

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

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

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

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

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

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

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

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

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

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

12 CHAIRMAN BRASS: Dr. Gilliam.

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

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

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

3 CHAIRMAN BRASS: Dr. Davidson.

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

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

21 DR. DAVIDSON: That's combining both
22 studies?

23 DR. FRIEDMAN: This is PREDICT.

24 DR. DAVIDSON: Right. Give me just OTC.

25 DR. FRIEDMAN: It's actually a little

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

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

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

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

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

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

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

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

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

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

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

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

14 DR. FRIEDMAN: Yeah, now don't forget in
15 this group right here, this is the moderate-risk
16 group. The mean baseline was 155, so their goal was
17 130 and 80 percent reached that goal. Here, which is
18 the lower-risk group and again, the guidelines, and
19 this one for initiation was 160. Again, 95 percent
20 reached the NCEP goal.

21 CHAIRMAN BRASS: Reached the goal of less
22 than 130?

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

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

4 DR. FRIEDMAN: 160.

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

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

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

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

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

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

16 DR. FRIEDMAN: Yeah, It think that the
17 overall impression is that the group was split about
18 half and half moderate and lower-risk and the mean LDL
19 was 165 for the lower-risk, 145 for the moderate-risk
20 and 65 percent of people achieved an LDL of less than
21 130 in this environment. And again that was not with
22 a physician doing anything to get that lower-risk
23 group down to 130.

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

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

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

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

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

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

1 DR. FRIEDMAN: No we did not.

2 DR. DAVIDSON: Thank you.

3 CHAIRMAN BRASS: Dr. Grady.

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

12 DR. COHEN: Yes.

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

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

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

4 (Laughter)

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

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

25 DR. COHEN: This is based, it says it

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

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

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

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

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

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

16 CHAIRMAN BRASS: Let a statistician talk
17 to a statistician.

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

20 (Laughter)

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

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

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

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

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

25 DR. ELASHOFF: I mean, in essence,

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

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

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

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

25 DR. GRADY: What are the cardiovascular

1 outcomes?

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

7 DR. GRADY: Thank you. It's also
8 interesting if you look at what the relative risk is
9 there, it's about a 25 percent risk reduction in the
10 50 year old females, about 20 percent in the 40 year
11 old males, and only about 12 percent in the younger
12 men.

13 CHAIRMAN BRASS: Dr. Johnson.

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

17 (Laughter)

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

20 (Laughter)

21 CHAIRMAN BRASS: Dr. Krenzelok.

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

1 PravaCare program newsletters which I think are very
2 informative and so on, but depending upon what age is
3 ultimately the bottom age, it probably would be really
4 good to have consistency between the indications and
5 the newsletter, for example. I was reading one and it
6 just struck me that, sort of suggestive that young
7 people should begin to take this. On the front page
8 of one of them it said, if you're over the age of 20
9 chances are you need to begin to manage your
10 cholesterol level now. So maybe it would be a good
11 idea to introduce some consistency and raise that to
12 35 or 40, or somehow incorporate some other issues
13 into it.

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

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

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1 questions?

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

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

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

20 CHAIRMAN BRASS: Dr. Blewitt. Dr.
21 Jenkins.

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

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

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

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

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

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

1 (Laughter)

2 CHAIRMAN BRASS: Dr. Neill.

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

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

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

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

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

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

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

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

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

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

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

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

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

11 CHAIRMAN BRASS: Dr. Katz.

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

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

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

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

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

14 (Laughter)

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

17 (Laughter)

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

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

23 CHAIRMAN BRASS: That's correct.

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

1 expectation of a cardiovascular benefit.

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

11 (Hand vote taken)

12 DR. TITUS: Thirteen yesses.

13 CHAIRMAN BRASS: Opposed? Abstained?

14 DR. UDEN: Yes.

15 (Laughter)

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

1 DR. GRADY: Well, obviously, I think all
2 of us would be much more comfortable if there were a
3 trial with real clinical outcomes because what we're
4 doing here is using a surrogate outcome which is
5 changing LDL cholesterol as a predictor of real
6 clinical benefit. And I'm always leery of surrogate
7 outcomes. On the other hand, this is one of the best
8 surrogate outcomes that we have studied over the past
9 ten years. I would say that if we believe that this
10 magnitude of change in LDL is a predictor of real
11 clinical benefits in this low-risk population,
12 whatever their HDL cholesterol happens to be, then we
13 can probably expect that the magnitude of that benefit
14 is something on the order of one in a 100 to one in
15 250 or something like that over a five year period,
16 which again brings up the importance of people
17 sticking with this therapy over a five year period.
18 Because I don't think any clinical benefit can be
19 expected over six months to a year. You don't ever
20 see that even in trials. So there are a lot of steps
21 I think and that's my worry, is there are a lot of
22 steps we have to make assumptions that everything is
23 going to go well. If everything went well, I think
24 there is the expectation of clinical benefit.

25 CHAIRMAN BRASS: And the agency can

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

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

14 CHAIRMAN BRASS: Dr. Molitch?

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

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

4 CHAIRMAN BRASS: Dr. Davidson.

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

14 CHAIRMAN BRASS: Dr. Elashoff.

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

24 CHAIRMAN BRASS: Dr. Johnson.

25 DR. JOHNSON: I have a question for Dr.

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

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

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

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

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

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

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

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

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

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

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

17 DR. SILVERSTEIN: Just the 10 mg.

18 CHAIRMAN BRASS: That is correct.

19 DR. SILVERSTEIN: Okay. Okay, I see.

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

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

4 DR. JOHNSON: What does "is" mean?

5 (Laughter)

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

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

23 (Hand vote taken)

24 DR. TITUS: One yes.

25 CHAIRMAN BRASS: All those who feel the

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

2 (Hand vote taken)

3 DR. TITUS: Thirteen noes.

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

14 (Hand vote taken)

15 DR. TITUS: Thirteen yes.

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

18 (Hand vote taken)

19 DR. TITUS: Zero no.

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

22 (Hand vote taken)

23 DR. TITUS: One abstention.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 30 percent who actually do take it. It's not who
2 decided not to do it. It's not the people who aren't
3 compliant. It's those that are that would tend to be
4 served by this, by this OTC availability of this drug.

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

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

22 CHAIRMAN BRASS: Dr. Uden.

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

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

13 CHAIRMAN BRASS: Dr. Blewitt.

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

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

4 CHAIRMAN BRASS: Dr. Johnson.

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

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

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

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

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

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

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

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

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

3 CHAIRMAN BRASS: Dr. Davidson.

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

17 CHAIRMAN BRASS: Dr. Silverstein.

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

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

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

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

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

4 CHAIRMAN BRASS: Dr. Grady.

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

25 CHAIRMAN BRASS: Do you believe there are

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

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

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

1 and tell them to start you on monitoring treatment.

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

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

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

18 CHAIRMAN BRASS: Dr. Uden.

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

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

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

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

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

22 (Hand vote taken)

23 DR. TITUS: Eight yesses.

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

1 (Hand vote taken)

2 DR. TITUS: Six noes.

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

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

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

17 CHAIRMAN BRASS: Dr. Davidson.

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

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

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

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

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

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

24 CHAIRMAN BRASS: Dr. Tamborlane.

25 DR. TAMBORLANE: I want to get back to

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

12 CHAIRMAN BRASS: Dr. Molitch.

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

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

1 package insert. Dr. Blewitt.

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

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

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

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

14 CHAIRMAN BRASS: Yes.

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

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

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

1 antifungals where it asks people not to use it until
2 they've at least been diagnosed with this condition
3 previously by a physician. Yet I think approximately
4 40 percent of people who used them had never had it,
5 or had not sought a physician's diagnosis before. So
6 it's not just reading the label, but understanding it
7 and following through with it.

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

16 (Hand vote taken)

17 DR. TITUS: Eleven yesses.

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

20 (Hand vote taken)

21 DR. TITUS: Three noes.

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

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

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

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

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

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

19 CHAIRMAN BRASS: Yes.

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

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

5 (Laughter)

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

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

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

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

5 DR. KATZ: That's correct.

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

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

18 (Laughter)

19 DR. JOHNSON: I mean, as it's written, age
20 35 and age 45, I guess my vote is no because I feel
21 that that is too low a risk population to target. If
22 the age was 40 and 50, that sort of changes my comfort
23 level. If it's 45 and 55, it might change it even
24 more. I also feel that it's not ready just to
25 absolutely sign off on. I think there does need to be

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

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

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

8 CHAIRMAN BRASS: Dr. Blewitt.

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

17 CHAIRMAN BRASS: Dr. Grady.

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

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

19 CHAIRMAN BRASS: Dr. Davidson.

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

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

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

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

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

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

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

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

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

8 DR. FRIEDMAN: I think when you look at
9 these people that come in, you know, somewhere between
10 15 and 30 percent of them are at their NCEP goal. We
11 did have a cohort of 321 people and when they saw the
12 study physician, that felt more appropriate to be on
13 prescription therapy because of being at higher risk,
14 either because of their levels or their risk factor
15 profiles.

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

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

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

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

25 DR. KATZ: That's correct. Actually we

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

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

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

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

18 CHAIRMAN BRASS: Post-marketing. Post-
19 approval studies. Post-approval studies, not--

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

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

4 (Hand vote taken)

5 DR. TITUS: Two yesses.

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

8 (Hand vote taken)

9 DR. TITUS: Twelve noes.

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

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

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

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

22 CHAIRMAN BRASS: Yes.

23 DR. UDEN: Okay.

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

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

3 CHAIRMAN BRASS: You've also promoted him.

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

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

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

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

6 CHAIRMAN BRASS: Dr. Molitch.

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

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

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

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

8 CHAIRMAN BRASS: Dr. Williams.

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

18 CHAIRMAN BRASS: Dr. Krenzelok.

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

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

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

9 CHAIRMAN BRASS: Dr. Neill.

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

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

4 CHAIRMAN BRASS: Dr. Johnson:

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

20 CHAIRMAN BRASS: Mr. Kreston.

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

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

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

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

22 CHAIRMAN BRASS: Dr. Davidson.

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

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

9 CHAIRMAN BRASS: Dr. Silverstein.

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

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

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

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

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

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

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

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

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

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

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

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C E R T I F I C A T E

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

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

Date: FRIDAY, JULY 14, 2000

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
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Rebecca Davis

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