but understanding it and following through with it.

CHAIRMAN BRASS: Other questions or comments about the safety in the OTC setting? If not, we'll proceed to a vote on that question. So again the question is, has the sponsor presented adequate evidence that consumers will be able to use pravastatin 10 mg. safely in an OTC setting? All who feel the answer to that question is yes, please raise your hand.

(Hand vote taken)

DR. TITUS: Eleven yesses.

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

(Hand vote taken)

DR. TITUS: Three noes.

CHAIRMAN BRASS: Any abstentions? We'll move on to the next question, which is approvability. Assuming that the sponsor has provided sufficient information to support the safety and effectiveness of

pravastatin 10 mg. for the proposed indication and the target population, has the sponsor-- Start all over again. The question now is, has the sponsor provided sufficient evidence that pravastatin 10 mg. can be used safely and effectively in an OTC setting? Open for discussion. Dr. Neill.

DR. NEILL: Should I note the exclusion of the phrase "in the target population"?

DR. KATZ: In the target population" should stay there.

CHAIRMAN BRASS: It's implicit, again, in terms of the--, that's correct. It's implicit in the OTC setting phrase. Comments or questions?

DR. SILVERSTEIN: The one thing that hasn't been done is the label has been changed so much that we don't really know the comprehension of the new label. I think that would need to be tested before, you know, it could be put on the market.

CHAIRMAN BRASS: Yes.

DR. GELATO: Also, I guess I would like clarification on what we mean by "effective now". Do we mean just the lowering of the cholesterol or do we mean that it has an associated benefit in terms of cardiovascular, or are we just looking at it, can lower--

CHAIRMAN BRASS: Well, this turns out to be the, this question we're about to vote on turns out to be the $64,000 question. And so, that's actually degrading it, I guess, in the current game show.

(Laughter)

CHAIRMAN BRASS: But, and so, as we did yesterday, the issue of effectiveness is as you define it for clinical approvability. So is there effectiveness when used in an OTC setting that in your mind using whatever effectiveness, so LDL and, as a surrogate, or anything else you want to use to assess that clinical effectiveness in making the overall risk-to-benefit. Because this is in fact the risk-to-benefit equation. So it now is implicitly that you're defining what that magnitude about benefit is, what the magnitude of that risk is, and is it favorable in the OTC setting and justify approval?

DR. JOHNSON: I have sort of a procedural question. If we vote yes on this, is that saying to the FDA, yes, everything is perfect in this package, and it's ready to go out the door. Or can there be yes with qualifications, or how's this go?

CHAIRMAN BRASS: Well, I'll let you correct me. But yes means approvability of the NDA as submitted with suggestions for post-approval studies.

If you feel that there are additional studies that are not in the NDA that are required to document the approvability, then the vote should be no, is that correct?

DR. KATZ: That's correct.

DR. DELAP: If I could just add on these questions. I mean, the votes are important but the discussion around the votes is at least as important, so you know, if you do decide to vote yes, but you think that something should be done before it's approved you can say that. Or if you want to vote no and say, but I would vote yes if you had this additional piece of information, you can do that, too. So we're going to look at what people say as well as how they vote.

DR. JOHNSON: Well, in that case, I'll say what I wanted to say.

(Laughter)

DR. JOHNSON: I mean, as it's written, age 35 and age 45, I guess my vote is no because I feel that that is too low a risk population to target. If the age was 40 and 50, that sort of changes my comfort level. If it's 45 and 55, it might change it even more. I also feel that it's not ready just to absolutely sign off on. I think there does need to be

a lot of work done on the label. There needs to be label comprehension studies. There may be could be a little bit more done to understand actual-use and sort of targeting on the people who do do this Rx-to-OTC switch and what behavior causes that and can that be prevented through education and those kind of things. So I, those are my concerns with the absolute package as it sits, you know, that we're looking at.

DR. GELATO: I would just like to say that I absolutely agree with that. I think given what we have in front of us it would be very difficult for me to just go ahead and say, oh yeah, go ahead with it. But I think with the caveats that Dr. Johnson has mentioned, because I think that this product comes really close to what you'd like to see, and I think with just a little bit more. At least that's my feeling. That you could, you know, put this right over the top. And I'd also like to say that I think that before, agreeing with Dr. Neill, that if somebody has a cholesterol of 280 and they decide to take this, I actually think that's a good thing. So, you know, if they're high-risk that's something else. But I think that, again, those patients or people may be at some point more likely to interact with a physician because of the fact that they are high-risk.

DR. DELAP: If I could just imply once more. I think, again, I think the construct that Dr. Brass had is a good one. I mean, the first part of the question is based on what you have in front of you today and then, what else do you need to persuade you? I think that's a good construct and we are interested in getting votes, so.

CHAIRMAN BRASS: Dr. Blewitt.

DR. BLEWITT: Yeah, it does, of course, permit you to approve this based upon additional work. So, you know, label comprehension study, the fact that you don't have one and you need one isn't a deal breaker. Now you can still say yes, but you know, you should do a few more things. In other words, just because some more work is needed doesn't mean that it's a no vote.

CHAIRMAN BRASS: Dr. Grady.

DR. GRADY: Well, it's kind of an odd situation, isn't it? I mean, we all voted that there's inadequate demonstration of benefit, but I think that in my mind the reason I voted that way was because I think that the, as the NDA's framed, the likely benefit is very small in the population targeted. On the other hand, the risk is very, very small. On the other hand, I think those two things

come much closer together the lower the targeted population gets. So I very much agree with Dr. Johnson. I think it's a targeted population at somewhat higher risk. And they're were lots of issues about the label. The label was changed too much for my comfort. I think there need to be better labeling studies. I think that it'd be nice to repeat a prevent-style study after, it this is improved. And then the final I worry about that we haven't brought up today that I tried to bring up yesterday is that I think there need to be efforts to convey risks better. I think it would be inappropriate, you know, for all, you know, 45 year old men with cholesterols of 239 to rush out and start taking a drug. But that's because people don't understand risk and they don't understand risk reduction, so I'd really like the company to take some responsibility for conveying risk and risk reduction in more understandable ways.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Well, it would be nice if a cholesterol of 240 would hurt a little and a 260 would hurt more so the patients will take the pills more often. You know, but it doesn't happen. Then the deal is, you know, my question from yesterday it remains the same. If we do that and patients will

take a 10 mg. pravastatin, are we going to give them a sense of security that does not exist, and therefore, they're not going to go for medical care. And on the other hand, if we do, you know, maybe those patients will benefit because they will never go to medical care. And for the sponsor, one of the things that it important is how to reach the populations that are high-risk. And you did not prove, at least to me today, that in your trial you reached those populations that really need to be reached.

CHAIRMAN BRASS: I just want to follow-up on that. Because as somebody who has voted no to questions four and five, and as somebody who has been here through, since the very first NDA for a lipid-lowering agent, I just want to make a couple of observations. First of all, I think we are much further along than we were in 1995. I think that today we're talking about an agent that everybody agrees has efficacy in lowering LDL and that that LDL lowering is a potential benefit. Additionally I think that we're dealing with an agent that there is increasing confidence can be used safely in the OTC environment because of the characteristics of the drug. And those are two very different things. My residual concerns are in the absence of data on a

couple of critical points, some of which you have eluded to, that I remain concerned that we do not have adequate data to assess the impact of exposing a general population, regardless of how the target population ends up getting refined and redefined, and I agree there's lots of opportunities to improve the risk-to-benefit ratio by doing so. But given the lack of demonstration of patients to self-select into that target population, that the impact on a truly general population without queues and queues to follow-up, et cetera, other than what's on the package, has simply not been demonstrated.

And I remain concerned about the hypothetical non-optimal therapy associated with that and I believe that it is possible to demonstrate that in the general population, the use would be associated with predicted benefit. I just don't think we have seen that data and I think there's the opportunity to get that data. The other point that I would make in terms of the generalized ability of this in terms of the OTC setting is the definition of the benefit and this is what Dr. Grady was eluding to, and I think even some of the constructs we saw in a preliminary fashion this afternoon if defined in a way that would allow an assessment by the agency to critically review

that and make an endorsement as to whether or not that is a logical risk benefit assessment in the target population would go a long way to reassuring us that that potential benefit will in fact be measurable and in a way that whatever population ends up getting exposed to it is justified to whatever risk that will represent. Dr. Johnson?

DR. JOHNSON: The sponsor might want to clarify this. We've, there's a lot of focus on the high-risk people who maybe go from Rx-to-OTC, but if a recall correctly, they also had data on people who in a sense got in to the system and remembering 20-something percent, but I don't know it's 20-something percent of what, so I'm wondering if that you can give us a little clarification, because there may be a tradeoff. We may have some percent that actually get into the system and get higher level of care than is available OTC and at the same time we lose some Rx into the OTC and maybe that balance becomes equal.

CHAIRMAN BRASS: I don't disagree with that except that we don't have the data. For example, this population which did include, I acknowledge, a sizable cohort that ended up on therapy one way or another represents a highly motivated population, 85 percent of whom have physicians, and there's no

natural history study of that population to see how many would have ended up on some form of therapy without the queues provided by the study. So I'm not disagreeing with, I'm not saying my hypothesis is right. All I'm saying is we do not have the data presented to us that allows us to make that assessment.

DR. FRIEDMAN: I think when you look at these people that come in, you know, somewhere between 15 and 30 percent of them are at their NCEP goal. We did have a cohort of 321 people and when they saw the study physician, that felt more appropriate to be on prescription therapy because of being at higher risk, either because of their levels or their risk factor profiles.

When we contacted those people, the 321 people at the end of the six months, we found that 46 percent of them had gone to see their personal physician, and none of these people of course were on therapy to begin with. At the end of the day, 29 percent of them had gone on to prescription therapy. So we actually did bring people into the medical system and on to appropriate care. We didn't look at the number of people that got dietary counseling and all that other, the other aspects to it.

CHAIRMAN BRASS: Because we're about to lose people to airplanes, I'm going to, unless there's an objection, ask for a vote on this question with an opportunity to continue the discussion on relative points and suggestions afterwards. Are you objecting? Because he's going to leave right now.

DR. KRENZELOK: I see that, but I'm objecting, even though I know he has to get to a plane at 3:30. It seems like the previous conversation we've had really illustrates that we shouldn't make this a yes or a no vote. That the vote should be an oral vote, you can say yes with reservation, with these types of enhancements or improvements, because it seems like it would be inappropriate to vote yes or no on the issues based on our conversation.

CHAIRMAN BRASS: Well, again, I will let the FDA tell me what they would like to hear, but I disagree. I think we have been presented with an FDA--, an NDA and asked for an opinion about that, and as Dr. Delap pointed out, the discussion actually matters more than the vote. They will do whatever they want anyway. And that taking into account our discussion, I think, will be much better integrated than taking into account oral vote.

DR. KATZ: That's correct. Actually we

would like to get an actual vote, and for those people who have to leave right after the vote is taken, if you can give your opinion before you walk out the door it would be appreciated if you want to have an additional comment, and then our discussion could continue.

DR. DELAP: And we are interested in a vote based on the information you have on the table before you and not on other information that you might get.

CHAIRMAN BRASS: Okay, you're at risk of losing votes, but go ahead, it's your choice.

DR. GILLIAM: I want to make a quick comment is, you can still vote yes even if you have reservations about other studies that need to be done. I mean it says here if yes, are there any other studies that are needed?

CHAIRMAN BRASS: Post-marketing. Post-approval studies. Post-approval studies, not—

DR. KATZ: Again, what I would like to request is that be, if there are any additional comments from sponsor, to do it after the vote because I would really like to get everybody's opinion before would have to leave for their, to catch their planes. Thank you.

CHAIRMAN BRASS: Okay. I won't reread the question. All who are in favor of the proposition, please raise your hand and vote yes.

(Hand vote taken)

DR. TITUS: Two yesses.

CHAIRMAN BRASS: All opposed, please raise your hand and vote no.

(Hand vote taken)

DR. TITUS: Twelve noes.

CHAIRMAN BRASS: Any abstentions? Dr. Gilliam, would you like to make any comments before you run to catch your plane?

DR. GILLIAM: Nothing other than what's been said earlier.

CHAIRMAN BRASS: Dr. Elashoff, you're next on the plane trip list. Any comments? Okay. Now, if you'd like to make some comments for the discussion or we, okay please. Why don't you go to that, I think this microphone's live.

DR. UDEN: Do you want to have sponsor before you have our feedback, Dr. Brass?

CHAIRMAN BRASS: Yes.

DR. UDEN: Okay.

CHAIRMAN BRASS: Now if you'd like to make, I want to-- You've intimidated him.

DR. UDEN: That's the first time I ever intimidated the President of a company.

CHAIRMAN BRASS: You've also promoted him.

DR. UDEN: I would have voted yes if in fact the labeling issues and population issues would have been taken care of. So I was voting actually as the question was on the NDA.

CHAIRMAN BRASS: Other comments? Yes, Dr. Neill.

DR. NEILL: I would encourage you to come back, and I would encourage you to consider other higher doses which might make it easier for you to show a clinically meaningful benefit in a population that may be slightly different, meeting a higher age and perhaps a different total cholesterol and LDL range for which benefit has already been shown in other studies. This seems to be a very safe drug meeting most of the safety considerations for OTC-ness. And given that I think the already existing approvals for the Rx drug make me want to consider why it has to stay that way. And those considerations seem to revolve more around the ability of the consumer to self-select, to monitor the condition pure of the other things that have already come up. I mean, this otherwise seems to be an approvable thing.

I would agree that the label issues need to be very clear, but I think that's implicit in the discussion about the target population. I wouldn't just change the target population, I would ask you to consider making my life easier by considering the dose as well.

CHAIRMAN BRASS: Dr. Molitch.

DR. MOLITCH: I was certainly for you in favor of empowering patients and physicians and having patients come to us with demands for medication when appropriate. And in fact if the studies, what were to happen with this is this were approved if it went exactly true to form that the patients had to see the physician at two months and couldn't get any further drug until they saw their physicians, were checked out, had laboratory testing, I would have no real problem with this. I'm concerned about patient, the inappropriate use of inappropriate patients that wouldn't be caught with a compulsory two-month look, or some sort of a look that had to be done at two months.

CHAIRMAN BRASS: Isn't that called prescription therapy? Dr. Tamborlane.

DR. TAMBORLANE: I think from the NDA point of view, I think I share some of your views. I thought the study design was really good bringing

people in. It was very undifferentiated. But there are too many queues with whence you are in the study to see what I would have considered a real use situation where a lot of people don't read the labels and don't go to the doctors. So I think that that kind of data would be what I would be looking for in further studies.

CHAIRMAN BRASS: Dr. Williams.

DR. WILLIAMS: My comment is usually the one from last meeting we had and that is about the aged population, those people who can't see the label. Many individuals who are in the aged population are using over-the-counter medications and they bring it in to the doctor's office, unbeknownst to the doctor. And I just wanted to see more data about their usage as well as the safety that's in their possible usage of the medication.

CHAIRMAN BRASS: Dr. Krenzelok.

DR. KRENZELOK: Well, I think a lot of people in this room probably have served as an expert witness before and have been in court and they always hold you to a reasonable degree of medical or toxicological or pharmacological reason and so on.

CHAIRMAN BRASS: Are you arguing against less than .05 health?

DR. KRENZELOK: We could look at that too. But if you look at 51 percent as being a reasonable of certainty, I think that they've really presented far beyond that 51 percent and I don't know that we could hold them to a hundred percent or anybody for that matter. So I'm a little bit disappointed that we've held them to such a high degree of responsibility and answerability and that's why I voted in favor of it.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: We're holding them to that high degree of responsibility within the target population that they defined. And the reason that I think that it's appropriate to do that in that target population is because I don't believe absent a huge undurable trial that a benefit will be shown given the competing co-morbidities that exist within that group. Could it? Yes. Will LDL's be lowered? Yes. Will it prevent those 35 year olds from dying in automobile accidents, AIDS, homicides, suicide, all the other things that befall them in some other respect, probably not. Making the differences of such a small size that the power and the numbers necessary to drive power to see those small differences would be huge. Which is why I think we've made comments about the target population, the age which are related to

changes in the label, and also perhaps, in my instance anyway, changes in the actual cholesterol and LDL levels.

CHAIRMAN BRASS: Dr. Johnson:

DR. JOHNSON: I want to make again clear, my vote was no. And the reason was not because I don't believe this is approvable, but not that it was approvable as it stands and again my major concern is age and I think you should determine the age not 40 and 45, not sort of picking things out of the air, but really looking at epidemiologic data or whatever you can as you did this afternoon. To really sort of well define your target population where you can derive the most benefit. And, as I made comments earlier, but since now it's sort of official after the vote, I think we need label comprehension studies and a few more things to understand actions and behaviors of the consumer population, but I congratulate you on some very nice studies that you did perform.

CHAIRMAN BRASS: Mr. Kreston.

MR. KRESTON: Thank you very much, Dr. Brass. First of all, I want to thank the committee for what I think were extraordinary deliberations today. It was a, feels to me that there has been tremendous progress made and we've gotten a lot

greater clarity on the issues. And one thing I'd like to request at this point since it feels like there was a lot of uncertainty relative to continuancy of approval versus definitive approval to ask for some direction from this committee right now that if we were to commit to changing the label and modify it to be the 40 year old and 50 year old population and also agree to do additional label comprehension if you could give us your sense of perspective on the approvability.

CHAIRMAN BRASS: Well, I think you're hearing that from the discussion, but I think any negotiation should be done between you and the agency based on the general discussion. And we'll try to bring out those points rather than trying to, is that fair?

DR. DELAP: That's fair, and I would add that we may choose to ask members of the advisory committee to participate in those discussions as well. We can legally ask for one or two members to participate without having a full-blown meeting again.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: I think one thing that will help greatly is if we can look back and see why the self-selection did not occur well. You know,

retrospectively, you may learn some things that may be important for us. Second, you know, why some of the special minorities did not stay in the program. That will help us, will help you. You know, but I agree with everybody else. We want to congratulate you because you presented good data, you tried very hard, you know, and you have a good safe product. Thank you very much.

CHAIRMAN BRASS: Dr. Silverstein.

DR. SILVERSTEIN: This is a question that I'm just curious about the answer to. Since this was an unusual population, at least compared to the patients I see, you know, most of the people had physicians, most of them saw them annually, the HMO sees them free, so the more you see them the better bargain you get. In general, are people who buy over-the-counter drugs a more compliant group, a more, are they different from the general population for instance?

DR. GANLEY: The general population buys over-the-counter drugs. So I think that probably goes hand-in-hand. I just want to make a few comments and it deals with some of the discussion we've had already and I totally agree with Dr. Neill. It would be a lot easier if we could identify a population that was, had

a little higher cholesterol and a little more risk and achieved some more benefit by individually titrating therapy to a higher dose. But I guess the one thing goes back some of Dr. Davidson's comments, and it really belonged, it really has to do with the paradigm that they've created where it brings the physician into the OTC setting. Are we to include a statement in the label, "Do not use if you don't have healthcare"? Or should the patient have some sense of high long the duration of therapy is prior to purchasing this product, where many of the studies that they're pointing to require several years of therapy so these curves starting to separate. Should that be conveyed to a person also before they initiate this type therapy? And I think the, the one issue that we got on yesterday was about dose titration and they've included the physician in this paradigm as to help along with that. But everything we've heard here is the physician's aren't doing it right. And if you don't educate the physicians that this is an appropriate population, then we're wasting our time.

CHAIRMAN BRASS: I think, again, extrapolating what I heard from the committee over actually the past two days, I think emphasis on the long-term treatment is something the committee would

endorse, as being as explicit as possible as early as possible. Is that fair? Dr. Neill?

DR. NEILL: With one admittedly minor caveat. I'm a young doctor and I remember telling patients that I have put on Propanolol, "You'll need to take this blood pressure medicine for the rest of your life", which of course, has been usurped by any number of other classes of medications, and my difficulty in requiring or asking about label instructions that say, "this is a life-long medication", and I'm talking specifically about those words, cannot be supported by any evidence even given our expectation that the cholesterol will need to be lowered, given our utter inability to tell what's going to happen three years down the road. In fact, the evidence says exactly the opposite. They're going to take it as long, and until, the next best thing comes along. That's what the evidence shows.

CHAIRMAN BRASS: I think that's right. I think those are all fair comments and I think that the specific syntax could get the point across without violating that construct. Other comments, questions, issues, random desires? If not, I will again-- Oh, see I knew I was too slow.

DR. JENKINS: No, I waited till you had no

other comments. I just wanted to thank the committee as well and also thank both of the sponsors. Because I think there has been a tremendous amount of learning that has occurred in the public hearings we had a couple of weeks ago and in the discussions we had yesterday and today, particularly about this issue of OTC cholesterol lowering. I think we at the table from the agency would have learned a lot and will be taking from your learnings and trying to use them as best we can.

CHAIRMAN BRASS: And I will add my appreciation to the members of the committee, the sponsor, and the FDA for their very excellent contributions. And this meeting is now adjourned.

(Whereupon the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Advisory Committee was concluded at 3:56 p.m.)

# C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE ENDOCRINOLOGIC AND METABOLIC ADVISORY COMMITTEE

Before: FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: FRIDAY, JULY 14, 2000

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis

**Look-See Concordance Report**

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UNIQUE WORDS: **3,541**
TOTAL OCCURANCES: **22,408**
NOISE WORDS: **385**
TOTAL WORDS IN FILE: **58,917**

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SINGLE FILE CONCORDANCE

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CASE SENSITIVE

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NOISE WORD LIST(S): **NOISE.NOI**

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INCLUDES ALL TEXT OCCURRENCES

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## – C –

## – D –

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## – H –

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## – K –

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