is greatly underestimated. And the reason it was underestimated, because these women were not given the opportunity to be enrolled. Of 11,065 who called the call center, we don't know how many were women of childbearing age. Of 1,924 subjects randomized to over-the-counter group, 720 purchased the drug. 553 consulted a physician within two months. And 499 of those ended up taking Pravachol. The last column represents a proportion of the subjects who did not qualify for the treatment. A total of 266 subjects, or 37 percent of those who purchased, did not qualify for the treatment as it says by the study physician based on the person's risk factors or the lipid profile. Of this 266 also comes from those who consulted a physician, so almost half of those who consulted a physician did not qualify for the treatment. I would like to remind you what qualification for the treatment was based on. It was different from the label use. The guidelines for treatment included only risk factors and LDL cholesterol value. It also had a goal specified for the treatment. This goal, less than 130 or less than 100 of 60 mg. per deciliter of LDL cholesterol was not listed on the label. And now then you're looking at the baseline lipid profile of qualified and treated

population as assessed by study physician. Mean LDL cholesterol value of 162 corresponds with total cholesterol of mean or median 245, showing that more than 50 percent of population who were assessed as qualified did not meet the label requirements for total cholesterol between 200 and 240. Looking at the behavior of the treated population in over-the-counter group, data show that 58 percent withdrew from the study. And most common reason for the draw was withdrawal by a physician. This 123 subjects withdrawn by the physician represents one-quarter of total treated population in the over-the-counter group, showing poor self-selection for the treatment. Discontinuation rate due to adverse events in over-the-counter group, even though not statistically significant was a little bit higher in over-the-counter group, eight percent versus five percent in Rx group. 53 subjects in the OTC treated group required titration to a higher dose, and this titration was done at assessment three which was eight weeks after the first visit to the doctor. Compliance in the PREDICT study even though it was not strictly monitored was assessed by a pill count and self-report and defined as 80 to 120 percent, and was not ideal in both groups. 54 percent in over-the-counter, and 65

percent in Rx group. Mean duration of the treatment was significantly short in over-the-counter group, 109 days versus 152 days in Rx group. I talked about consumer behavior, self-selection and compliance. Now I would like to touch on one other issue for Pravachol availability as nonprescription drug. Are consumers able to self-diagnose hypercholesterolemia? Subjects involved in PREDICT and OPTIONS study did not have to know their own cholesterol values. They had to go to the doctor, their own other physician, other study physician, to get their lipid profile tested. Now though the sponsor, a part of consumer behavior, attempted to test consumer cholesterol awareness and knowledge about cholesterol. And even though 96 percent enrolled in this study stated that they were very concerned about their health and their cholesterol, 74 percent answered that total cholesterol less than 200 represents a healthy level. The knowledge in certain demographic subpopulations and lower literacy was lower, but overall 74 percent said that less than 200 is a healthy level. However, knowledge about LDL cholesterol was significantly lower. Only 12 percent stated that LDL cholesterol less than 130 represents a healthy level. 80 percent had no idea what LDL cholesterol values should be.

And knowledge about HDL cholesterol was not tested in this study at all. And all of these values required for self-diagnosis and the treatment of hypercholesterolemia according to the current guidelines. Now I would like to talk about second actual use trials submitted to this NDA, which was called OPTIONS. The population targeted and enrolled in this study was not really representative of overall U.S. over-the-counter population. The study was restricted to certain geographical areas. Only six states participated in this study, and all of the participants had healthcare insurance and prescription drug coverage, and this may not be necessary the case in the real over-the-counter setting. The label used in these studies also were some comments. Criteria for the treatment on the label: you had a total cholesterol between 200 and 240, no LDL cholesterol was listed on this label, and a specific age, more than 35 for men and more than 55 years for women were stated on the label. Now the primary objective of the study was similar as in PREDICT to determine the proportion of subjects who have purchased Pravachol contact their own healthcare provider within two months of using medication. Out of 161,322 subjects targeted only by the mailer, 2,207 came to the

screening or the enrollment site, and 782 were enrolled into the study. Out of 782 who were enrolled, 404 purchased the Pravachol, 321 ended up taking it, and only 178 consulted a physician, their own healthcare provider within two months. This 178 subjects represents only 44 percent of total purchase population, meeting the primary objective of the study. Looking at the behavior of the treated population, you can see that only 49 percent continued on treatment for more than 56 days. And 51 percent withdrew from the study. The most common reason for withdrawal was noncompliance. Withdrawal by a physician was done in 20 cases in this study. This slide points out certain self-selection errors observed in this study. 24 percent of purchase population were not recommended Pravachol by their own healthcare provider, based on the risk factors or the cholesterol level. Now as you remember the label stated that this product is indicated for those whose total cholesterol was within 200 and 240. Median total cholesterol of purchase population at baseline was 235. Again, showing that almost 50 percent of those who purchased Pravachol did not meet the label requirements. As you may also recall, age for women stated on the label was 55 years or older. Now

looking at the demographics of purchase population, data show that 60 percent of women who purchased the drug were less than 55 years of age. And this self-selection error is very important for two reasons. First of all, these women less than 55 years old may not be at risk for coronary heart disease and will be taking the drug unnecessary. On the other hand, they may be of childbearing potential and therefore may be a safety risk for taking Pravachol during possible pregnancy. As I finish up my talk I would like to make few comments about the proposed label. It is unclear what population is being targeted for Pravachol nonprescription use. Proposed label initially submitted to this NDA stated that this product is indicated for those cholesterol values what I mentioned before. There was no age requirement for buying this product on the initial label. This label was modified and new label has been submitted by the sponsor just a few weeks before this advisory committee meeting. And it stated the same cholesterol values, however the age and the targeted population now is different. For men more than 35 years and for women more than 45 years of age. In conclusion based on the information I have given to you, the actual use trials showed low consumer understanding of specific

serum cholesterol values, especially LDL cholesterol value. It showed substantial number of self-selection errors, a high withdrawal rate and poor adherence to the therapy. Behavior of childbearing-age women was not addressed in these two trials and consumer understanding was not assessed about the goal, length of the therapy and titration to a higher dose. Targeted OTC population under current proposed label has not bee studied and therefore it's not clear how the data from the two actual use trials could support this new OTC target population. And on this note I would like to finish my talk and invite the next speaker, Dr. Karen Lechter. Thank you for your attention.

DR. LECHTER: I'm Karen Lechter with the Division of Drug Marketing, Advertising and Communications, and I'm going to be discussing the label comprehension study for Pravachol 10. The label in this study is different in the format from the one that was submitted with the NDA and its content varies somewhat from the NDA label. And in your agenda packets this morning, we have attached a copy of the study label and the NDA label for your reference, right behind the questions for the committee. I will be discussing the Pravachol study characteristics and

results, the potential for misuse, the tested label versus the NDA label, and conclusions. The Pravachol study had six open-ended and sixteen multiple choice questions for the label materials. Two questions were asked without the label present and there were no questions about the materials that would be inside the carton. For three questions, knowledge was assumed that should have been tested, making it easier to answer correctly. These were questions asking what should be done before use and after one year, and a question stating that people with some medical conditions should not use the product, asking who they were. These questions assumed that people knew they needed to do something before use and after one year, and that persons with certain medical conditions should not use the product. We don't know if the participants knew this information before the questions were asked. Results for the two open-ended questions were confounded because they were combined. What diseases preclude use, and what other diseases are mentioned on the label? The results should have been separated because some diseases mentioned on the label do not preclude use. Fortunately there were other questions asked in a different way about the three main medical conditions precluding use that give

us another opportunity to assess knowledge in this area. Due to the nature of the questions asked in this study, we do not know if consumers can apply the information to a variety of use situations. There were no questions involving the application of the information to hypothetical situations. If such scenario questions had been asked, biased questions could have been avoided and we could have been more comfortable about accepting the results for some of the questions. There were no questions about whether participants could use the product themselves, which would have been cross-checked against their medical history to determine if they answered correctly. The design of label comprehension study should begin with a set of communication objectives. I discussed these yesterday and I won't go into them again today. The sponsor said that the primary objective for this study was whether consumers understand they should see a doctor before using Pravachol 10. The secondary objectives begin with the product purpose: to lower cholesterol if it is between 200 and 240 after diet and exercise. There were no questions about diet and exercise. The secondary objectives also asked about those who should not use the product as listed in the second bullet here. The secondary objectives included

who should use the product including non-pregnant females age 55 or above, males age 35 or above, and people with total cholesterol of 200 to 240. The objectives included understanding the need for follow-up and that muscle pain should be reported to the doctor. The tested label requires application of several sections of the label at once: the use section giving total cholesterol and the ages for men and women, the warning section, and the "ask the doctor before use" section. The questions in this study did not test if consumers could apply all these requirements simultaneously or even a combination of some of these requirements. The "ask the doctor before use" section says: Ask the doctor if you smoke, have high blood pressure, or a family history of heart disease, or if total cholesterol is more than 240 and HDL is very low. It does not define very low HDL. There were no communication objectives or questions about this section. These are the characteristics of the participants. I think you've seen them already. 163 of the 612 participants were low-literacy. There were no differences in responses from the low-literacy group compared to the non-low-literate group based on t-tests at $p \leq .05$, with no adjustments for multiple comparisons. Despite the

shortcomings of some of the questions, we can conclude that certain concepts were well-understood. They include the following: the purpose for using the product, understood by 90-95 percent; 97 percent were able to list one of the three diseases precluding use; however, only 71 percent could name all three. In three multiple choice questions, they were asked to identify the three diseases that preclude use, and they did so at a rate of 88 to 90 percent. However, each of these three questions had either one other choice or none of the above choice, making them fairly simple questions. They understood at fairly high rates that they should not use the product if they are pregnant or drink three or more alcoholic beverages on most days. Additional concepts that were well-understood were that it was not for people with normal cholesterol, pregnant women or those with hepatitis, and they should see a doctor if they have unusual muscle pain or tenderness after use. Concepts that were not as well understood were the ages for men and women. The results were 77 to 80 percent. They moderately understood the fact that they must see a doctor after eight weeks; however, this question was multiple choice and two of the choices mentioned that something had to be done in eight weeks, perhaps

suggesting to participants that they do something at that time, which they may not have realized until they saw that question. Due to the wording of the questions, it is not clear that consumers understand that according to the label they must see a doctor before use, and to see a doctor for a cholesterol check after taking the product for one year. These questions suggested that there was something that needed to be done at certain points in time. One question about seeing the doctor before use was answered by 82 percent of participants. This question was asked without the label present. The other questions about seeing the doctor before use were asked with the label in view and resulted in higher scores. Based on the results, the tested label needed improvement in these areas, to clarify that persons taking erythromycin should not take the product. 65 percent got this one correct. In the NDA label, this warning was eliminated. It was deemed to be unnecessary. The label needed to be strengthened in the warning not to use Pravachol 10 if you are taking prescription cholesterol-lowering medicines. 73 percent understood this message. The NDA label says to ask a doctor or pharmacist if you take other cholesterol medicines. The label needed to be

strengthened in the message about cholesterol levels for which the product is appropriate. 76 percent were correct, but 17 percent said that it was appropriate for total cholesterol of 250 to 300. And the label should have been strengthened in the information about the ages of men and women to use the product. 77 percent were correct for men and 80 percent for women. The proposed NDA label does not have age limitations other than not to use it under age 18. But the later-submitted label says that the product is for men over 35 and women over 45. There were some important concepts that were not tested. There were no questions asking participants if they could use the product. We generally like to see these questions to determine if consumers can apply the label information to their own circumstances. If this question had been asked, the responses would have been checked against the medical information that the patients provided to determine if they responded correctly. However this question about self-use was not asked. There were no questions asked about applying multiple criteria for use or non-use at once. We don't know if consumers will understand they need to meet certain cholesterol levels, perhaps certain LDL levels, maybe age by sex requirements, and must not have a broad list of

conditions in order to be able to use the product appropriately. There were no questions asking these special circumstances on the label under which a doctor should be consulted before use, only the general advice to see a doctor before use was tested. Yet the label said to consult a doctor before use if you have the factors listed in the first bullet here. There were no questions to test understanding of treatment failure, success, or long-term benefits of use. There were no questions about the need for diet and exercise. We also do not know if consumers understand what a healthy cholesterol is from this study. The label tells them to continue taking Pravachol 10 if they have reached a healthy cholesterol level. It tells them they may need a prescription dose of Pravachol if they have not reached a healthy cholesterol level. No questions were asked about their understanding of healthy cholesterol. 17 percent said Pravachol 10 was appropriate for cholesterol of 250 to 300. This misunderstanding may be the basis for inappropriate use. In addition, we don't know whether consumers understand they must apply a combination of characteristics to use the product, based on total cholesterol, sex, age, and perhaps LDL. It is

possible that some will assume if they qualify under one characteristic, for example, total cholesterol, that they can use the product. There were substantial differences between the tested label and the label submitted with the NDA, and the subsequent label that we have not evaluated. These were differences in content and format, making them sufficiently different that the results of this label comprehension study may not apply to the NDA or later labels. I will point out the most significant differences between those two labels and, again, you may want to refer to the copies of those labels in your agenda packet. The tested label says at the top, "Before you start see your doctor to check cholesterol labels and discuss risk factors for heart disease." The NDA label has nothing at the top about seeing a doctor. The tested label has a pictogram of a doctor and a patient on the side of the use section with the statement, "See your doctor before use." The NDA label does not have a pictogram or a separate statement to see the doctor before use. The tested label says it is for cholesterol of 200 to 240. The NDA label says it is for cholesterol of 200 to 240 plus LDL greater than 130. The tested label was for men age 35 and over, women age 55 and over. The NDA label had no age

limitations in the use section, but did say, "Do not use if you are under age eighteen." And the recently submitted label said that it is for men age 35 and above, women age 45 and above. The LDL requirement that was not tested would be especially important to test to see if consumers could apply it simultaneously with the total cholesterol and other requirements for use and non-use. The tested label said, "Do not take the product with erythromycin." The NDA label has nothing about erythromycin. The tested label had a "do not use" section with six bullets. The NDA label has a "do not use" section with three bullets. The tested label had one "ask the doctor before use" section. Some of the do not use information from that label was moved in the NDA label to four sections about asking a doctor, pharmacist or a healthcare professional before use. It is significant that the appearance of the NDA label and the label submitted subsequently are quite different from the tested one. Formatting often has substantial effects on comprehension. The tested label was not in the Drug Facts format that we currently require for all NDA OTC products. It had four pictograms and a double column in the use section. The NDA label and subsequent label are in the Drug Facts format, and the NDA label

had two pictograms with no double columns. These format changes coupled with the content changes I described may affect comprehension. In conclusion, because the label was substantially modified in content and format after this label comprehension study, we do not know how well the new label would be understood by consumers. Participants appear to understand some important aspects of the label; however, some issues were moderately or poorly understood or the results were unclear. Further critical information was not tested. For the tested label significant numbers may not understand the age by sex requirements, when to see a doctor based on time, contraindicated medications, and the total cholesterol required for use. We have inadequate information whether consumers would understand the simultaneous requirements for use, whether they can apply the information to a variety of common situations, or if they can self-select appropriately to use the product. In summary, we cannot conclude from this study that consumers can understand the label sufficiently to use the product safely and effectively in an OTC setting.

CHAIRMAN BRASS: Thank you. At this time we'll open the format to questions to either sponsor

or the FDA from committee members. Dr. Blewitt.

DR. BLEWITT: I have a question of Dr. Lechter and that regards to Drug Facts format. It's my understanding that the whole industry is moving to the Drug Facts format because it has been determined that this is a format that is better understandable and better conveys the content of the label to the consumer. So it's my understanding that there's an assumption that the Drug Facts labeling is better than whatever existed before. Secondly, then, I would ask if there is an industry-wide move to, now that the industry is moving as a whole towards the Drug Facts format label, that if the industry is now testing all of these labels because they're in the new format.

DR. LECHTER: I don't know what the industry is doing. We did some testing before the regulation was finalized and did find that the Drug Facts format was an improvement over the other formats we had tested. I don't know what testing is currently being done by industry.

DR. BLEWITT: Well, it just leads to my question of should it really be necessary to test the revised label that's in the Drug Facts format when in fact this is a perceived improvement over what has existed before, and if there are no substitute changes

in the content of the label?

DR. LECHTER: Theoretically, if we're just taking the same content and moving it into the Drug Facts format, there should be no reason to retest. However, in this case there were substantial content changes. There was removal of some very prominent warnings to see a doctor before use, there was an addition of the LDL requirement, there was movement of materials to sections about--, from the "see your doctor" section into the "see your doctor, your pharmacist, your healthcare professional", and so that not only was the format changed, there were content changes as well that we think may affect comprehension.

CHAIRMAN BRASS: Dr. Krenzelok.

DR. BLEWITT: I'm sorry. If I could just follow. My question is whether--, I know the erythromycin was removed, but whether there has been removal or just whether it has just simply been moved. The "see your doctor" which was on the original label was now not appropriate because, it would not be appropriate in the Drug Facts label. So in fact you're moving that to ask a doctor before--, you're moving it down into the label, but's it the same question.

DR. LECHTER: I think the strength of the warning in the new label is greatly reduced from that of the tested label and the strength of the warning to see a doctor before use, and therefore may not come across to readers as clearly as the advice to see a doctor had been on the tested label.

CHAIRMAN BRASS: Please identify yourself.

DR. FRIEDMAN: Dr. Friedman. Dr. Lechter, that's correct. We did take the see your doctor warning from the top of the Drug Facts label because it is precluded by that regulation of having it there. We would be willing, we agree with you that it is very important to have it there and we would be very willing to work out some way that we could have it there. The other mentions about healthcare professionals such as pharmacists are also mandated by Drug Facts. We do not in any way want to dilute that message and would be very happy to work within the confines of those requirements to make that as strong as possible. But I think the number of messages to see your doctor are the same, and as I think Dr. Blewitt eluded to, things have been moved to conform with the requirements and certainly our intent is to have that message as strong as it can be—

DR. LECHTER: Right.

DR. FRIEDMAN: --as it can be within the regulations.

DR. LECHTER: They've been moved but they haven't been tested, so we don't know how well they come across.

CHAIRMAN BRASS: Dr. Krenzelok?

DR. KRENZELOK: Thank you. Safety is a very important aspect that we're asked to consider in reviewing these applications. I noted that the sponsor had approximately, I think it was sixteen reports of overdose, and I think it's well established that this is a fairly safe drug in overdose, certainly. But did either the agency or the sponsor acquire information from the American Association of Poison Control Centers and examine that data?

DR. FRIEDMAN: Yes we did. I can show you the slide if you like, but basically--, you'd like to see the slide? I think there are about 1600 reports, there are no deaths. There is one case reported of rhabdomyolysis in a man who had diabetic ketoacidosis, and there are three hepatic events which are listed only as increased transaminase levels. This is sort of the-, you know the highlights from the reports.

DR. KRENZELOK: The AAPCC data breaks it down by no effect, mild, moderate, major, fatality and

so on. Did you break it down just in tabular form at all just by those particular categories?

DR. FRIEDMAN: No, we didn't. I guess the overall look at that data was that there were no different conclusions from our database as well as the FDA FOI database, so we really just summarized it this way.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Three questions, quick questions. Do we test, does the agency test the label in Spanish? Have you seen a review of the Spanish label to be sure that it's proper Spanish?

DR. LECHTER: I'm not aware of any--, first of all, the agency does not do the testing. The sponsors do the testing.

DR. DAVIDSON: The review.

DR. LECHTER: I have not seen any submissions that show testing of the label in Spanish.

DR. DAVIDSON: Okay, thank you. The second question for Dr. Parks. 60 patients with normal cholesterol, you know, were not allowed in this study, but do we really know what the normal lipids for those 60 patients were? Because, you know, if it's physicians making the decisions, it may be lipids that should be treated.

DR. PARKS: The reason listed as normal cholesterol was obtained directly off of forms where the physician checks it off, so we don't have a corresponding--, or I didn't see a corresponding level with that reason normal cholesterol. With regards to cholesterol in that population, the data I reviewed were of the entire 285 in that qualified and treated subgroup in the OTC group. I did not look at the individual 60 in the normal population.

DR. DAVIDSON: Okay.

DR. FRIEDMAN: Could I clarify that? We actually did look at that 60.

DR. DAVIDSON: Okay.

DR. FRIEDMAN: And about 50 percent of those people had LDL cholesterols above 130 mg. per deciliter and about half of them had levels below.

DR. DAVIDSON: Fifty percent?

DR. FRIEDMAN: Yes, about that.

DR. DAVIDSON: Over 130?

DR. FRIEDMAN: Yes.

DR. DAVIDSON: Thank you. And then, for Dr. Shetty, you have 200 patients, close, that did not qualify for the study. Could you tell us why they did not qualify?

DR. SHETTY: I don't have all the exact

numbers, but based on the risk factors and the lipid profile that was based on those specific guidelines used in the PREDICT study. Either LDL was too high or too low, or the risk factors were more than two.

DR. DAVIDSON: Thank you.

DR. SILVERSTEIN: My question's for Dr. Friedman. I don't know how to do this.

(Laughter)

DR. SILVERSTEIN: I'm moving this. Okay. As you said appropriately you had, in the PREDICT study, a very motivated population and in the absent study you had a population that had ready access to healthcare. How many of those--, I somehow missed it in going through the two books--, how many of those people who enrolled in this study knew their total cholesterol and HDL cholesterol levels before enrolling?

DR. FRIEDMAN: In terms of the enrolled population, about high 70's knew their total cholesterol before enrolling. Again, there was no education, they didn't have their levels at the enrolled site. They only had their levels in PREDICT if they saw the doctor. So of the enrolled population, about 75 percent of people knew their total cholesterol. Of the people who actually

purchased the product, it rolls to about 80 percent or so. In terms of LDL cholesterol knowledge, that was really much less and I think that does show that knowledge of LDL cholesterol is really, you know, we haven't gotten that message out to the public. I think that we hope that as we put that on the label, people will start to inquire, and the purpose there is really that they need to see their doctor or talk to their doctor about their full lipid profile.

DR. SILVERSTEIN: Could I ask a second question? And that was my concern, too, about appropriateness of patient selection. The second question has to do with the fact that this is a chronic disease and not static, and to really somehow get the message across to the patients that because of that their dose may change over time. And do you have, as part of your education program?

DR. FRIEDMAN: Yes. Certainly the patient educational booklet that is enclosed in the starter kit talks specifically about that. We thought it was important to talk about all cardiovascular risk factors and how they should all be modified and as well, I think it's important that we saw in the PREDICT study without the prompts that these people do go back and see their doctor annually or talk to their

doctor after they stop medication. So, and some of them as was mentioned got titrated up appropriately as, you know, their profile may have changed over the course of time.

CHAIRMAN BRASS: Dr. Molitch.

DR. MOLITCH: I'd certainly like to applaud the sponsor for all the educational materials that they're planning for the patients in this over-the-counter portion of treatment. I would hope that those materials are also provided to all the patients who are getting the same medication by prescription, whether this is approved for over-the-counter or not, because it certainly would be beneficial for those patients. I have a couple of philosophical questions that perhaps the sponsor could answer. I agree that lowering cholesterol perhaps in this patient population is important. And how about--, what would be the difference in doing the approach that you're taking here versus perhaps trying to educate physicians in treating these patients and prescribing the drug at these lowered cholesterol levels? So that's one question. And then the second, and this is partially borne out by the survey that was reported by you, that perhaps the over-the-counter designation of this drug in fact denigrates hypercholesterolemia in

patients' eyes as a serious problem. Because you can get this drug over-the-counter, it's not such an important problem, and so that they may not take it as seriously. Perhaps you can address those two questions.

DR. FRIEDMAN: I think certainly as a company, Bristol-Meyers Squibb is absolutely committed to ongoing education in the medical and lay community. As you know we put forward huge efforts, as does the rest of the industry, government in academia. I think really one of the reasons we are here today is that it appears that that may not be the only complete approach, or perhaps another approach, an additional approach, may enhance those efforts. And what we're looking for here is an approach to a lower-risk population. You know right now the current efforts are really focused on secondary prevention people. Very, very few people in primary prevention are being targeted either by the major organizations or industry, and you know, I think that here's a group of people that we can add to the people that are currently being targeted and add to being treated appropriately. It is a lower-risk population. It's not a population without risk. But as Dr. Cohen showed earlier, there is vast, vast under-treatment of

this population. Certainly less than ten percent of them are being treated now.

DR. MOLITCH: But why couldn't that be addressed by educating physicians to treat them?

DR. FRIEDMAN: Well, perhaps I can call on some of my colleagues here who have been involved in development of the guidelines. Certainly those programs have been well under way. The results of the megastatin trials have been known now for, you know, almost a decade. And, you know, we still seem to have this problem. There certainly is huge efforts going on to educating physicians. And maybe I could ask Dr. Brown from, as a perspective who did work on the guidelines to address that.

DR. BROWN: Yes. In 1986 we met in this very room to begin the NCEP, and I am one of the old guys who actually worked on that original panel that created part of this problem. We, in 1986, the first Pravachol studies were just getting underway. The report that we wrote came out in 1987, the year that Lovostatin was released on the market. That was eight years before we had the first clinical trial that showed prevention of vascular disease with a statin, that was 1994. So what we were working with here are principles that have become dogma that would horrify

me because that was certainly not our intention to create dogma that we call the NCEP. My feeling is that it's time for us to reexamine the thought that was made, the principles that were laid down 14 years ago. And it's time for us to do something new because what we did made tremendous progress but we're reaching a plateau in its impact. If we had everyone in America follow the NCEP guidelines with regard to those above 240, we would still have in this country the number one cause of death as cardiovascular disease. It would still outrank cancer as a cause of death. These people would just move into this 240 down to 200 group where we would still have a very high incidence of coronary events. So this is a very serious problem. It is not low cholesterol that we're dealing with here. And I would say, I think David Orloff said this very well about the agency's approach to over-the-counter drugs, if I might digress a moment. And that is that there is a tradition that the agency has adopted which has served them well in dealing with over-the-counter drugs, but I would submit to you that tradition, when dealing with a recalcitrant problem that just won't go away, maybe it's time to do something that's nontraditional, to think about a new approach to this problem. And I

think the learned intermediary that we depend upon greatly to support that tradition should not only be viewed to be the doctor. There are many other learned intermediaries that the doctor needs to deal with this problem. We need people who are educational specialists. We need other people who can get involved in this problem if the over-the-counter measures were taken. They would be incorporated into this. It would be a natural way to bring in a whole series of other individuals to help us as physicians deal with the problem that continues, and will continue to be during my lifetime and your lifetime, the number one cause of death in America. And so my plea to you is to think outside the box a little bit and help us doctors deal with this problem. I think the approach that this company has taken is absolutely on target. It is not to remove cholesterol treatment from the doctor's domain, but it's to help the physician deal with the problem that he is having, or she is having, a tremendous struggle with and is not doing very well with.

DR. MOLITCH: I'm sorry. Neither speaker has addressed the question that I asked because I agree that perhaps we want to lower those guidelines for therapy. I'm not disagreeing with that at all.

I'm just asking for the approach to that lowered guideline, whether that should be through the physician being educated to have a lower guideline for recommending therapy versus this coming up through the patient who is doing this with, perhaps, a little less guidance in this sort of borderline situation.

DR. BROWN: I thought I was answering the question. Let me clarify why I thought I was answering it. The guidelines are written for us to use the tools that we currently have appropriately. And what we're asking for here is a new tool so that new guidelines can be written. The physician if followed the guidelines would not address this issue. I don't care how well educated they are. We've made tremendous efforts over the years. I must have 10,000 cholesterol talks over the last 15 years trying to educate physicians. The issue, I think now, is to again, think outside the box and get the physician some help here, you know. And that will help educate those doctors who are somewhat less educable. And so we need to do something new. No, just more speeches to doctors is not going to answer the question.

DR. FRIEDMAN: Yes. I also I think want to answer this from the data that we have from PREDICT and OPTIONS. You know, we're not talking just about

getting people to treat to lower levels. Even if you look, and I think the information was in the briefing book we provided to you, if you look at the people who came into the PREDICT and OPTIONS trials who had access to healthcare, who saw their doctors every year, very few of them were actually at their NCEP, the current NCEP goals. If you look at the people with heart disease, it's about 10 or 15 percent, and in the other populations it's not much better. So I think if you, you know, I think that's actually exactly the point here that, you know, here is almost the best that we can do and, you know, this was very consistent in both studies in a population that maybe is, you know, even a little bit better than overall. So I don't think it's a question of bringing the guidelines down. Even with the current guidelines, the under-treatment is enormous and we've documented that in our studies.

I think the other question you raised about the denigration of cholesterol lowering to sort of a frivolous undertaking, you know, I think everyone knows they need to lower their cholesterol and sort of a question of how they're going to do it. I think that we saw that the people here are really committed to lowering cholesterol. I think they do take it

seriously for those of you who heard the results of the National Consumer League study and independent study when they asked people if they would just start an OTC statin, what they'd do, and the vast majority, again confirming our data, said that they would speak to their doctor. I think these people do take it seriously. It's a very disease prevention-minded population. If you look, for instance, you know, what these people are doing. The postmenopausal women who came into this program, 50 percent of them were taking hormone replacement therapy, much higher than the average. Look at the incidents of smoking in this population, ten percent compared to 20 percent on average. These people want to do something. And, you know, I think there is some kind of failing here that maybe this kind of program can address.

CHAIRMAN BRASS: I just want to follow-up on Dr. Molitch's point because it really sets up a central dilemma. I have a lot of specific points, but I can't get over this really central dilemma in my mind. In both of your studies which have some really outstanding features, incidentally, which I hope we have a chance to talk about later, the primary outcome was go see your doctor. And I have this circular paradox in your mind where we're all acknowledging the

central role of the learned intermediary, whether it's a pharmacist, physician or whatever, in this process, and yet at the same time considering an OTC NDA. And not at all am I the only one. But I'm having a lot of trouble getting past this. We say the doctor is critical, so let's make it available without the doctor. I can't resolve that paradox.

DR. FRIEDMAN: I think we certainly say that the doctor is very important. And I guess the question really is, you're right, is OTC diametrically opposed to doctor involvement? And I think we see from our studies that it isn't. Here are people who do see doctors. Twice as many of them are taking OTCs to lower their cholesterol as taking prescription therapies. And you know, we also do have OTC recommendations that we do have in our practice. You know, we recommend certainly diet, we recommend dietary adjuncts to lower cholesterol. And there are other OTC therapies, certainly aspirin, for secondary prevention, is one of the great successes. So you know, I think that perhaps the thought that an OTC approach is antithetical to a doctor approach may be not borne out by the data.

CHAIRMAN BRASS: Dr. Grady.

DR. GRADY: I'd also like to compliment

the sponsor on the PREDICT study and I think that the results of it are really kind of crucial, at least to me, to understand whether this is a good OTC product. But the interpretation of the PREDICT results by the agency and by the sponsor seems like they're quite different. So I have some questions that I'm hoping that the two of you together could answer. And it seems to me that one important one was that the randomized groups were the 1,900 patients who were randomized either to OTC or to prescription. But I guess as I'm understanding it you were not able to measure cholesterol at the end of the study period in this whole, in the whole 3,800, is that correct?

DR. FRIEDMAN: That's correct. You know, I think the importance here, the difference between PREDICT and a randomized control trial, is that what we call randomize was randomizing to environments. And then it was really, I guess it was almost when they saw the doctor that that's when we could screen because, you know, there's no screening when you go and buy an OTC product. And that's really where the standardization, if you will, for certain parameters occurred. In looking at cholesterol reduction or whatever in one environment or another, that's I guess where we've done the usual screening criteria that is

done in a usual controlled trial. The doctor has sort of done that and leveled the playing field for those evaluations.

DR. GRADY: But the 2,400 who saw a physician were not, that group was really not followed up at the end either, right? Is that correct in terms of measuring cholesterol?

DR. FRIEDMAN: No, not all for measuring cholesterol, because again, it was a real world situation. For those that we could, we did measure cholesterol. But I think what we wanted to do, the objective was to see whether cholesterol reduction in one environment, the current prescription one versus the cholesterol reduction in an OTC environment, for people for whom ultimately it was appropriate would be the same. Because certainly in the OTC environment people could stop taking it, you know, over a period of time, a year. You know, no one had to go back, and in fact they didn't get their medication at the doctor's office. They had to go specifically back to the retail site.

DR. GRADY: So the only group whose cholesterol were measured were the ones who were qualified and treated in both groups?

DR. FRIEDMAN: The cholesterols were

measured initially in everyone who consulted.

DR. GRADY: At the end, though.

DR. FRIEDMAN: At the end, you know, again we had--, I think that the follow-up was not adequate enough to answer that. I think what you're looking at is a--, in those groups of everyone who came in--, I mean I think that the importance is that everyone who came into the OTC group, or the prescription group, not all those people, they had lots of places to go. They were randomized to the environment. It's really as if you were randomized to, you know, go to a supermarket to buy your drug versus being randomized to go to a pharmacy. But it doesn't mean that the drug is right for you. You just came in, you were interested in the ad, and then a lot of things could happen.

DR. GRADY: I understand that, but it just makes it not a randomized comparison and I know it's difficult to do. I think there is more, a better randomized comparison of who actually did see a doctor and got consulted.

DR. FRIEDMAN: Perhaps just from that perspective and the issue--, because I know this is a big issue in a consumer trial, the issue of randomization and when to make appropriate

comparisons, and perhaps I could ask Dr. Cook to comment on that from a statistical point of view.

DR. COOK: Yes, my name's Gary Cook. I'm a statistical consultant to Bristol-Meyers. The randomization basically created two groups at the time of randomization, but each of those groups was going to go down a different path. If a patient was in the Rx group, then they had to make the decision to actually see a physician for a prescription and then to decide if they then qualified and got a prescription, whether they would follow through with that. It does turn out that, my understanding is that there were 405 patients who qualified and consulted with the physician and there were 50 of them who basically didn't fill the prescription. So not necessarily all of the patients who qualified and were thought to need a prescription on the Rx side actually filled a prescription and followed through. 350 of them did. Now on the OTC side, we had something like 499 patients who were treated, but not all of those patients saw the doctor. We basically had 90 percent of the patients ultimately saw a doctor, but it was a somewhat smaller percentage who saw the doctor initially. Now when they saw the doctor several things could happen, and most of those were good

things. They could be told they had a normal cholesterol which they didn't know before ever seeing the doctor or even coming in contact with the OTC option. So these were patients who in some sense were out of the system, but because they chose to purchase the OTC product and then go see the doctor, they found out they had a normal cholesterol and they were fine, and there were about 60 such patients who did that. That's a correct decision. That's actually a success for the OTC product. And then there were another 30 some patients who, when they saw the doctor on the OTC side, they were actually found to have much higher cholesterol than would be appropriate for OTC, and so they got put on a prescription for that particular product. And that's a correct decision for them as well. The right thing happened to them because they purchased the OTC product and then were ultimately given a prescription for what was actually the right thing. Some of them were told that they already had a prescription, and that was the correct thing in that they didn't need the OTC product. So there were about 120 some patients who when they actually saw the physician they found that it was inappropriate for them to use the OTC product, but they didn't know that until they actually saw the physician. But because

this is a physician-assisted use of an OTC product, they eventually did find out the right thing. Now the groups do not become actually comparable until the doctor has seen them on both sides and now you basically have patients who have both qualified and treated. And at that point you can see what happens to their cholesterol. Now the real question here is not necessarily whether or not you have a formal randomized comparison at the level at which you have qualified and then treated, because at that particular point you have groups that in some sense have gone through somewhat different pathways to get where they are. And so you can't necessarily on the basis of randomization alone as in a classical clinical trial compare the reduction in cholesterol of those groups with one another. The only question that you can really directly ask is, "Is the reduction that these individuals had consistent with what you might expect them to have on the basis of what was seen in previous randomized trials and is that reduction greater than what the reduction might have been had those patients been hypothetically randomly assigned to placebo?" Now my understanding from placebo-controlled trials is that when patients are randomly assigned to placebo, they either have very little change or cholesterol

slightly increases, or at most it decreases by two or three percent. Now in these patients, there was a decrease of approximately 18 percent, which is consistent with what would be expected from the randomized clinical trials. So each of the two groups performed as expected, and each of the two groups performed better than what a hypothetical placebo would, and in that sense each of the two groups showed comparable efficacy. It's a different line of reasoning than what a classical randomized trial would do, but for this particular type of care, one doesn't really need a classical clinical trial to show that Pravachol at a dose of 10 mg. reduces cholesterol. That's already been established. All that was needed was to see that in each of these two arms that qualified for treatment and that used treatment, that the reductions that you got were consistent with what you'd expect. But it's not a classical randomized trial. It was never intended to be that.

DR. PARKS: I just want to add that I do agree with you that I think that there are some really nice unique features about PREDICT and one of them is that the eligibility criteria, the list of exclusion criteria were not very extensive, and so when the study was opened up to the public here, or the

consumer, there was a lot of capture of a lot of people and we were able to see who was going to use this product without a physician. I think what becomes complicated is when they actually went in to see the physician at, in the OTC group it would be the second visit. And at that point those treatment guidelines were applied, the intervention started by the physician in that setting there. And then when they limited the lipid response evaluation to just that group of the qualified and treated, that's an enriched population in the OTC group. As I mentioned, there are about half of them in the OTC group that took the medication and we don't know anything about them. You really want to know in the real world use of this product, of the people who are not going to meet this protocol-defined qualified and treated subgroup, how are they going to actually do and the agency doesn't really know because those data were not available.

DR. FRIEDMAN: I think just for clarification, we do know of the people who took the product, who purchased and took the product, we know about all of them except for 72 who didn't consult a doctor, so we don't know their lipid levels. We know they're self-reported risk factor profile and what

they had done in the past. And I think, you know, as you look sort of in a broad picture of first of all that these people did see a doctor, so that's good, and then if you also look as to why the doctor said this wasn't appropriate, for the vast majority would have gotten benefit, either their levels were high and they weren't doing anything about it anyway, so then it's philosophical. Is it better to get a 20 percent reduction in LDL cholesterol when it would have been best to get a 30 percent, but now they're not getting anything. For the vast majority of them, they needed some cholesterol reduction. And I, sort of in my mind, is the big picture. That's sort of the question.

CHAIRMAN BRASS: Dr. DeLap.

DR. DELAP: Yes. There is one other aspect of this study that I'd just like to note. I think it was a very nice study in many respects and it answered a lot of interesting questions, but of course you can never totally mimic the OTC experience in a study. One of the things we've been talking about is how many people came back to see the doctor and how much good advice they got. Well, as I understand, the design of the study was such that if you wanted to continue on the product, you didn't have to come back

and see the doctor. So what we're not really capturing here is, without that incentive that you had to come back and see the doctor depending on the product, if you could just go to Wal-Mart and buy it, would they still have come back?

DR. FRIEDMAN: Well, we did capture it indirectly. People were--, you're right. There was an IRB recommendation that we do not let people go on and use the product for more than two months if they had not seen the doctor. So if you look at the people, the 72 people that we classified as not seeing the doctor, there is a 72--, 62 rather, never did see the doctor. Ten people attempted to go on and purchase more medication without seeing the doctor. We classified them as never seeing the doctor because they--, so we know that of this cohort who purchased medication, 720, that there were only 10 who decided to go on and try to repurchase, keep going with this, without seeing the doctor after two months. So we actually do have that information. We can't say anything more about them because we intervened. We said that they had to see the doctor. But we actually classified them as not seeing the doctor. So I think we do have some information from the study.

CHAIRMAN BRASS: Dr. Lukert.

DR. LUKERT: Did patients have to pay out of their own pocket to see either their own doctor or the study doctor?

DR. FRIEDMAN: People paid out of pocket to purchase medication. They were ultimately reimbursed at the end of the study, but they didn't know that during the study. The study physician visits were free. Many people did see their own doctor which, you know, was part of, and they did that as part of their normal care. So if they had coverage they got it, if they didn't, you know, they did as they normally would in their lives. But the specific study physician visits were free of charge. And I think we've talked about this before, we struck a balance of making people pay for medication in a study, but we did let people see the study doctor for free. I think it's important, though, that for many people this was an inconvenience because they already had their own doctor. So they actually made a specific visit to a study doctor. Maybe this is even showing how motivated people are to see a doctor because 80 percent of these people already have a doctor that they're used to seeing, but they actually made, you know, went out of their way to see the study doctor.

DR. SHETTY: I would like to point out that the OTC group had the access for the medication only for two months. Their supply was given only for two months and they had to go to the doctor in case they wanted to continue in treatment, so that forced them to go to the doctor within two months.

CHAIRMAN BRASS: Dr. Lukert, now when you say you're going to change the subject, it will be about cholesterol? Okay.

(Laughter)

DR. GRADY: Could we stick with PREDICT? I'm sorry I set off that whole thing. I just had a couple of very specific numbers questions about PREDICT. Could we do those first? Is that all right? Well, here's the other puzzling thing to me and that is, this issue of the 499 who were treated in the over-the-counter group. So these were the ones who were qualified and actually got treated. The FDA staff stated that 266 of those were really unqualified for treatment and Dr. Davidson, I think, asked why they were unqualified. Now, that was unqualified based on the actual guidelines of PREDICT? Or is that unqualified based on some physician's recommendation?

DR. PARKS: I just want to clarify that of the 499 who were treated, not all of them were

qualified. These are just individuals—

DR. GRADY: Well, those are the numbers I'm trying to get. How many were qualified and how many were unqualified, and why?

DR. PARKS: Okay. Of the 499 who took any amount of medication, 315 were qualified for treatment. And of those 315, 285 were actually treated. Now with respect to qualification, it was based upon that set of treatment guidelines I told you, and it was based on whether or not they had a baseline, if there was no evidence of diabetes or cardiovascular risk factor or established heart disease, or two or more risk factors, then they had to have a particular LDL to actually get started on the treatment. So if we look at—

DR. GRADY: Okay, but they were unqualified based on the sort of outline of the OTC program.

DR. PARKS: Based on the treatment guideline, exactly.

DR. GRADY: Okay, but 90 percent of those who were qualified did get treated?

DR. PARKS: Yes. 285, about 285 of the qualified got treated.

DR. GRADY: Okay. Thank you. And

finally, you said that a quarter of persons who took the OTC medication were subsequently recommended by a physician to stop. Is that the same group that we're talking about, who were the unqualified group?

DR. PARKS: It was a quarter out of the 499. So yes, they would be part of the unqualified group.

DR. GRADY: Okay. That's not an additional group that subsequently recommended to stop.

DR. PARKS: No, it's part of that--, yes it's part of that 499.

DR. GRADY: Okay, thanks.

DR. COOK: Gary Cook here. But the reason they were recommended to stop was because for many of them when they saw the physician, they learned that they had normal cholesterol. So that was the right thing. Or they learned that they actually should be on an Rx dose, which also was the right thing. And if they had not actually participated in the OTC environment, they would not have learned either of those is the right thing.

DR. LUKERT: I want to go back to the basic question about if we're trying to solve an educational problem with an option that indirectly

will bring about education. It seems to me that what we said that the major problem is that a lot of people who are seeing doctors regularly with cholesterol levels within the range that we're trying to address with the OTC are not being treated because the current guidelines don't indicate treatment for those levels of cholesterol. And it seems to me that the major problem is that we have to rewrite the guidelines, educate physicians and educate the public to be advocates for this position. But we're trying to avoid that issue. We're not trying to avoid it, we think that issue's going to be difficult to solve so we plan to solve it by offering yet another option for the person with an over-the-counter preparation that may or may not be effective. We've already said that the people have difficulty identifying who should be eligible, even when they're given very specific guidelines. The consumer has difficulty with that. And we're going to have people who are going to be taking a drug in a sub-optimal way. They're not going to be titrated to the target. So it's just going to be another choice out there among all the other supplements and choices that they have that may actually delay them from getting effective treatment. And I don't think we're solving the problem of getting

yet another possibly ineffective option instead of addressing with massive attempts to educate both the public and the physicians.

DR. FRIEDMAN: Can I just clarify? I think we're talking about two different issues here. One is that--, one there's expanded access to a lower risk population. But the other is the issue that even within the current guidelines, people are not being treated according to those guidelines. Yeah, so, but this is not--, and just bringing the guidelines down, though, are not going to answer that.

DR. LUKERT: No, I think it has to be, you know, the guidelines certainly have to be something that you can defend so that the physician isn't getting confused by, you know, the guidelines are telling us one thing, and then by some other people being told something else. So we have to be consistent. And then certainly we have to make patients advocates for themselves and doctors, we have to keep pounding away at this problem making doctors address the problem.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: I have a couple of questions, and some of these are open-ended and some of them are close-ended, trying to follow good types of questions.

Did the sponsor consult with the FDA prior to the design of PREDICT and OPTIONS?

DR. FRIEDMAN: The design of PREDICT and OPTIONS was the result of previous meetings that we've had with these committees for considering lipid-lowering therapy. When we developed the OTC Pravachol program, the FDA had a policy in place that they were not discussing protocol designs about this issue because of the guidance to industry.

DR. UDEN: My second question actually refers to the new proposed label submitted with the NDA. I didn't hear any rationale presented why the age restrictions were eliminated and now it's only over 18, it's only restricted under 18 years of age.

DR. FRIEDMAN: The proposed label--, you know, I think our intent and certainly the people that you see who are interested in this are generally middle-aged population. We saw very few people under the age of 35 and very few older people who were interested. And that was always our intent, how to capture that ideally, we have been working on. Actually the label that we have submitted is for men above the age of 35 and for women above the age of 45, yes. And I'm not sure if that's actually the label that you have in front of you. If not, we'd be happy

to give you the proposed label that has been submitted recently.

DR. UDEN: Okay, given that label, then I want to ask a question of Dr. Shetty. In the OPTIONS trial, you stated that 59.8 percent of women less than 55 years selected the drug. How many of those women were less than 45 years who selected the drug?

DR. FRIEDMAN: I can show you that if I can—

DR. SHETTY: Less than 35 and above 35.

DR. FRIEDMAN: This is the age distribution in OPTIONS, and you can see that of course most people, this is PREDICT and OPTIONS. So most people did fall above the age of 55. And then you know, the majority of people were then between 45 and 55. And if I could just follow-up actually, you know, not only with age, one thing to point out that the mean age of menopause in United States women is 51 and a half. And then the next slide, actually, goes on to their cardiovascular risk and how many of these women below the age of 55 had total cholesterol levels greater than 200. Of the purchasers you can see that over 90 percent in PREDICT and OPTIONS of the women below the age of 55 who purchased drug in fact had total cholesterols greater than 200.

DR. UDEN: Thank you.

CHAIRMAN BRASS: Dr. Tamborlane.

DR. TAMBORLANE: I was waiting for somebody to raise the HDL question, but I guess I have to do it. I suppose I direct this to Dr. Cohen. Specifically if you want to show slide 2-9 from your presentation. I think the question that has come up is what is, you know, how can we extrapolate from using cholesterol and cholesterol changes as a surrogate marker for ultimate clinical benefit? And I don't think we've actually yet had that question resolved. My reading of this slide, which looks at the effect of placebo versus Pravachol, stratified by entry HDL, is that these data was for all total cholesterol and LDL values. So the question is what are these efficacy outcomes if you only look at the target population of entry total cholesterol of 200 to 240 and then LDL over 130? This related and second question is how did the lipid-lowering, what was the reduction in LDL and total cholesterol in these studies? I'm only a pediatric endocrinologist and I don't follow this literature. This was a optimized titrated dose. What kind of outcomes did you get? What was the actual lipid-lowering effects?

DR. BELDER: To start with the last point

in all the prevention studies that we did we only used 40 mg., so we never titrated. Another issue is that Pravachol lowers cholesterol very uniformly, independent of what the baseline levels is of triglycerides, HDL or total cholesterol. So the reduction is very uniform, around to 30 percent.

DR. TAMBORLANE: Excuse me. I just want to highlight that. So it was 30 percent in these--, about 30 percent in this study versus 18 in the 10 mg.?

DR. BELDER: That's correct.

DR. TAMBORLANE: So it was significantly less.

DR. BELDER: Now your first question was the influence of the level of HDL on the relative risk reduction in our studies, and then for the target population. Unfortunately, in the West of Scotland study, we did not have to target population. However, in the CARE and the LIPID studies, you know that the CARE study was a study that was performed in patients with normal cholesterol levels. We did have to target populations; however, it was a secondary prevention study. If we looked, and we did an analysis according to the baseline cholesterol levels and we took the patients who had a baseline cholesterol level of 180

to 240, and we did another analysis that did the same thing, but then from 200 to 240, and we looked at the baseline of HDL because it continues variable and we did not see that there was any influence of the baseline HDL level on the relative risk reduction and clinical events.

CHAIRMAN BRASS: Do you have that on for us to see?

DR. BELDER: Unfortunately I don't have a slide because we did-- yesterday, we did the analysis.

(Laughter)

CHAIRMAN BRASS: Because I agree with his point and I--, this is really a poor surrogate. Because the issue is raised by the AFCAPS sub-analysis, which showed no risk reduction with another statin, and so the point you're making now is very important.

DR. BELDER: And I would also like to emphasize that the CARE study had patients with relatively normal HDL levels, so it was unlike the AFCAPS study that was selected for patients with low HDL levels. So we did that for both LIPIDS and for CARE, and we did not find that the level of HDL at baseline influenced the relative risk reduction. Another point that I would like to make is that we

also looked at the change of HDL during the study, and very—

DR. TAMBORLANE: Before you move on to that, statistics are great. Relative risk is one thing, but absolute rates are also important. I think you can have a relative risk of twofold, at a rate of one to two, versus seven to 14 percent, so I think that you really need to look at this in a hard way to really convince the committee that there's a clinical benefit because you're trying to use the surrogate. So relativity may not be the important issue.

DR. BELDER: I can address that issue. Of course the CARE and the LIPIDS study had relatively high-risk patients included because they were all secondary prevention. However, the data that has been shown consistently is that independent of the baseline risk of the patients, the relative risk reduction across all studies was similar. They were all approximately 30 percent relative risk reduction independent of the baseline risk of the patient. And so in the AFCAPS/TexCAPS study there was the lowest risk population that has been studied that the relative risk reduction was the same. The absolute risk reduction of course is much smaller, but the relative risk reduction is the same. And the other

point that I wanted to make is that we also looked at the change in HDL levels during the study. And we found that if a patient's HDL level changed, went up during the study, that did not influence the relative risk reduction that the patient received on the basis of his LDL reduction. So the LDL reduction would predict--, I should say it differently. That if a patient do, let's say for instance, exercise would raise his HDL level, he would still have the same magnitude of benefits, due to his LDL-C lowering. So you can add those two benefits more or less together.

CHAIRMAN BRASS: I just want to emphasize his point about absolute risk, because relative risk may be constant but as you go to a lower risk population, the absolute risk falls, or the absolute benefit falls. But if there's a risk of exposure, that risk will not fall. So the risk to benefit equation will fall. And I'm not saying this is an issue, but I'm just re-emphasizing why the absolute risk in this population is important.

DR. FRIEDMAN: I guess also, though, I do want to remind the committee that we're not asking for an indication for event reduction. And I guess the question is, is cholesterol lowering an appropriate end point? It certainly is for prescription

cholesterol lowering therapies. And I think we brought this up, you know, really because there had been a lot of discussion yesterday about the issue of HDL and it was really--, I hope we didn't confuse more than clarify. But I think we do want to be very clear that the indication that we are looking for here is to lower cholesterol.

DR. TAMBORLANE: I guess I'm confused because I assumed that that would be an indication based on data for clinical outcome resulting in lowering cholesterol.

DR. FRIEDMAN: Yeah, though again, as a reminder, for prescription approval for a cholesterol lowering drug, there is no requirement for event reduction or clinical outcome. There are only LDL markers.

CHAIRMAN BRASS: So I think to summarize, I think that a label that says LDL reduction may be an approvable label are part of our assessment is what the extrapolation of the risk to benefit of that surrogate will be, and that will be part of our deliberations and discussions. Dr. Johnson?

DR. JOHNSON: I want to come back to the age issue and clearly, I think there were three variations on the label which has, I think, importance

in terms of label comprehension and selection. But I have a more fundamental question about why you picked 35 and 45 when I think the people that are interested aren't necessarily the people we want to target. We want to target the people who are interested and at some risk. And a man at 35 and a woman at 45 is probably a good 20 years from their first event, so we're going to ask those people, or try to convince those people that they should take this drug for 20 years before they're really even at risk for an event. So I guess I'm curious why 35 and 45 and not 45 and 55, which are the defined risk factor cut points in the NCEP guidelines?

DR. FRIEDMAN: Yeah, I think the determination of ages are a very important one and certainly one that deserves a lot of discussion now and as we move forward with this. I think we picked this--, first of all the 45, 55 are risk factors because the feeling is at that age one is already starting to have, by that age, a burden of atherosclerosis. And we see this as a prevention kind of issue by the age of 35 and 45, respectively, men and women are now starting to have, significant numbers of people are coming in to the higher cholesterol levels that will benefit from this. And

I guess we see this as a prevention option for people who are already--, and I think the other thing that's important is these people are already taking steps to lower their cholesterol. So that, you know, we saw that. Twenty-five percent of them are already pursuing nonprescription therapies to lower their cholesterol. We see this as a meaningful option for those people who are interested in doing that. And maybe Dr. Cohen has a couple of perspectives on the risk benefit because I think also, to your point, the safety issue is absolutely of paramount importance. We recommend to everybody that they follow a diet and probably will recommend to many people that they take dietary adjuncts to lower their cholesterol. So I think the question is in risk and benefit, what is the risk of which is really the safety profile of the drug to what is the ultimate benefit for that given period of time.

DR. COHEN: Thank you for that question. It's a good question and it's one that I think we've given considerable thought to. And as a clinician and a cardiologist, you come back to the disease process we're trying to prevent. And the number one cause of death in men over the age of 35 is coronary heart disease. The number one cause of death in women over

the age of 45 is coronary heart disease. That's what we're trying to prevent. And as I mentioned in my preamble, in fact, about 35 percent are sudden first-event deaths. You don't have a chance to see them, and this is the kind of patient we're trying to get at. And who is that patient? It's not a guy with a cholesterol of 300. It's a guy who may smoke, who's got a blood pressure of 142 and the doctor says, that's not so bad. And he's got a cholesterol of 235. That's the high-risk man. And he doesn't realize it because he's looking at individual numbers, and none of the numbers knocks your socks off, except when he dies everybody says this was a high-risk guy. Let's pay attention to the risk factors. Let's focus on the high-risk people, men age over 35, women 45 and over.

CHAIRMAN BRASS: But you'd agree that dropping the age to 35 would represent an additional extrapolation of the surrogate variable in terms of risk event rates, et cetera?

DR. COHEN: Yes, I would agree with that. And at some point I hope to be able to show you a slide that kind of puts it into a perspective overall. I'm not going to do that now, but I hope that we can get back to this issue of this question. It's a very important one, obviously, thank you.

DR. ORLOFF: Dr. Brass, may I make a point of clarification, stepping back right here.

(Laughter)

DR. ORLOFF: We need to get straight on this for the purposes of our discussion. The indications for use of any drug are a reflection of an expectation of benefit. And LDL-lowering indication is an implied indication to reduce the risk of cardiovascular disease of the occurrence of some atherosclerotic disease event. In those instances where we grant indications for the use of these drugs based solely on the LDL-lowering data, that is because the judgment is that under the conditions of use recommended in the labeling, the benefit to that population of patients will outweigh the risk. That's the problem that we need to get to today.

DR. COHEN: Mr. Chairman, may I address that problem? David, we've talked about this and you've hit the nail right on the head in terms of this issue and I think it's one that we need to look at in terms of the totality of the data. And when you look at the totality of the data we have a clear evidence of efficacy in terms of the 18 percent reduction. Now let us look at a level playing field. There was a situation not long ago where an Rx switch was made to

OTC, and it was nicotine replacement therapy. Nobody ever said show me the data for preventing lung cancer. Nobody said show me you can forestall COPD down the road. What did you want? You wanted intermediate variable reduction that we know in the long run will translate into benefit. And that's what we're after here. We know from all of the science, the animal studies, the epidemiologic data, and the clinical trial data that exists, that an 18 percent LDL reduction will translate into a huge-- That's why the goal of 2010, the newest goal is 199 for everybody. Where are the data to support that? That's the U.S. government. That's all of us in this room collectively thinking about how we're going to prevent our number one epidemic in the United States of coronary disease. The answer is not defibrillators for preventing first-event sudden death in airports and in ballparks. That's not the answer to this disease process. The answer is dealing with the basic disease of atherosclerosis and we have it in front of us today, ladies and gentlemen.

CHAIRMAN BRASS: Dr. Gilliam.

DR. GILLIAM: Two questions. One, in your safety data you had 43 women who had taken this medication while they were pregnant. Do you have any,

how long did they take—

CHAIRMAN BRASS: Please be sure you talk into the mic.

DR. GILLIAM: How long did they take this medication, that kind of thing? And then the second question was in your use studies, a question about how many of these people were taking herbal products, other medications that are, to try and lower their cholesterol?

DR. FRIEDMAN: To first answer the pregnancy, I can show you the specific breakdown. The exposure for probably a third of the women or half of the women was well, it was about less than six weeks. We might have that slide. Maybe we can look for that. It was about less, it was six weeks or less, four to six weeks. There was another, approximately a third or so, or maybe a little less, it was six to 14, 15 weeks. There were a couple of women who took Pravachol throughout the full duration of their pregnancy. There's the slide. This is all during the first trimester and as Dr. Brown points out this is all during the period of organogenesis.

DR. ELASHOFF: As I recall you didn't know the outcome from a lot of those studies.

DR. FRIEDMAN: We know the outcome in 29

of these pregnancies and of those in which we know the outcome there were no cases of teratogenicity.

CHAIRMAN BRASS: Dr. Davidson.

DR. DAVIDSON: Well, first I want to congratulate the sponsor for being inclusive, you know, for the material you are producing. And I have to agree with Dr. Cohen. It would reduce the LDL 18 percent, it would get a lot accomplished. The problem is I don't know if your studies and going over-the-counter will address the problem. Number one, in your studies, 85 percent of the population already have medical attention. And in 50 percent of the patients that the drug was prescribed, the drug was discontinued by the physician in patients without normal lipids. And that's a problem. It's a problem not for the consumer; it's a problem of education that we all need to do. Then you know, your studies really don't solve the problems. Second, your population at target was not a low-literacy population or the average American. You know, if you look at the answers, you know, actually your low-literacy did better in the answers than the over ninth grade deal. Then who did you choose for the studies? You know, people who already have insurance, that have HMO options. Either your material that you used was too

good and actually easy to understand, or you know, your population was really more educated than you think. Then those are the first parts of my questions, if you can answer. I have a couple of more after that.

DR. FRIEDMAN: I think to your first point about access to healthcare and that is clearly a very important issue for every aspect of healthcare. We actually see this as potentially an additional venue that could, where we could use other access to healthcare and bring the message out in additional ways that may, in the current prescription environment, not be reaching so many people. I do want to make it clear that we didn't choose anybody. We advertised and we made sure that the demographics of the media represented the community. We also augmented the advertisement in minority radio stations and magazines.

And we also specifically placed the sites in minority communities so we could get the reach that we did. I absolutely agree, and also the messages on the package and then the ad whatever the person bought, are really what we intend to have in the true OTC environment. We didn't have in the study some of the additional tools that we would want to have in an

OTC environment, such as audiocassettes for low-literacy people, audiocassettes in Spanish, package inserts and label in Spanish, which we would intend to have. But for one, we did not exclude people if they did not speak English, and we actually had healthcare professionals at some of the clinics that we chose that were reflecting the communities. So I think we tried as much as possible to do that. I totally agree with you that this is a big issue of access, and as Dr. Cohen said there are a lot of Healthy People 2010 goals and narrowing that gap is one of them and maybe this can help.

DR. DAVIDSON: The second part was, you know, even if they have over-the-counter, if the physician will discontinue the therapy, you know, is a big problem. And those are things you need to address.

DR. FRIEDMAN: Absolutely.

CHAIRMAN BRASS: But if I could just interrupt for one second, because I think this concept-- Well, we all agree the healthcare system is doing a non-optimal job. I think we all agree on that. But I think this bashing about primary prevention of this population is being overdone. The PREDICT study was done in 1998. The amount of

randomized placebo-controlled trials that demonstrated a positive risk-to-benefit ratio in this low-risk population in 1998 was simply not available. And to say that physicians were acting inappropriately in 1998 based on the information available in 2000, I just don't think is necessarily an accurate reflection of what physician behavior in primary prevention is going to be over the next five years.

So I think we have to be a little bit careful about--, and again, nobody's questioning that there is a lot of room for improvement in the healthcare system. I just think we're looking at an absolute worst-case scenario when we look at how primary prevention was being done in that period of time for what was then a low-risk population with limited evidence for indication for treatment. If you could identify yourself, please.

DR. PFEFFER: Yes. Mark Pfeffer. I'm a consultant for the sponsor. And some of the issues you brought up about safety and the issues you're bringing up about time are really very important because these are all moving targets. And I'm here as a care investigator and when we started, this drug wasn't even approved for use to lower cholesterol. And we all had our preconceived notions. As a matter

of fact, if you think of the safety profile as it was rolling out, we had to do slit lamp exams to make sure that we weren't getting corneal opacifications.

And with dialogue with the agency and with data that barrier was removed in the midst of the study. We had to do very careful surveillance labs which was brought up that you don't do that in real life, and that had to be done. And because of that, and because we've now pooled three studies together, we have a quarter of a million samples that say we can't detect the difference between placebo and the act of therapy.

Now this wasn't known to the investigators. The pravastatin pooling project started before the lipid study came out, which just came out a few years ago. In 1992 the investigators from these studies with sponsor support, develop the pravastatin pooling project.

You're seeing numbers here that the world doesn't even know yet. And that was put together to look at efficacy, to look at pre-specified subgroups, and I happen to be the lucky one to say, "Let me do the safety analysis." And because of that we now know that there is no difference over placebo that could be detected. Now you could never be that certain about

safety, and then we have the 22 million patient years. So I think now, we're in a different place, and we need a new step to help with the education of both the consumers and the patients.

DR. DAVIDSON: I didn't finish. You know, still my point is that if this product goes over-the-counter, you know, if we want to use it properly, you know, there will need to be a lot of healthcare education, otherwise it won't happen. When you're going to have an 800 number, who is going to mind that 800 number and what are the qualifications of those people? And is the 800 number a bilingual 800 number?

DR. FRIEDMAN: Could I have the schema of 107, please? This is the schema of the toll-free 800 number that would occur during the hours of eight to ten. Consumers' calls would come in and by an automatic triage they would select English or Spanish. Then they would also get, beyond that, there would be a phone triage to an automated handling which would go to Pravachol Partners enrollment, and then consumer promotion increase.

For most OTC products, that's the largest amount of increase that's come in. Then the next would go to a consumer affairs specialist, and again, now they have already selected English or Spanish, and

then they would have a script that could answer questions about product use that would go through a script. If there were medical related questions, they would be directed to the personal physician or to the healthcare professional.

DR. DAVIDSON: Why only eight to ten?

DR. FRIEDMAN: We have another, if I could have the next slide, please.

DR. DAVIDSON: No, no. Let's finish.

DR. FRIEDMAN: It's 8:00 a.m. to 10:00 p.m.

DR. DAVIDSON: Right, I know. Eastern or Standard time? Which leaves a lot of people out of the loop.

DR. FRIEDMAN: Sure. Well, that's something we'd be happy to extend. We do also have an off-hours 800 number.

DR. DAVIDSON: Okay. Could you go back to that slide?

DR. FRIEDMAN: Sure.

DR. DAVIDSON: You know, who is your consumers affairs specialist? What is the qualification for that person?

DR. FRIEDMAN: That person is someone who has been trained in the use, to answer questions per

the labeling and the fact book. That person is not intended to take the place of that person's physician and it's really just to be able to using the information, being able to provide that information to that consumer that's already in a fact book that actually the consumer would more or less for him or herself, but might need some clarification.

DR. DAVIDSON: Yeah, I really still don't get my question out. What is the background of that person?

DR. FRIEDMAN: That person would probably have a college education and then have specific training from a healthcare professional.

DR. DAVIDSON: Thank you.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: Why did you ask for approval for the 10 mg. dose as opposed to 20 or 40?

DR. FRIEDMAN: Why are we asking now for approval? Why are we asking for approval for 10 versus other doses?

DR. NEILL: Yes.

DR. FRIEDMAN: I think for several reasons. First, Rx-to-OTC switches have historically been at lower doses. And I think, very importantly, the choice of the lower dose actually has come, has

evolved from discussions from these committees and with FDA where there was a real concern and interest in differentiating the lower-risk person who could take this OTC from the higher-risk individual who really needed much more intensive intervention with a physician. And we think that we accomplish this by this dose.

We, in fact, the last time we were before this committee, we had a much broader reach in our program, and in fact it was a great concern of the FDA and the committee that perhaps that would be confusing and distract people from the healthcare system. So our intent here is to have a lower dose for a lower-risk population, who most of whom will achieve a meaningful benefit or get to their goal on this dose.

DR. NEILL: Why did you choose this lower-risk population for that low dose for your indication?

DR. FRIEDMAN: Again, it was because of discussions that we've had with the FDA and this committee. The concern that the higher risk population really needs to be under intense medical supervision, and that this could potentially be a distraction. That was a concern voiced at our last meeting. We heard it and this is how we've responded.

DR. NEILL: And last question for FDA.

Given the move of cholesterol monitoring outside the physician's office, I could imagine a time when this medication is available over-the-counter and that even higher-risk patients given access to cholesterol testing could appropriately manage themselves with an OTC medicine and with OTC testing. My question to you is, that's a real shift.

Yesterday you discussed the extent to which patients currently titrate other OTC medicines for symptom-related conditions. And I sat trying to imagine or come up with any medication that is already OTC that has a symptom of a condition that I felt was as serious, or the consequences of which were potentially as serious, or the safety profile given incorrect use of this OT medicine might be as serious as coronary heart disease. I couldn't come up with any. Can you?

CHAIRMAN BRASS: You can answer it very briefly, but really I think that's more for our general discussion this afternoon and let's focus. But if you want to go ahead and make a brief comment.

DR. DELAP: I think that you've hit a very important nail on the head, there, and that's partly why we've spent two days out of our lives with this meeting.

DR. GANLEY: The example would be insulin. Insulin's essentially an OTC drug and people self-monitor, and that's why I bring up the issue. If it's under-treated in the higher-risk populations, then why aren't we focusing on those populations, also? If there's going to be self-monitoring, which seems to be a requirement for the treatment of cholesterol, I think we should try to maximize benefit and individualize therapy and not look at it just on a population basis.

CHAIRMAN BRASS: Dr. Jenkins.

DR. JENKINS: I have a question for the sponsor, but first I want to go back to what Dr. Orloff was trying to clarify about the indication. Because you can't separate an indication for cholesterol lowering from an expectation of cardiovascular risk reduction and cardiovascular benefit, because you can't interpret the benefit of a cholesterol reduction unless you can interpret that in the context of what you think that benefit translates into for a cardiovascular benefit. And that's what you'd have to take into your risk benefit equation, which is what stands behind the agency's decision to approve a drug or not. So you can't just say that this is an indication just for LDL lowering. That

doesn't make any sense. LDL in and of itself doesn't mean anything until you translate it into what does that mean for reduction in cardiovascular risk. So you have to apply that process to this, what we consider to be a new indication, for the treatment of people 200 to 240, LDL greater than 130. You have to translate the LDL reduction into some benefit whether you do it through extrapolation or data for a cardiovascular benefit, and then you have to calculate in your mind or someway whether that benefit outweighs the risk.

That's just a clarification of the indication. The question I wanted to ask goes back to the question we started with with Dr. Uden a few moments ago, and that's about the age criteria for the labeling. And I have to say I still haven't heard a very clear answer on how you arrived at the criteria. As I looked at the information that Dr. Lechter shared with us, the label you tested in the label comprehension study said men over 35 and women over 55. The label that was then submitted to the NDA only mentioned if you were under 18 you shouldn't take the drug. The label you're now proposing is over 35 for men, over 45 for women, which as we heard from yesterday's discussion is somewhat different from the

other company's proposal which was, I think, 40 and over for men and greater than or equal to one year postmenopausal for female. Clearly a decision to treat patients has to be based on a calculation that the risk benefit ratio for treatment in that population is favorable. So I'd like to understand, why have you migrated in your program and how did you arrive that it's a favorable risk benefit treatment option for people as young as 35 if they're male, and as young as 45 if they're female? What's the scientific rationale? The only rationale I've really heard so far was, that's when people seem to indicate they want to start taking drugs.

DR. FRIEDMAN: I think first starting with the risk equation, certainly there are, as you get younger especially in women, I think it's very important to assess the risks and I think we've been very careful to ascertain that the risk is extremely minimal and no different from men or women. As you look at the risk of developing coronary disease for a 45 year old woman and a 35 year old man, it's essentially the same reflecting that ten year difference. And again, we don't have clinical outcome trials on this issue. But I think what we've been hearing is that people are looking to lower

cholesterol, that lowering cholesterol is a good thing. We have approved therapies to lower cholesterol, dietary adjuncts, that we have accepted to recommend to people, foods and dietary adjuncts, because of the feeling of safety. And you're right, it is a risk benefit assessment. I don't think, I don't want to today say that it has to be 35 or 45. You know, I think that it has to be something that is beneficial of a prolonged dialogue as to what is the best age. But I think that as we looked at it, given the incredible safety profile of this drug, we saw extremely minimal risk and benefit for people who are looking to do this anyway.

DR. JENKINS: Can I just follow-up with that? On the issue of risk of cardiovascular disease in these target populations, can you give me any estimate or any idea about a 35 year old male who has no other risk factors other than his total cholesterol is within the 200 to 240 range and the LDL is greater than 130, do you have any estimates on what's the time-to-event frame that we're looking at for a cardiovascular event? What's the expectation for--, when will you see an event in a 35 year old male with those as his only risk factors? On average, I understand that it has to be average data.

DR. COHEN: That's a good question and I think that we don't have clinical trial data to look at. You saw yesterday from the AFCAPS/TexCAPS, which is the lowest-risk population studied in placebo-controlled trials, the curves begin to separate after six months. And in that population, which isn't quite the same age but it's the lower-risk end that we're really discussing here, and age is really a surrogate for a lower-risk individual if you're talking about a lower age person.

But the trials continue to separate over time, and that was pointed out. So at five years, the benefit continues to digress, to diverge, and all of the analysis that you can do, when you come to randomized clinical trials, minimizes the benefits. Why is that? It's because all of these trials have intention to treat analysis by design. And so people who are not taking a drug on treatment are counted as taking the drug. In addition, we're looking at defined event rate over five years in time. We know with the digression that the benefit is going to be high down road. I don't know when a 35 year old man's going to have a heart attack, nor do you. Or maybe he'll get hit by a truck tomorrow. No one in this room knows that. All we know is the United States of

America has this huge problem. I don't know if it's John Doe or Jane Smith who's going to have that problem, and so we have to face it from this kind of issue. Then you put it in the perspective of primum non nocere, what's the risk? And if you can assure yourself that the risk is vanishingly small, I will show you slides later that might suggest what the benefit can be. And I can tell you in this population, Dr. Jenkins, the risk is above average.

DR. JENKINS: No, I understand that point. I don't think you answered my question, but I don't think you have the data to answer the question. Let me just point out, though, I don't think anyone disagrees with your public health message, that those are important critical goals, but one of the fundamental tenants of drug approval is that the benefit is going to be derived from the patient who takes the drug and that the risk is carried by the patient who takes the drug, so I'm just trying to put it into perspective. Not the public health societal benefit of reducing cardiovascular disease, which will be a wonderful societal benefit. The question I'm trying to frame is what's the benefit to Joe Doe individual—

CHAIRMAN BRASS: I'm going to interrupt

now.

DR. COHEN: Could I just answer that question briefly? The benefit is a calculated risk reduction that we could do. And so if you know his cholesterol is x and he goes on a lipid-lowering drug, Pravachol 10, over-the-counter, and its 18 percent point less than x, then we can estimate from many, many data that his risk is that much lower in the order of magnitude of 20 to 30 percent.

DR. JENKINS: The only point I'm trying to make is that's the risk calculation we should be addressing for approval in a drug, not your public health goals, which are wonderful, but that's not the drug approval risk benefit calculation.

CHAIRMAN BRASS: I'm going to interrupt now, and we're going to take our lunch break at this point. We will reconvene at 1:30 and continue the general questions prior to getting to the FDA-specific questions.

(Whereupon, the proceedings went off the record at 12:30 p.m. for a lunch break.)

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

(1:33 p.m.)

CHAIRMAN BRASS: Okay. If we could come to order, please. At this point we're going to continue the discussion of the presentations by the sponsor and the FDA. The sponsor, based on questions this morning, has taken advantage of the lunch hour to complete another pivotal trial with 10,000 patients.

(Laughter)

CHAIRMAN BRASS: But unfortunately the data analysis won't be ready for another five minutes.

(Laughter)

CHAIRMAN BRASS: So they will be making some additional comments about the risk issue in just a few minutes. But while they pull that together, I thought we would continue the questioning. And perhaps I might begin with just a couple of issues. Could you comment on any pharmacokinetic and safety data you have on patients with renal insufficiency given the right of elimination of this compound?

DR. BOTORFF: Mike Botorff. I'm a professor of clinical pharmacy at the University of Cincinnati. When you compare the pharmacokinetics of the various statins, most of them are very lipid-soluble and you hear repeatedly that pravastatin is

more hydrophilic or water-soluble. It is eliminated by several mechanisms, involving the kidney as one, when an oral dose is given. Generally, the renal excretion unchanged is about 20 percent or a little bit less. It's been studied both in single dose and in multiple doses in patients with various degrees of renal insufficiency, including those on dialysis, resulting in really no change in the pharmacokinetics at all. Both those papers have been published.

CHAIRMAN BRASS: Thank you. I want to turn a little bit more to understand the target population and its behavior in the OTC setting. And much of the discussion earlier today was related to the qualified who took drug and that very small cohort.

I'd like to go back to a slightly larger cohort and make sure I understand something. In the PREDICT trial, there were 2,400 plus patients who were designated after randomization as appropriate for consultation. I'm looking at page 89 of your briefing, and that was called the consult group, post-randomization.

So that, again, on page 89 it's 3,800 visited, 3,600 were randomized, 2,500 consulted. And I want to look at the characteristics of that 2,500

patients in contrast to patients who actually completed. And before I even start, though, I want to emphasize that I think the sponsor did a variety of innovative things in their two actual use studies that has generated the kind of data we often don't see about actual use populations. So that many of the issues that might come up for discussion, in fact already have, would even have been raised in many of the conventional trial designs. So I really do congratulate the more innovative context of some of this trial design.

But my understanding is these 2,500 patients had to opportunity to review the carton and after reviewing the carton thought that they were in fact appropriate users. Is that correct?

DR. FRIEDMAN: The 2,500 patients represent both the OTC and prescription environments. So for the OTC people, they reviewed the carton and a prototypical OTC ad.

CHAIRMAN BRASS: But that's prior, is that prior to randomization?

DR. FRIEDMAN: No, after randomization. So they were randomized to these environments without any knowledge at all. Okay, they came in and they were randomized to the two environments without

showing them anything. So that is truly without any selection bias. And then after randomization the OTC participants could see the OTC package and a prototypical OTC ad that you would see in a magazine. The prescription people, the people that were randomized to prescription, those 1,900 saw a prototypical DTC ad and did not see anything else.

And then when they left the site, they, you know, then they left the site. The OTC people could have purchased at that point, but that was the only information given to the people at the site.

CHAIRMAN BRASS: Okay. Again, I apologize for the confusion, but try and understand.

DR. FRIEDMAN: Yes.

CHAIRMAN BRASS: On page 89, there is a population of 2,466 identified as the consult population.

DR. FRIEDMAN: That's correct.

CHAIRMAN BRASS: On page 91, it's indicated that there were 1,900 randomized OTC and 1,900 randomized to prescription.

DR. FRIEDMAN: That's correct, because about two-thirds of people, after they left the site, decided to consult. That was up, you know, whatever reason they had.

CHAIRMAN BRASS: I see. So there was a patient-based selection.

DR. FRIEDMAN: That's correct.

CHAIRMAN BRASS: Once randomization occurred, not to follow-up.

DR. FRIEDMAN: Not to consult. That's right. That we don't know because we did not, we didn't ask them at the end of the six months and we didn't intervene, but for whatever reason they could just say they weren't interested, or whatever. So two-thirds of the entire cohort who were randomized decided to consult.

CHAIRMAN BRASS: Okay.

DR. FRIEDMAN: And that's why you get that drop-off. The information that they had before making the decision to consult was the package for the OTC and an OTC ad, and a DTC ad for the Rx, and that's it.

CHAIRMAN BRASS: In the 720 patients who then saw the label and elected to purchase.

DR. FRIEDMAN: Yes.

CHAIRMAN BRASS: Okay. Do you have what the cholesterol profile is of that 720?

DR. FRIEDMAN: Yes. This is the total cholesterol and LDL cholesterol. Is that the information you want?

CHAIRMAN BRASS: Yes. Now I'm interested in, there's a little bit of flopping between the LDL 130 and 160 number, and for primary prevention, in fact, earlier in your document you indicated that 160 would be the level that would be indicated for treatment and was your criteria for those who should enter the trial. But then, subsequently, very often you used 130. Could you just clarify that difference?

DR. FRIEDMAN: Yes. The treatment guidelines that we gave to the physicians-- Again, we wanted as uniform treatment guidelines so we could then follow behavior and LDL reduction, you know, in a systematic fashion in this study, which we didn't do in OPTIONS, but in a systematic fashion. So we gave treatment guidelines more or less following the principles of NCEP. So for the lower-risk primary prevention population, we had treatment guidelines of 160 to 190, and for the higher-risk, 130 to I think it was 190.

CHAIRMAN BRASS: Right, so the 130 here is a little misleading in terms of them representing the target treatment population of this study. Because wasn't the intent to treat, and again, I'm just—

DR. FRIEDMAN: Well, this is the profile. I can give you the lipid levels of the people who were

in fact treated, if that would be helpful.

CHAIRMAN BRASS: Okay. Well, let me switch back then. You subsequently say that 80 some-odd percent ultimately met targets.

DR. FRIEDMAN: NCEP goal. That's correct.

CHAIRMAN BRASS: Was that, were those goals the 160 number or the 130 number?

DR. FRIEDMAN: It depended on where we thought we-- The goals were defined by the NCEP, so if you were a lower-risk primary prevention, it was 160. If you were a higher-risk primary prevention, it was 130. So that was the guidelines given to the doctor. The number reached, so that's what that 83 percent represents. If you would like to see the number specifically of the percent reaching LDL less than 130, it was about 63 percent. But again the doctors were not told, you know, to go any higher.

CHAIRMAN BRASS: Okay. One of the positive aspects of the OPTIONS trial, while it is limited because of the population all being accessible to physicians, one of the advantages is that you have gold standard medical histories by looking at the charts.

DR. FRIEDMAN: Yes.

CHAIRMAN BRASS: And one of the things

that was kind of interesting to me if I understood it right in OPTIONS was that 26 percent of the patients who were currently on prescription lipid-lowering agents selected themselves to take the OTC, and that's page 127 of the, it's on 26 and 27. Does that number ring a bell? Is that consistent with?

DR. FRIEDMAN: I don't know if, I know that at the end of the three month period, when we looked, there were 99 people who came in on prescription therapy. And we looked at their behavior at the end of—

CHAIRMAN BRASS: But at the start 27 of that 99 took Pravachol 10 mg.

DR. FRIEDMAN: Yes, there were some OTC purchasers who took and then went off it and went back on their prescription, that's correct.

CHAIRMAN BRASS: Well, what I'm trying to extrapolate that experience to is the unsupervised OTC use of the compound. And it seems that theoretically that represents two potential risks. If 27 percent of all the people currently on hypolipidemic prescription drugs begin in an unsupervised way, whatever our intent is, to begin taking the OTC products, it seems there are two potential risks associated with that.

One, if you believe that the risk of

rhabdo is increased by co-administration of statin and fibrates. They may be putting themselves at increased risk. Or, two, they may be putting themselves at risk for discontinuation of the more effective therapy. And when you start talking about 27 percent of that cohort beginning to discontinue drug in an unsupervised setting, who is most likely a higher-risk population, that again, the risk-to-benefit comes into question. Could you comment on those issues?

DR. FRIEDMAN: Yeah, two comments. First about the use with other prescription-lowering therapies and a potential, though I don't think it has been positively associated, potential for increase safety issues, I think we can go back to the label comprehension study where there is a comprehension of the warning, "Do not use if you're taking other prescription-lowering medicine", and that was well understood.

CHAIRMAN BRASS: Well, except that's not a real use comprehension study. And whereas those 27 percent of the patients on prescription drugs who started, had the carton in front of them, presumably had the opportunity to read that carton, and yet start it. And I think that kind of actual use data is much more powerful than the multiple choice question on the

comprehension study.

DR. FRIEDMAN: Yeah, I, certainly I think the consumer use studies really give us a lot of information and I think the other piece of information that these give us is that, one, if people don't consult, you know, most people don't continue on with the therapy.

And when we saw that, at the end of the three month period, these people had an evaluation, in fact it was 11 percent who shifted from prescription to OTC in OPTIONS and in PREDICT, it was two percent who shifted from prescription to OTC. In OPTIONS you could say that, well, it's an HMO population. They all have healthcare. In PREDICT, it's a much broader population.

So, you know, I think the reality is there may be a little of that. That's probably what will happen. But I think that these numbers are really quite small and you have two studies to evaluate that. And so that is the issue of the shift. Then the issue of the safety, I think perhaps you can think about with the label comprehension.

CHAIRMAN BRASS: Well, I understand again, the absolute magnitude of the number who shift may be small and it may be anywhere between two and 27

percent, given the confidence intervals on those numbers. It's something in that range. My point is that the absolute risk in that population for cardiovascular events may be substantially higher evidenced by the fact that some doctor, even our limited healthcare system, decided they needed therapy, and so the absolute increase in risks from a small percentage of patients discontinuing prescription therapy versus a large number of low-risk patients accessing therapy, I think, is a legitimate question in the room.

DR. FRIEDMAN: I agree with you. I think, though, that what's central though to your hypothesis is exactly that a doctor did put them on therapy. So it is a person, you know, I think what you were concerned is the people who don't see the doctor. But here are people who are in the system, have been seeing their doctor, and you're right, some of them may not go back.

But I think our data, what you brought up was, well here are people who have doctors, so what about the people who don't? Well, the people who don't probably wouldn't have been put on therapy. So people who have been put on therapy have doctors.

CHAIRMAN BRASS: And I recognize that

we're talking hypotheticals. So neither of us can definitively address this. But one of my concerns, and I realize PREDICT was biased to shifting in one direction, but that an interpretation of this is that patients who have had physician relationships, are on prescription therapy, may say, may say, I don't know, may say I no longer need to go to my doctor because I can take the drug over-the-counter and discontinue the healthcare relationship. I don't know to what degree that will happen.

DR. FRIEDMAN: The other piece of data, though, to think about is the one year data where, again, people in the OTC environment were just as compliant with going back and getting that annual visit with a doctor compared to the prescription environment. I agree with you. It's a theoretical risk. We've tried to evaluate it with these pieces of data.

CHAIRMAN BRASS: And one last question. Of the 720 OTC PREDICT patients, what percentage of them had cholesterols over 240? You showed us over 200. What percentage had over 240?

DR. FRIEDMAN: Just a moment. We have a lot of data. The book is very heavy. I can show you—AB109. Now again in PREDICT, now this is—that's not

it. In PREDICT, we only know the cholesterol because those are people who consulted, so we don't know the cholesterol of all the purchase people.

CHAIRMAN BRASS: I see.

DR. FRIEDMAN: I can show you the baseline for both PREDICT and OPTIONS. The baseline total cholesterol distribution for the people who purchased. But again, for PREDICT, that will only be for the people who consult.

CHAIRMAN BRASS: Fair enough.

DR. FRIEDMAN: So, yeah, AB103. And that gives you for PREDICT in yellow and OPTIONS in blue, the total cholesterol distribution.

CHAIRMAN BRASS: So adding up quickly, a little over 40 percent were over 240? Is that fair?

DR. FRIEDMAN: That's right.

CHAIRMAN BRASS: Okay.

DR. FRIEDMAN: Again, though, the important thing also for PREDICT is that these people all consulted a doctor.

CHAIRMAN BRASS: I understand. I understand. Are you ready for the risk data or do you want some more time for that?

DR. HENNEKENS: Well, I'm Charles Hennekens. I'm a preventive medicine consultant to

Bristol-Meyers Squibb. Dr. Friedman asked me to speak to the issues you raised just before lunch, both the committee and the FDA with respect to the quotient points about benefit and risk ratio and with respect to age as a former clinician and epidemiologist, I would tend to raise the lower limit from 35 to 40 in men and 45 to 50 in women simply because this is the time at which the event rates begin to rise exponentially.

But even this needs to be viewed in the context that years ago working with Sidney Blumenthal and Mary Jane Jesse we demonstrated that children of men who had an MI by age 50 already exhibited hyperlipidemia in childhood, so certainly in early middle age one could pick up this upset of the population in men in their 30's and women in their 40's.

Now the data from AFCAPS/TexCAPS for this OTC target population indicates five year cardiovascular event rates of about five percent for this target population over five years. Now as expected, this is slightly lower than the projections one would get from an observational database because of the selection of people into the trials. But even after adjusting for the expected poor compliance that

one would get in the OTC population, this would translate conservatively to at least a 20 percent reduction and the absolute event rate to four percent among those who were taking Pravachol 10.

This is because the 18 percent reduction in LDL-C from Pravachol 10 would be expected from epidemiologic data and with good compliance in the trials to really achieve about a 40 percent to about an absolute risk down to three percent.

CHAIRMAN BRASS: If I could just interrupt. In the discussion yesterday and part of that discussion was inferred in the conversation this morning, there was concern that the AFCAPS population does not represent the OTC target population because of the HDL cutoff. And that part of the discussion this morning, and I apologize for the degree, it was a continuation of a discussion from yesterday, is trying to define in the OTC target population as defined by sponsor what the risk rates will be and extrapolation of benefit.

DR. HENNEKENS: Yes. Well, I think the HDL issue is a red herring here because even in the AFCAPS/TexCAPS study one has to conclude that if you look at the overall database, there is no heterogeneity in the reduction of LDL-C and people

with low, medium and high HDLs. There is a significant benefit even among those with high HDLs.

CHAIRMAN BRASS: Again I apologize, but yesterday we saw data that showed the event rate was different.

DR. HENNEKENS: Yeah. Well, the issue of yesterday, there were two issues I heard yesterday. One was that there was no significant benefit at the high HDL levels in AFCAPS/TexCAPS. This was based on a comparison of 21 versus 23 events. This was a subgroup of a subgroup. The overall HDL analysis is a data-derived subgroup and it is statistically significant in favor of benefit.

The subgroup of the subgroup, defined inexplicably by the sponsors based on those that would be eligible in their OTC target, left you a subgroup of a subgroup that had 21 versus 23 events. So I reject the notion that there's no benefit in the high HDL. It is true that there's some gradient across HDL levels, but that's also true in all populations one looks at.

And I think that that--, it's an independent risk factor. One sees benefits of LDL lowering at the highest levels of HDL in men and in women alike. So at any rate, I make this a fairly

conservative small absolute risk reduction which, as you know, is in marred contrast to a secondary prevention population where during this five year period you'd expect reductions--, a 20 percent reduction would lead you from 20 percent to 20 percent from 25 percent in the placebo group. So it's a much bigger benefit in the higher-risk secondary prevention group.

But this 20 percent reduction in secondary prevention has a far greater impact in the individual then in primary prevention, but for a safe drug like Prava 10 I think this reduction is important both from a clinical and public health impact. And indeed estimates could be made that the 20 percent reduction and secondary prevention, even though it has a bigger benefit to the individual might avoid 10,000 events whereas in the population in primary prevention over five years it would avoid about 100,000 events.

Now with regard to the fact that one can demonstrate a benefit of cholesterol-lowering in this population, I did serve on the NCEP coordinating committee as the College of Preventive Medicine representative. In 1986 the guidelines called ATP I were based on the totality of evidence that included randomized trials of drugs and diet that gave LDL

reductions of 11 percent.

This translated to benefits on coronary events, but equivocal findings on total mortality. Prava 10, as you know, reduces LDL-C by 18 percent. In 1992, ATP II guidelines were changed primarily to make a more targeted goal of an LDL less than 100 for secondary prevention.

Now, these are the current guidelines. They don't reflect or have anything to do with any of the statin trials that have been completed in the last six or seven years and they show marked reductions on MIs, stroke, vascular death and total death. And the point I want to make here is that these guidelines are reactive to accumulating data and positions taken. If the FDA were to approve OTC use of Prava 10, then I would assume that they would be incorporated into future guidelines to react to the data as they accumulate it and become accepted.

With regard to adherence to the current guidelines as the Chairman and others have said, nobody would disagree that they're sub-optimal; however, I think it should be stated that with 13 years of NCEP, six years of landmark statin trials, widespread advertising in the medical journals, educational programs and perhaps, last but not least,

drug detail people at the doorstep of all the healthcare providers on a daily basis, Dr. John LaRosa has published in the American Journal of Cardiology in the last year or so results from the NHANES data, which quantitated this to be, in secondary prevention and people with events, less than 15 percent are achieving the current guidelines. In primary prevention, less than five percent are achieving the guidelines.

So I think the introduction of Prava 10 into the OTC as an OTC option has to be looked at in the context of a current situation that is complementing a big existing need. Now with respect to the risk side of the equation, I concur completely with Dr. Belder's safety analysis, but I think that it's important to point out the suggestion that their liver failure associated with Pravachol has to be viewed in the context that this has no, is nothing in excess of the background. And secondly, that with regard to rhabdomyolysis, the risk is either exceedingly small or nonexistent, so I would think that I would not be able to conclude that there are small but significant risks associated with this drug. So in principle I would say that I concur that OTC options for a prescription drug require particularly