

1 some pre-clinical studies in animals where we deter-
2 mined that giving a dose continuously is more effec-
3 tive than giving the same total, cumulative dose in an
4 intermittent fashion. And therefore, that's why we
5 designed our trials the way we did.

6 We do know that we can maintain bone mass
7 with continuous therapy; we know that we get bone loss
8 when we discontinue; and therefore we feel that
9 continuous therapy with five milligrams over the long
10 term is the appropriate approach for prevention of
11 osteoporosis.

12 ACTING CHAIR CRITCHLOW: Dr. Molitch.

13 DR. GOLDMANN: Dr. Critchlow, I think that's
14 important enough -- I'd like to have Dr. Siris give a
15 clinical perspective of estrogen alendronate treatment
16 in this population.

17 DR. SIRIS: I'd like to start by saying that
18 I certainly am an advocate of informing all post-
19 menopausal women of the great values of estrogen
20 replacement for cardiovascular benefit, bone benefit,
21 and for the relief of menopausal symptoms.

22 But I think there are a great many women for
23 whom the primary issue is bone: women who do not have
24 cardiovascular risk factors; have normal blood
25 pressures and cholesterols; whose parents have lived

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1 long lives without cardiovascular disease; women who
2 have no post-menopausal symptoms whatsoever, but who
3 have low bone mass -- who are concerned because of a
4 mother who has had a hip fracture.

5 And my position would be, that in such a
6 woman one should individualize therapy to that woman.
7 And in some of those women, estrogen may not necessar-
8 ily be the drug of choice. The pros and cons of the
9 various options need to be considered in each woman
10 and the appropriate medication chosen for that woman
11 -- one that would work for her, one with which she can
12 be compliant -- and I think that would be the perspec-
13 tive I would take.

14 ACTING CHAIR CRITCHLOW: Thank you. Dr.
15 Marcus.

16 DR. MARCUS: Mark was actually first.

17 ACTING CHAIR CRITCHLOW: Okay. Dr. Molitch.

18 DR. MOLITCH: I'm glad that the issue of
19 cardiovascular disease was brought up and that we are
20 no longer operating in a vacuum here. And I would
21 have to agree with Dr. Kreisberg that I think that in
22 general, estrogen is probably the best treatment for
23 most women at the time of menopause to help prevent
24 both osteoporosis and to prevent cardiovascular
25 disease or help ameliorate what might be a progressive

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1 cardiovascular disease.

2 And I would also prefer to see a statement
3 of some sort in that same package insert to say that
4 in women in whom estrogen therapy or hormone replace-
5 ment therapy might be contraindicated or not desired
6 -- or something of that sort -- but to have at least
7 -- it mentioned that estrogen therapy would be, sort
8 of the primary treatment then that alendronate would
9 be a substitute treatment when it's not desired.

10 DR. MARCUS: I would like to register just
11 a voice of concern about, that I have great sympathy
12 with the opinions that have just been expressed by my
13 colleagues and by Dr. Siris. There is the possibility
14 -- a very real possibility -- that there may be some
15 women in whom both hormone replacement therapy and
16 alendronate might be called for.

17 And if you just state in the package insert
18 that -- the wording implying that it's one or the
19 other I think, would also -- we should avoid that.
20 Such a woman might the patient who, even on what is
21 considered to be effective doses of hormone replace-
22 ment therapy, is losing bone, or a women who for
23 various reasons, needs to be on a dose of -- or in
24 preparation of hormone which is not known to be
25 effective.

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1 And so the possibility of even additivity at
2 full doses is something that I know Merck is currently
3 undertaking a study of. I don't know whether there
4 are any interim data that they could tell us about at
5 this point but if so, it might be helpful. But I
6 think we just have to be alert to this issue also, of
7 combined therapy.

8 ACTING CHAIR CRITCHLOW: I did notice in the
9 briefing document some mention in one of the trials
10 that there were women on estrogen?

11 DR. YATES: We have an ongoing, 2-year
12 clinical trial to look at the effects of -- in an
13 osteoporosis treatment population -- to look at the
14 effects of estrogen alone, alendronate alone, or the
15 combination of alendronate and estrogen, or there is
16 a small group that received placebo to both agents.

17 And these were women who had hysterectomies
18 which helps to at least give us some change of
19 blinding, although it's always difficult with estro-
20 gen. That study is still ongoing so we don't have the
21 final results from that.

22 ACTING CHAIR CRITCHLOW: Dr. Kreisberg, then
23 Dr. Hirsch.

24 DR. KREISBERG: Cathy, I don't want to
25 continue to belabor this point, but what caught my

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1 attention is when they listed the risk factors they
2 listed early menopause as a risk factor. And then
3 presumably for osteoporosis. It is probably a more
4 important risk factor for cardiovascular disease, and
5 I wouldn't like the implication carried forward that
6 early menopause can be addressed by using a drug like
7 alendronate; that there is more at stake here than
8 just the skeleton.

9 DR. YATES: Dr. Kreisberg, I certainly agree
10 with you and there is no intention on the part of
11 Merck to indicate that estrogen is not an appropriate
12 therapy for women during early menopause, particularly
13 those who are symptomatic and who derive benefits from
14 estrogen.

15 So I think that the issue really is, the
16 benefits and risks of treatment for individual
17 patients and what is needed is choices for patients,
18 for women, and their physicians so that they can be
19 able to make the most educated and best choice for
20 them in terms of a therapy that can maintain their
21 bone mass.

22 We just know that a lot of women are not
23 taking estrogen today, and clearly there is a need for
24 alternatives.

25 ACTING CHAIR CRITCHLOW: Dr. Hirsch.

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1 DR. HIRSCH: Essentially the same point was
2 the one I wanted to address. Namely, that it either
3 ought to be made clear if this is the truth or not,
4 that there's no advantage of taking this over estrogen
5 if some people who don't want to take estrogen for
6 other reasons.

7 But for those who are on estrogen therapy,
8 there's no reason to consider this -- or there is --
9 I mean, whichever way it goes. And I think that's an
10 extremely important consideration so that -- because
11 people will obviously get the notion, why not take
12 both. It may be a better thing since osteoporosis is
13 such a devastating thing to have, and as of this
14 moment that's rather a silly thing to do. It seems
15 like, unless we learn otherwise.

16 The other thing -- I do think that the
17 notion should come across that this is no way a
18 substitute for the other practices, namely: physical
19 activity, calcium, and say vitamin D, etc. -- the
20 general recommendations. Weak as they all are
21 individually, but nonetheless collectively they may be
22 important additions to the treatment and prevention of
23 osteoporosis.

24 So again, I just wouldn't like anyone to get
25 the notion that we've hit upon a specific here that in

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1 some way is better for the treatment of osteoporosis
2 than anything we've had before. This is a substitute
3 for other techniques, it seems like.

4 ACTING CHAIR CRITCHLOW: Dr. Marcus.

5 DR. MARCUS: I'm so glad somebody used the
6 word "choice" here. This is not Lake Woebegone. Not
7 all people start out with a bone mass of Z-score of
8 zero; that is, at the mean.

9 I challenge the notion that all we want to
10 do to prevent osteoporosis in the early post-menopaus-
11 al woman is to hold onto what she has. Let us not
12 forget that 16 percent of those women will enter
13 menopause with a bone density which is down one
14 standard deviation and a doubled fracture incidence.
15 As a physician I want to increase your bone mass, I
16 don't just want to hold on.

17 Furthermore, there's some complexity here in
18 the bone density measurement if you realize that about
19 30 percent -- particularly of Caucasian young women --
20 have a more than a one standard deviation variance
21 between their spine density and their hip density, and
22 by and large it is a lower hip density. You would
23 like to do something, even if their spine density may
24 be near the mean level, to at least promote some hip
25 density.

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1 I would like to argue that we should think
2 flexibly in terms of doses for a drug like this,
3 rather than being locked into a single dose. The
4 manufacturer has proposed five milligrams. There are
5 some things in the Agency's statements suggesting that
6 perhaps two-and-a-half milligrams might be better.

7 I, as a physician, would want to have the
8 choice of using two-and-a-half milligrams in some
9 individuals, five in others, and maybe even ten in
10 others -- purely as a preventive dose, not talking
11 about actual treatment of osteoporosis.

12 ACTING CHAIR CRITCHLOW: Are there other
13 questions? Okay, I just have one. We're clearly
14 right on time. You've mentioned some subgroup
15 analyses in the briefing document, and basically made
16 the statement that there essentially was no difference
17 in alendronate effect in these various groups.

18 Could you just please describe the types of
19 subgroups that you specifically looked at in the
20 prevention studies?

21 DR. YATES: I'm going to show slide B-7. We
22 did a number of different subgroup analyses to look at
23 the effects of variables that may be expected to have
24 an effect on bone mass. And this is a histogram to
25 show you the continuous variables.

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1 And we split the patients into tertiles of
2 age, years since menopause, fine BMD, baseline bone
3 turnover, and their dietary calcium. And these are
4 the patients in the EPIC study and these patients we
5 did not supplement with calcium. They were allowed to
6 take that supplemental calcium, they were recommended
7 to have adequate diets in calcium, but we did not give
8 supplements. So it had a wide range.

9 And this is the difference in bone mass
10 between the alendronate five milligram group and
11 placebo, so this is the total treatment effect. And
12 what you can see is for each of these continuous
13 variables there is essentially a very comparable
14 effect of alendronates irrespective of tertile.

15 The only difference being that those who
16 were within the earliest tertile maybe had a slightly
17 greater bone mass, and that was because -- that was
18 the group with the highest rate of bone loss. As we
19 know, there is a faster rate of bone loss very early
20 after menopause. But you can see treatment effect is
21 very consistent.

22 ACTING CHAIR CRITCHLOW: Are there any other
23 questions from the committee? If not, we'll reconvene
24 at 11 o'clock with the FDA presentation.

25 (Whereupon, the foregoing matter went off

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1 the record at 10:38 a.m. and went back on
2 the record at 11:03 a.m.)

3 ACTING CHAIR CRITCHLOW: Is the FDA ready to
4 begin? Dr. Dutta? I think we'll go ahead and start
5 now. Just one announcement prior to Dr. Dutta. I
6 just want to mention to everyone that the current FDA
7 Osteoporosis Guidelines for Treatment and Prevention
8 Trials are included in our folders and copies are
9 available on the table outside of the room here.

10 Now we'll have Dr. Dutta to start the FDA
11 presentation.

12 DR. DUTTA: We have heard the presentation
13 by the sponsor, Merck Research Laboratories, about the
14 efficacy and safety of FosamaxTM for prevention of
15 osteoporosis as well as for prevention of osteoporotic
16 fractures in post-menopausal women.

17 The first three slides present clinical
18 review, also overall impression on the controlled
19 clinical trials carried out by the sponsors.

20 FosamaxTM is an approved drug for the
21 treatment of post-menopausal osteoporosis and the drug
22 was approved in September 1995. FosamaxTM has met the
23 pre-clinical and clinical criteria set by the FDA
24 guidelines for its safe and effective use in preven-
25 tion of post-menopausal osteoporosis.

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1 Fosamax™ is indicated for the treatment and
2 prevention of osteoporosis in post-menopausal women.
3 For the prevention of osteoporosis, Fosamax™ should
4 be considered in post-menopausal women who are at risk
5 of developing osteoporosis and for whom the desired
6 clinical outcome is to maintain bone mass and to
7 reduce the risk of fractures.

8 And here we have identified all the risk
9 factors that are being proposed in the latest revision
10 of the package insert. Let me read from my slides.
11 We have concluded that Fosamax™ has provided adequate
12 evidence in support of the revised package insert for
13 prevention of osteoporosis as well as for the preven-
14 tion of fractures in osteoporotic women.

15 The current package insert has all the
16 adverse events that were presented in controlled
17 clinical trials as well as from post-marketing use of
18 the drug.

19 Now, if I go back to the prevention indica-
20 tion as you have seen the language for the prevention
21 of osteoporosis, I would like to draw your attention
22 on this language for the prevention of osteoporosis.
23 We basically agree with the sponsor's definition of
24 the target population for prevention as proposed.

25 Nevertheless, we would like to raise an

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1 issue about sponsor's recommended five milligrams per
2 day dosage regimen. Merck Research Laboratories
3 conducted the study number 055 with five milligrams
4 per day and 2.5 milligrams per day dosages.

5 . And data obtained from a relatively large
6 arm of the study on alendronate with about 452
7 patients in that arm showed that 2.5 milligrams per
8 day was as effective as five milligrams per day in
9 maintaining bone mass, particularly spine BMD.

10 Also to note in this slide, that spine BMD
11 was the primary efficacy endpoint in all three
12 prevention trials. The right hand column shows the
13 mean percent change in spine BMD at 24 months, and the
14 magnitude of increase at 2.5 milligrams per day in
15 study number 055 is quite comparable to that seen with
16 five milligrams per day in studies 029 and 038.

17 If the desired clinical outcome for preven-
18 tion is to maintain bone mass and to reduce the risk
19 of future fracture, then 2.5 milligrams per day dosage
20 regimen seems to achieve that goal and it could well
21 be the minimum effective dose for prevention.

22 In selecting the dosage regimen for preven-
23 tion, the safety of long-term administration of
24 Fosamax™ would also be taken into consideration.
25 Fosamax™ for prevention has to be administered for

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1 the prolonged period of time to a relatively large
2 number of subjects.

3 Thus, for this indication bone mass could be
4 adequately maintained at 2.5 milligrams per day dosage
5 regimen with minimum risk of observed and perceived
6 adverse events.

7 Thank you.

8 ACTING CHAIR CRITCHLOW: Thank you. Let me
9 ask a quick question on this slide. Is this taken at
10 the same timepoint -- at two years?

11 DR. DUTTA: Two years; 24 months. Because
12 the only -- study 038 and 055 were for 24 months, and
13 029 was for 36 months.

14 ACTING CHAIR CRITCHLOW: Dr. Marcus.

15 DR. MARCUS: If you just consider the
16 changes at the hip, would you draw the same conclu-
17 sion?

18 DR. DUTTA: Yes.

19 ACTING CHAIR CRITCHLOW: And then total
20 body?

21 DR. DUTTA: There was a marginal, negative
22 value in the total body BMD, but the changes in the
23 total body BMD was significantly different from the
24 placebo. That means that there was significant
25 attenuation of bone loss at total body.

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1 ACTING CHAIR CRITCHLOW: Are there other
2 questions from the committee?

3 DR. HIRSCH: I just have a -- something was
4 just put on our -- this is a study form -- 055 --

5 MR. MARTICELLO: That's the next presenta-
6 tion.

7 DR. HIRSCH: -- and others. And if you look
8 at these, what you say it seems to have to be modified
9 somewhat because the five milligram produces much
10 greater mean percent change --

11 MS. REEDY: Dr. Hirsch, would you speak into
12 a microphone.

13 DR. HIRSCH: Oh, I'm sorry. Maybe this is
14 related to something else, but I guess several pages
15 were put on our desk here during the intermission and
16 I'm just beginning to look at these now, and this is
17 --

18 MS. REEDY: That's the next presentation.

19 DR. HIRSCH: That's for the next presenta-
20 tion, okay. Because these speak against what you're
21 saying so maybe that will become rectified, then.

22 ACTING CHAIR CRITCHLOW: Dr. Dutta, are you
23 making a specific recommendation based on these data?

24 DR. DUTTA: We are making recommendation
25 that 2.5 milligrams could be taken into consideration

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1 as the minimum effective dose for prevention of
2 osteoporosis because of the other observed and
3 perceived adverse experience that we have, particular-
4 ly post-marketing experience with ten milligram dosage
5 for treatment of osteoporosis.

6 There may be, you know -- I'm not sure how
7 we can do that, but if possible that we can start with
8 2.5 milligrams and then we could increase the doses to
9 five milligrams. But again, in that case probably you
10 have to also monitor the total body BMD changes in
11 patients, and we have some difficulty in even monitor-
12 ing the BMD at spine in general populations, and as we
13 have been told by the sponsors and we also understand
14 that.

15 ACTING CHAIR CRITCHLOW: Is it the commit-
16 tee's preference to reserve that type of issue for the
17 discussion period later? Are there other questions
18 for Dr. Dutta? Now we'll hear from Mr. Marticello.

19 MR. MARTICELLO: Let me start out by
20 apologizing for the confusion regarding which handout
21 went with which presenter. But everybody at the table
22 should have a collection of three handouts clipped
23 together with a paperclip. I've also supplied copies
24 to members on each side, and there are two additional
25 copies at each end of the table here. They are

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1 clipped with a paperclip.

2 My presentation will commence -- I have some
3 slides -- and to make it easier, the first two of
4 these handouts can be used on a side-by-side basis:
5 the first handout, tabular data for the three preven-
6 tion studies; the second handout, graphical data for
7 the three prevention studies. The third handout we'll
8 get to in a little while. That deals with the FIT
9 study.

10 Now, this first slide -- that is table 1 on
11 your first handout -- deals with the spine BMD results
12 for study 029. Now, in looking at this slide you
13 notice that we have the five treatment groups where
14 the patients were randomized to, we have baseline, the
15 month 36 results, and the mean percent change.

16 For example, the placebo patients exhibited
17 a negative change of 3.51 percent, and the proposed
18 dose of five milligrams alendronate, there was an
19 increase of 2.89 percent. Each of the alendronate
20 groups significantly beat placebo, even the one
21 milligram group, but the one milligram group -- in
22 common with the placebo group -- had a significant
23 decrease from baseline; pointing out that that is a
24 sub-optimal dose. Ten milligrams also beat five
25 milligrams and five milligrams beat one milligram.

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1 Now, most of the effect was shown in the
2 first year as you can see on figure 1 in the second
3 handout, where we have a graphical display of that
4 data. Figure 2 in your second handout, coupled with
5 table 2 in your first handout, deal with some thresh-
6 old values to give you an idea of what percentage of
7 patients experience what kind of increase in bone
8 mass.

9 For example, in table 2 if you look under a
10 threshold, say, of four percent, reading across you'll
11 see that 1.2 percent of the placebo patients experi-
12 enced an increase in excess of four percent in spine
13 BMD, 6.48 for one milligram, 44 percent for five
14 milligram, and so on. And certainly the five milli-
15 gram, the proposed dose, 44 percent was significantly
16 better than the 1.2 percent showed for the placebo
17 patients.

18 The next slide deals with study 055. This
19 is table 3 in your first handout. And these are the
20 patients randomized to placebo, alendronate 2.5, and
21 alendronate five milligrams. And notice here the mean
22 percent changes are -1.78, 2.28, and 3.46. Each of
23 the alendronate groups -- 2.5 and 5 milligrams -- had
24 a higher mean percent change significantly, than
25 placebo, as well as five milligram -- the 2.5 milli-

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1 gram.

2 I want to get into that in a little while.
3 It's really not contradicting what Dr. Dutta was
4 saying about the 2.5 milligrams -- and I'll get into
5 that in a minute -- because you have to consider the
6 goal of the therapy is to maintain bone, and 2.5
7 milligram is doing just that. In fact, five milligram
8 yes, it's true, significantly outperformed 2.5.

9 And getting back to a comment that Dr.
10 Marcus made about ten milligrams, the same arguments
11 put forth by the sponsor in favor of five milligram or
12 2.5 milligram, could probably be put forward in favor
13 of ten milligram versus five milligram. We'll talk
14 about the 2.5 in a few minutes.

15 Now once again, most of the effect was shown
16 in the first year as you can see in figure 3 in the
17 second handout, which is a graphical display of the
18 data in table 3. And table 4 in your first handout --
19 which is the next slide -- displays the 12 month
20 results. And notice once again, we have significance
21 in favor of 2.5 and five milligram over placebo, -1.05
22 percent, 1.92 percent, and 2.74 percent.

23 So if you compare those percent changes
24 between table 4 and table 3 you can see that most of
25 the increase has already taken place at the 1-year

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1 mark.

2 Figure 4 in your second handout coupled with
3 table 5 in your first handout, visit the threshold
4 analysis. And keeping in mind that the goal of the
5 therapy is to maintain bone, if you look at table 5
6 across from a threshold of zero, you'll notice that
7 75.9 percent -- essentially 76 percent -- of the
8 patients randomized to alendronate 2.5 milligrams, did
9 not lose bone. That's compared to 86 percent on a
10 five milligram. Yes, 86 percent is significantly
11 bigger than 76 percent, but yet 76 percent maintained
12 bone.

13 If you go up that table a little bit to say,
14 -4 percent -- now I'll leave it to the clinicians to
15 decide what's a clinically-relevant bone loss -- but
16 if you look at -4 percent of the threshold, under the
17 alendronate 2.5 milligram -- once again, this is in
18 table 5 -- you'll see 96 percent compared to 97.5
19 percent in the alendronate five milligram.

20 Now subtracting those from 100 percent, what
21 that means is that you had four percent of the 2.5
22 milligram patients losing more than four percent,
23 versus 2.5 percent of the five milligram patients. So
24 the difference, of course, goes away as you go up that
25 scale or down the scale, depending on which way you

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1 want to look at it.

2 The next two figures in your second handout
3 -- figures 15 and 16 -- take a look at total body BMD.
4 Now this is the parameter that's been put forward as
5 a rationale for supporting five milligrams over 2.5
6 milligrams. Now keep in mind that this is a secondary
7 efficacy parameter. The primary efficacy parameter
8 was spine BMD, and as we just pointed out, 76 percent
9 of the patients on 2.5 milligrams did not lose bone
10 compared to 86 percent on the five milligram dosage.

11 Figure 16 shows a clear separation, and as
12 the sponsor indicated, 53 percent of the patients on
13 2.5 milligrams did lose bone. That's compared to 35
14 percent who lost spine BMD on five milligrams. But if
15 you look at figure 15 you'll notice that the negative
16 marginal loss in the 2.5 milligrams translated to a
17 loss of -0.3 percent. So on a mean basis there just
18 isn't that much loss with total body BMD.

19 So once again, if you're looking just to
20 preserve bone, 2.5 isn't completely out of the picture
21 even when you're looking at total body BMD. And if
22 you go back to that -4 percent level with regard to
23 total body BMD, it turns out that 3.2 percent of the
24 alendronate 2.5 milligram patients lost more than four
25 percent compared to 2.1 percent of the five milligram

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1 patients. That's 3.2 versus 2.1

2 So once you get down the scale away from
3 the zero, that difference really goes away as you
4 might expect.

5 Now the next slide -- and this is table 6 in
6 your first handout -- looks at that first stratum
7 where the patients had an opportunity to be randomized
8 to the estrogen/progestin group. This is the European
9 cohort; there were two European centers and two U.S.
10 centers. And let's just focus on the alendronate five
11 milligrams and the estrogen/progestin results.

12 And as you can see, the estrogen/progestin
13 increase of 5.14 is higher than the alendronate five
14 milligram increase of 3.34. In fact, the difference
15 was significant with a p-value of .008, less than .01.

16 The next slide -- table 7 on your first
17 handout -- looks at the U.S. cohort, the two centers
18 that were in the United States. And once again,
19 estrogen/progestin outperformed alendronate five
20 milligrams, 4.04 versus 2.85. In this case you had a
21 strong, statistical trend of p-value of .055 in favor
22 of estrogen/progestin over alendronate five milli-
23 grams.

24 The next slide which is table 8 in your
25 first handout, deals with study 038. Now there's a

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1 typo here -- alendronate 2.5 milligrams should be
2 alendronate five milligrams, and alendronate five
3 milligrams should be alendronate ten milligrams. And
4 these results are consistent with study 029 in that
5 alendronate five milligrams and alendronate ten
6 milligrams both outperformed placebo, and alendronate
7 five milligrams statistically outperformed alendronate
8 2.5 milligrams.

9 Now, figure 5 in the graphical handout,
10 coupled with table 9 in your first handout -- which is
11 the very next slide -- take a look at the two addi-
12 tional treatment groups. Patients were also random-
13 ized to five milligrams for six months followed by
14 placebo, or ten milligrams followed by placebo.

15 In this case, you can see from six to 24
16 months, once that crossover is made, that the latter
17 two treatment groups -- the decline sets in essential-
18 ly comparable to the placebo group.

19 So once you take these patients off of five
20 or ten -- in fact the five milligram treatment group
21 outperformed significantly, the 5/0, and correspond-
22 ingly the ten milligram outperformed the 10/0. So
23 once you take the patients off of alendronate you
24 start to lose bone again.

25 Now the last table on the first handout is

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1 a summary table -- that's this slide here -- where the
2 values in parentheses under study 029 are the 3-year
3 results. All other figures are 2-year results.

4 And if you look at the five milligram row
5 you'll notice that you have comparability between the
6 three studies. The 029 mean percent change was 2.65,
7 038 it was 2, and 055 it was 3.46.

8 And as Dr. Dutta mentioned earlier, if you
9 go up one line across from 2.5 milligrams, under the
10 055 column you'll see an increase of 2.28 percent,
11 which is certainly in the ballpark as the five
12 milligram increases are -- although, granted, there is
13 a significant difference in favor of five over 2.5 in
14 study 055.

15 So to wrap up the three prevention studies,
16 studies 029, 038, and 055 demonstrated an alendronate
17 treatment effect with regard to prevention of spine
18 BMD loss. Each alendronate treatment group experi-
19 enced a significantly more favorable BMD response than
20 did the placebo group.

21 Placebo patients experienced a significant
22 reduction in spine BMD over the 2- to 3-year treatment
23 period; however, patients who received alendronate 2.5
24 milligrams, five milligrams, or ten milligrams daily
25 experienced a significant increase in spine BMD over

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1 the same time period.

2 Study 038 demonstrated that the cessation of
3 alendronate therapy after six months resulted in a
4 reversal of the treatment effect -- reversal in the
5 sense that patients started to lose bone once they
6 were off alendronate.

7 Study 055 demonstrated that alendronate was
8 not as effective as estrogen/progestin in increasing
9 spine BMD. And clinicians should assess the sponsor's
10 recommendation of alendronate five milligrams given
11 the positive spine BMD results experienced by patients
12 who received alendronate 2.5 milligrams in study 055.

13 Now we can move on to the third handout
14 which addresses the FIT study. This is the vertebral
15 fracture study which is one of the two components of
16 the FIT study.

17 The sponsor indicated that there were no
18 meaningful differences between the placebo and
19 alendronate treatment groups with regard to adverse
20 experiences. Well, if you look at table 1 -- the
21 first table on your third handout -- you notice that
22 there were significant differences.

23 I don't know if these are clinically
24 relevant but there were significant differences in
25 favor of placebo over alendronate with regard to ankle

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1 sprain, broken tooth, diarrhea, and eye disorder.

2 The second table gives you the fracture
3 rates, and as already been mentioned, the alendronate
4 rate was eight percent versus a 15 percent placebo
5 rate. The result was highly significant; the relative
6 risk was .53 -- less than one in favor of alendronate
7 -- and the 95 percent confidence interval excluded
8 one, a lower bound of .41 and an upper bound of .68.

9 Now, the .53 is very consistent with the .52
10 relative risk that was experienced in studies of 35
11 and 37, which formed the basis for the approval of
12 Fosamax™ for the treatment of osteoporosis. Those
13 studies were discussed in a prior advisory committee.

14 The third table breaks down the treatment
15 groups with regard to the number of fractures experi-
16 enced. And these results are consistent in the sense
17 that if you looked at the number of fractures -- the
18 actual number of fractures experienced by the patients
19 -- in each case the placebo rate was higher than the
20 alendronate rate.

21 For example, one fracture was 10.2 percent
22 versus 7.4 percent; two fractures, 2.7 percent versus
23 0.2 percent; three fractures, 0.8 percent versus 0.3
24 percent; and four or more fractures, there were 13
25 patients in a placebo group for 1.3 percent and no

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1 alendronate patient had four or more fractures.

2 Now, as was new vertebral fracture -- the
3 primary efficacy parameter in the vertebral fracture
4 study -- any clinical fracture was the secondary
5 efficacy parameter. Any clinical fracture is also the
6 primary efficacy parameter for the clinical fracture
7 study component of FIT, which is not being discussed
8 today.

9 But looking at the last table, table 4 in
10 the third handout, you'll notice that the alendronate
11 patients -- the percentage, 13.6 percent -- was
12 significantly lower than the placebo rate of 18.2
13 percent, a p-value of .004 in favor of alendronate or
14 placebo with regard to the percentage of patients that
15 experienced any clinical fracture of the secondary
16 efficacy endpoint.

17 Now, subsets of any clinical fracture
18 endpoint are also displayed in the table: clinical
19 vertebral, hip, forearm, any non-vertebral, and other
20 -- other being fracture at sites other than the spine,
21 hip, and wrist. And as you can see, you have signifi-
22 cance in favor of alendronate over placebo with regard
23 to clinical vertebral, hip, and forearm.

24 You have a statistical trend, .063 in favor
25 of alendronate over placebo with regard to any non-

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1 vertebral fracture, and nothing going on with regard
2 to the other fracture categorization.

3 Thank you. Oh, I'm sorry -- one last thing.
4 Let me just make a few closing comments on the FIT
5 study. The FIT study was successful in demonstrating
6 a significant treatment effect in favor of alendronate
7 over placebo with respect that a percent of patients
8 who experience at least one, new vertebral fracture
9 over three years of double-blind treatment.

10 These results were consistent with those of
11 the previously reviewed studies, 035 and 037, which
12 were the basis for the approval of Fosamax™ for the
13 treatment of post-menopausal women. Statistical
14 significance was also detected in favor of alendronate
15 over placebo with respect to the incidence of any
16 clinical fracture as well as for the incidence of
17 clinical vertebral, forearm, and hip fractures.

18 There was a statistical association between
19 alendronate and the incidence of ankle sprain, broken
20 teeth, diarrhea, and eye disorders, respectively.
21 Thank you.

22 ACTING CHAIR CRITCHLOW: Questions? Dr.
23 Molitch.

24 DR. MOLITCH: I'm not a statistician as like
25 you are. I just have a question about your meta-

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1 analysis that you've done here on these dose compari-
2 sons between the different studies. And you're
3 probably much better at doing this than I am as a
4 statistician.

5 But I think the studies are somewhat
6 different -- use different machines in doing the bone
7 mineral density. If we look at the difference in the
8 placebo groups, at the changes, they are very differ-
9 ent from protocol 029 to protocol 055, and I think
10 different bone mineral density machines were used in
11 some of these different studies. And certainly in 055
12 I think they were mainly non-lunar machines; in the
13 other studies they were a mixture of machines.

14 And I was just wondering how valid it is to
15 do the type of meta-analysis that you've done when the
16 direct comparison in the one study -- where it really
17 clearly was a direct comparison using the same
18 techniques -- showed a very significant difference
19 between the 2.5 and the five? And how valid is it to
20 make this five comparison between the different
21 studies?

22 MR. MARTICELLO: You're correct; different
23 machines were used in different studies. In fact,
24 within each study different machines were used. But
25 the results were consistent within each study for each

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1 type of machine used.

2 As far as this comparison goes, the intent
3 is just to demonstrate that, if you want to focus on
4 study 055 by itself fine. I'm not going to dispute
5 that five milligrams doesn't significantly outperform
6 2.5 milligrams. There's no question about that; it
7 does. Ten milligrams significantly outperforms five
8 milligrams.

9 A case probably could be made for ten
10 milligrams over five milligrams using the same
11 argument that the sponsor did supporting five over 2.5
12 milligrams. Studies certainly weren't designed to ask
13 whether patients should start on 2.5 and then maybe be
14 titrated up to five and then ten -- studies weren't
15 designed.

16 But I think as Dr. Marcus pointed out, it's
17 conceivable that each one of these doses has a place
18 as far as the prevention of osteoporosis is concerned.
19 So yes, I agree with you, it's not completely clean
20 with regard to these different machines, but given
21 that the within-study results were consistent between
22 the different machines, I think one can look at this
23 -- this summary table, table 10 -- and note that the
24 2.5 milligram results are not that far off of the five
25 milligrams as far as absolute number. But if you're

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1 talking about statistically significant, you're
2 correct.

3 DR. MOLITCH: I agree. I think it's nice to
4 have the wide variety of dosages, but what I'm saying
5 is I'm not sure that the way that you presented the
6 data is a clear argument against there being a
7 difference between those two.

8 DR. MARCUS: Excuse me. May I just give you
9 a piece of information on that? It is actually
10 reassuring -- although there are systematic differ-
11 ences among manufacturers and machines and indeed,
12 even within models of a given manufacturer -- it
13 changes over time. It seemed to be pretty matched
14 across the whole panoply of them.

15 So there's something maybe in the software
16 program or in the edge detection device so that a
17 lunar machine reads a little bit higher than say, a
18 hologic machine. There are correction factors for
19 that. But if you look over time, you know, one
20 percent loss seems to pretty much match out as a one
21 percent loss, or gain.

22 MR. MARTICELLO: And you have to keep in
23 mind that these are controlled studies; we do have a
24 placebo group. And so, you know, you need to look at
25 the difference between the alendronate versus placebo,

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1 and that's where I talk about consistency with regard
2 to the machines.

3 ACTING CHAIR CRITCHLOW: So the machines
4 were consistent within center then, or within pa-
5 tients? So a patient was only done on a certain --

6 MR. MARTICELLO: Oh yes, definitely. Okay,
7 I think Dr. Hirsch and then Kreisberg.

8 DR. HIRSCH: Just for this 2.5 versus five,
9 I guess what one wants to know, and what I don't know
10 and perhaps should -- is the relationship between bone
11 mass density and reduction of fractures.

12 I mean, that's the key issue, because
13 otherwise -- I mean produce osteopetrosis or something
14 -- it wouldn't make any difference. I just want to
15 know, you know, the exact relationship between
16 fracture reduction versus bone mass density, because
17 without that, you can't come to any dosage conclu-
18 sions.

19 MR. MARTICELLO: Well, you're not going to
20 get that in these studies with regard to 2.5 because
21 we don't have any fracture results for 2.5. The
22 prevention studies were not designed to detect a
23 fracture difference. The FIT study only used five and
24 ten milligrams.

25 Keep in mind that the sponsor is looking for

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1 ten milligrams with regard to treatment. They're not
2 looking for five milligrams.

3 DR. HIRSCH: Then you could argue it the
4 other way and say look, nature's way of doing it is
5 the best way. That is, the estrogen -- and that's the
6 level then of minimal fracture. We don't know that
7 for a fact, but it would seem like a reasonable guess.
8 So if that's true, the whole 2.5 versus five argument
9 falls apart. You want to get as close to, at least
10 what estrogens did.

11 MR. MARTICELLO: There's no question. If
12 you look at study 055, certainly estrogen/progestin
13 significantly outperformed five milligrams and even
14 moreso with regard to 2.5.

15 DR. HIRSCH: I don't see how you can
16 conclude that 2.5 is as good as five.

17 MR. MARTICELLO: No, I'm not in the position
18 to conclude that. I'm just pointing out that if you
19 look at the primary efficacy parameter of increase in
20 spine BMD, and given an attempt as I understand it, of
21 the therapy to maintain bone -- that spine BMD -- then
22 2.5 does maintain. Now whether that's a clinical,
23 relevant statement or not I don't know.

24 ACTING CHAIR CRITCHLOW: Given that the 2.5
25 dose was only assessed in one study, I mean, how

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1 strong is your feeling that we should look at the 2.5
2 as a reasonable dose --

3 MR. MARTICELLO: That's a very good point,
4 but you have to keep in mind, if you look at table 10
5 that that one study was the largest study by far. You
6 had sample sizes of 461, 452, and 445 in study 055,
7 compared to sample sizes of less than 100 in each of
8 the treatment groups in the other two studies.

9 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

10 DR. KREISBERG: It seems to me all this
11 discussion hinges on changes in vertebral bone mineral
12 density, whereas I think the hip is probably more
13 important, and the changes that occur in the hip are
14 probably less than those that occur in the spine with
15 therapy. So do you have data that addresses the issue
16 of dose and what happens at the hip?

17 MR. MARTICELLO: I don't have any at hand
18 here, but I do remember a slide that the sponsor
19 showed, and I believe the hip BMD, the 2.5 milligrams,
20 there was an increase. It was only when we went to
21 total body BMD where we saw the decrease with regard
22 to the 2.5 milligram dose.

23 ACTING CHAIR CRITCHLOW: Would the committee
24 want to see that slide now, or reserve that discussion
25 for this afternoon?

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1 DR. MARCUS: I think it's very important.
2 I asked Dr. Dutta if he would make the same conclu-
3 sions based on the hip data and he said yes. I
4 certainly want to see it. While that's being obtained
5 I'd like to just answer Dr. Hirsch.

6 I should tell you that as an investigator in
7 the FIT trial I have a vested interest in that, but I
8 can tell you something about the data. And that is
9 that it is an article of faith in the bone field that
10 for every standard deviation below the mean level that
11 a person falls in bone mineral density, there's a 2-
12 to 3-fold increase risk for fracture.

13 Therefore, one would predict from that
14 relationship --

15 ACTING CHAIR CRITCHLOW: Over what period of
16 time?

17 DR. MARCUS: -- that dose relationship --
18 excuse me?

19 ACTING CHAIR CRITCHLOW: Over what period of
20 time?

21 DR. MARCUS: However you want to do it. Do
22 you want to follow for five years, do you want to
23 follow it for ten years? It will hold up. We had an
24 operating assumption in the FIT trial that we should
25 see a dose response relationship between improvement

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1 in bone density and reduction of fractures.

2 In fact as it played out, the number of
3 fractures -- the fracture experience was considerably
4 better than one would have predicted, simply from
5 knowing the change in BMD. And there's a lot of
6 consternation and discussion within the people who are
7 investigators in FIT, is to try to understand exactly
8 what that is.

9 Maybe there's some additional benefit just
10 showing down remodeling rate. The truth is, we don't
11 know. And it's also certainly not known whether
12 taking it in a preventive mode, whether a rise of X
13 percent of bone density would have the same effect on
14 fracture experience as in a treatment mode. We just
15 don't know that.

16 ACTING CHAIR CRITCHLOW: Dr. Yates or
17 Goldmann, did you --

18 DR. YATES: Yes. Certainly the one milli-
19 gram -- sorry, the difference between the 2.5 and the
20 five milligram dose at all sites was about one
21 percent, including at the hip which we just saw there.
22 The differences are highly significant at all sites.

23 One of the reasons for the differences that
24 we observed between the different clinical trials was,
25 as I indicated in my presentation, there were differ-

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1 ences in the patient population. The women in the
2 EPIC study shown here were on average, six years out
3 from menopause compared to those in protocol 029, the
4 dose range finding study, where they were on average,
5 two years out from menopause.

6 We've been able to show -- if I can show
7 slide A-11 -- that there are differences in the rate
8 of bone loss in those women, early post-menopause
9 versus those who are later post-menopause, which can
10 account for some of the differences pointed out by Dr.
11 Dutta between the different clinical trials.

12 And this is a slide that shows the women in
13 terms of their time post-menopause. You can see that
14 -- this is the two clinical trials. The protocol 055
15 is shown as the white symbols and protocol 029 is
16 shown as the blue symbols here.

17 And this is the loss in the placebo group --
18 shown on the bottom part of the slide -- over two
19 years versus the gain in patients on alendronate. And
20 you can see that within this period of time, less than
21 one year post-menopausal, the loss was actually very
22 rapid, at a rate of about two percent a year -- losing
23 down to about four percent.

24 It was a little less rapid in those between
25 one and three years post-menopause, and less beyond

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1 that timepoint. And you can see that there is a
2 parallelism here with the treatment effect of alendro-
3 nate.

4 So one of the reasons why I think 2.5 looks
5 as good as it did in the EPIC population, is that we
6 were including who were in this population here who
7 are five years or more post-menopause, and in our
8 other clinical trials our focus was on early post-
9 menopausal women.

10 When we match the time since menopause, as
11 you can see between the two protocols -- 029 in blue
12 and EPIC in white -- that the responses are very, very
13 similar in the two treatment groups. And actually,
14 that's in spite of some differences in calcium
15 supplementation and other things. These patients lose
16 about the same for their time since menopause.

17 ACTING CHAIR CRITCHLOW: Dr. Molitch?

18 DR. MOLITCH: No.

19 ACTING CHAIR CRITCHLOW: Do you have some
20 data on percent increase in BMD by baseline BMD?

21 MR. MARTICELLO: I don't have that here but
22 once again, the results were very consistent. I
23 believe the sponsor showed that slide a little
24 earlier.

25 ACTING CHAIR CRITCHLOW: In terms of

1 absolute increase?

2 MR. MARTICELLO: I think it was with regard
3 to percent increase.

4 ACTING CHAIR CRITCHLOW: In the percent
5 increase?

6 MR. MARTICELLO: Yes.

7 DR. YATES: P-10 -- okay, this is a similar
8 analysis to the one I just showed you. Looking at the
9 baseline BMD for the two protocols -- again, protocol
10 029 shown here as the triangles and protocol 055 or
11 EPIC, shown as the squares -- and baseline bone mass
12 of the spine is shown on the axis.

13 We looked at women with entirely normal bone
14 mass on the right; those with bone mass that was
15 moderately low in the middle; and those with low bone
16 mass on the left. You can see that there tends to be
17 less bone loss in those starting with the lowest bone
18 mass, compared to those with higher bone mass.

19 But again, the treatment effect is very
20 comparable at about five percent difference between
21 placebo and alendronate in these two trial popula-
22 tions.

23 ACTING CHAIR CRITCHLOW: Thank you. Are
24 there other questions from the committee? I think we
25 are about ten minutes ahead of schedule. We'll

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1 reconvene in one hour after a lunch break. So we'll
2 be back here at -- well, we'll start at one o'clock.
3 Be ready to start at one o'clock.

4 (Whereupon, a luncheon recess was taken at
5 11:50 a.m)

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

2 1:00 p.m.

3 ACTING CHAIR CRITCHLOW: This afternoon,
4 we're now at the point for discussion of the ques-
5 tions, but what I would first like to do is ask if
6 there are any comments or questions from the committee
7 on the presentations this morning -- either general or
8 otherwise -- before we proceed to a specific discus-
9 sion of the questions? Dr. Colley.

10 DR. COLLEY: I have a question about the --
11 with regard to the dosage range. Dr. Marcus brought
12 up an interesting point that there's a continuum of
13 degree of bone loss in women at post-menopause, and
14 the idea of a non-fixed dose of say, a 2.5, 5, 10
15 milligram dose range is attractive.

16 But for practicality's sake, I guess I'm
17 wondering how you would select patients to use a fixed
18 dose range with a preventative like this. Most
19 patients will be getting this from their primary care
20 provider and a 45, 50-year-old woman going into the
21 primary care provider may or may not even get a
22 mammogram, much less bone densitometry.

23 So what type of criteria outside of bone
24 densitometry would be appropriate to stratify patients
25 to different dosages?

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1 DR. MARCUS: Is that a question you're
2 asking me? Give me the simple question. Well, with
3 the Chairman's permission, is it ready to go into this
4 issue?

5 ACTING CHAIR CRITCHLOW: Please.

6 DR. MARCUS: I think it's probably the
7 critical issue we have to face this afternoon. We
8 have two issues here: one is scientific and the other
9 is basically health economics and access. There may
10 be 40 million women with osteoporosis or highly at
11 risk for osteoporosis, and there may be 4,000 densi-
12 tometers. And the densitometrists can't just surround
13 the others to get at them, so I'm sensitive to the
14 question of access.

15 And I think that there are techniques in the
16 offing that there are a lot of manufacturers stumbling
17 over each other to try to get them introduced into the
18 community, that will not substitute for dual energy x-
19 ray absorptiometry, but it will at least permit
20 screening of patients who would then be referred to
21 get a proper DEXA examination.

22 These techniques include everything from
23 non-radiologic techniques like ultrasound of the heel,
24 to peripheral bone densitometry such as peripheral
25 DEXA and peripheral QCT, which are becoming more and

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1 more objects of study and perhaps introduction into
2 the community-at-large.

3 I think that my selection of a dose of a
4 preventive agent, would be predicated on knowledge of
5 bone mass. I don't think that bone turnover markers
6 are ready for prime time. I don't think that any of
7 these questionnaires that you can fill out in the
8 magazines in the supermarket -- you know, questions
9 about whether you're white or Asian, thin, have gray
10 hair, etc., etc. -- give you anywhere the near the
11 specificity or sensitivity that would allow me to feel
12 comfortable with a dose of any medication.

13 So those are amusing and interesting objects
14 of study, but for making therapeutic decisions I want
15 a bone mass measurement.

16 ACTING CHAIR CRITCHLOW: Dr. Sobel.

17 DR. SOBEL: I just wanted to make a comment
18 about our Division's position. Well, actually at
19 lunchtime we talked it over and we felt perhaps we, in
20 our Division presentation, came across too directive
21 and strong in regard to the 2.5 milligram dose. That
22 is just a dose that we want to be considered among
23 other doses and among other regimens, and we really
24 don't want to direct the discussion as revolving
25 around that position, whether acceptable or not. It's

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1 just a consideration.

2 And I think Dr. Marcus, you raised some of
3 the issues that are involved in some of our analyses.
4 Does one want to maintain bone or increase bone?
5 Obviously, your statistical analyses and thresholds
6 change in regard to 2.5 and ten surrounding that issue
7 of maintenance versus increased. But it's clear that
8 ten is better than five and five is better than 2.5.

9 And intertwined with all of this is the
10 issue of adverse reactions. Should we find a dose
11 that answers both the questions best? What sort of
12 bone treatment do we want and at what adverse reaction
13 price, so to speak?

14 So this little introductory comment was just
15 to make it clear that we in the Division, have not
16 selected the 2.5. As far as titrating doses based on
17 bone mass, etc., I guess I tend to be empirical about
18 that. We have to look at the Merck database -- where
19 is the information and could we write labeling based
20 on empirical results as far as initial dose, titra-
21 tion, etc., and correlate it perhaps, to initial bone
22 mass?

23 Those are all very plausible positions but
24 in the final writing of labeling we always are thrown
25 back to what we actually have in our knowledge base.

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1 But the main thing I wanted to say is that we just
2 wanted you to consider 2.5 in reference to how you
3 look upon this treatment as maintenance, increase in
4 bone, and its intersection with adverse reaction
5 consideration.

6 ACTING CHAIR CRITCHLOW: Thank you. Dr.
7 Marcus, what would you -- I mean, do you have sugges-
8 tions at this point in terms of dosage in the label,
9 in a proposed label? Or is that premature at this
10 point?

11 DR. MARCUS: Never having written a label,
12 all I'm making a plea for is that a physician should
13 understand that he or she has flexibility to use
14 whichever dose seems indicated.

15 ACTING CHAIR CRITCHLOW: Based on the data
16 that 2.5 was effective in whatever situation, and five
17 was --

18 DR. MARCUS: Yes. If somebody showed me
19 that a woman had essentially no deficit in bone
20 compared to women her own age -- a Z-score of zero or
21 a T-score of zero -- then certainly there's no
22 compelling need to increase her bone mass. But she's
23 entering menopause; you could make a case that she
24 should have protection.

25 If she can't take estrogen for some reason

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1 or if, let's say this is a woman who has recently had
2 breast cancer and has been rendered menopausal, so
3 clearly, the standard of care would preclude her
4 getting estrogen. I would see no reason to use more
5 than two-and-a-half milligrams a day of alendronate if
6 her bone mass were okay.

7 If she were however, down a standard
8 deviation, I would probably start on five milligrams
9 in the hope of getting some increase. And if she were
10 down let's say, 1.8 standard deviations so that she
11 did not qualify as having osteoporosis on WHO criteria
12 but still it was substantially at risk, I would
13 probably go for ten milligrams.

14 All that being said, I want to avoid -- I
15 think we should avoid -- arbitrary bone density
16 settings because of what our nightmarish experience
17 has been in California.

18 Where, with the World Health Organization
19 criterion of a T-score worse than -2.5 as being the
20 diagnostic standard for osteoporosis, I have personal-
21 ly been in the situation of having patients turned
22 down for reimbursement of alendronate because they may
23 have had fractures and low trauma fractures, but their
24 T-score was only -2. And you know, somebody at the
25 insurance company would call me and say, we're turning

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1 your patient down; she does not have osteoporosis.

2 So I don't think we should be wedded to a
3 specific, gold standard, bone density, but I still
4 think that bone mass is the final analysis, the best
5 we have now for helping to select treatment and
6 patients for treatment.

7 ACTING CHAIR CRITCHLOW: Dr. Kreisberg, then
8 Dr. New.

9 DR. KREISBERG: I think there's another
10 issue here and it's really part of the educational
11 program; it's not part of the dose ranging type of
12 thing. And that is that many women who will be
13 assessed at the time of the menopause will not have
14 osteoporosis nor osteopenia by any definition, but it
15 does not mean that they will not develop that over
16 time.

17 So this almost has to be like mammograms
18 that are done at certain intervals in order to find
19 when a patient becomes at risk or becomes a candidate
20 for the drug. The implication in all of the discus-
21 sion is that this will occur at the time of the
22 menopause and a decision will be made. But it seems
23 to me that that decision always has to be revisited.

24 DR. MARCUS: Sure.

25 ACTING CHAIR CRITCHLOW: Dr. New.

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1 DR. NEW: I just want to make a comment but
2 then ask a question. Usually, menopause is defined as
3 the woman who stops menstruating for a period of six
4 months, but the hormonal changes of menopause are
5 very, very gradual and insidious, and therefore I
6 wouldn't be surprised if bone changes too a long time
7 to be evident, because the hormonal changes are very
8 slow.

9 DR. KREISBERG: I agree with -- do you want
10 me to answer that?

11 DR. NEW: Yes.

12 DR. KREISBERG: I agree with that, but if
13 you look at the doses of conjugated estrogen that seem
14 to protect the skeleton, that's equivalent to about
15 five micrograms per day of estradiol, and the low dose
16 birth control pills contain about 25. So it seems to
17 me that even though ovarian function is failing from
18 about the age of 40 until when it really stops, that
19 the failing ovary is still continuing to produce
20 sufficient estrogen to protect the skeleton until it
21 really just collapses.

22 DR. MARCUS: That's actually supported by
23 two studies I know of, looking at the peri-menopause:
24 one by Klaus Christiansen's group and the other by Bob
25 Recker's group. And both of them really show pretty

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1 good preservation, at least of spine bone density, up
2 until you know, within a few months of that last
3 menstrual period.

4 DR. NEW: Actually, my question is addressed
5 to you, Dr. Marcus. In the table 1 we see that
6 alendronate five milligrams changes bone mineral
7 density from .96 to .99 at 36 months. Now, I know
8 that that's statistically significant, but I'm asking
9 you as a physician who takes care of such patients --
10 which I don't -- is that biologically significant?

11 DR. MARCUS: It certainly was in the FIT
12 experience, which is really the only intervention that
13 you could look prospectively at fractures. It's about
14 what -- a three or four percent change, and based upon
15 the relationship of a doubling to tripling of fracture
16 risk for every standard deviation, one standard
17 deviation is about ten percent in bone density.

18 So we're talking about something like a 25
19 to 30 percent reduction in fractures just from that
20 amount, is what -- I'd hazard that guess. I think
21 that's about three or four percent, just calculating
22 on my feet is not my best suit.

23 DR. NEW: In the FIT study, if you look at
24 the reduction in fractures at the hip, from placebo to
25 alendronate -- and I don't know what dose that was,

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1 but I think it's five milligrams -- or is it ten?
2 It's five. Ten? It is ten. The hip fractures
3 reduced from 22 to 11, so it's about half.

4 ACTING CHAIR CRITCHLOW: Yes, Dr. Hirsch.

5 DR. HIRSCH: I thought one of the problems
6 was that we don't have a very good understanding of
7 the relationship between bone mass and fracture rate.
8 There's not a good mathematical, linear, or whatever
9 thing.

10 It's a guess, obviously, that the most
11 osteopenias the more the fracture -- so given that,
12 you almost have to say, like on scientific grounds,
13 that the bone density is a measurement of a risk
14 factor. But if you want to start thinking about a
15 therapeutic thing, you have to go on studies in which
16 an amount of drug was given and how many fewer
17 fractures there were.

18 So that the FIT thing would almost be the
19 dominant issue in drug decision, even though measuring
20 bone density is a terribly important risk -- is that
21 true?

22 DR. MARCUS: Well, you're quite right except
23 that the patient population is very different. The
24 vertebral arm of the FIT trial was restricted to women
25 who had already proven that they will have fractures;

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1 they had osteoporosis. It's not that they had a high
2 risk for having, but not necessarily 100 percent of,
3 you know, people with high risk will have it. So
4 that's the problem with that.

5 ACTING CHAIR CRITCHLOW: But bone mineral
6 density is, in and of itself, diagnostic. Am I
7 correct? I mean, when you're talking about it's a
8 market for a fracture --

9 DR. MARCUS: It is diagnostic of a very high
10 risk. If you satisfy the World Health Organization
11 criteria you are at a very high risk for fracture.
12 But there are some people within that who would not
13 have a porotic skeleton if you looked at it under the
14 microscope. It cannot ever be a gold standard, just
15 bone mass.

16 DR. McCLUNG: I'm Mike McClung from Port-
17 land. Let me comment about Dr. Marcus' point and
18 amplify a couple of things. One is about the bone
19 density difference and the relationship between the
20 bone density differences we saw and fracture risk.

21 There is a four percent difference in the
22 EPIC study between the placebo group and the treatment
23 group but that is a fixed point in time. And the bone
24 density values in the treated group have remained
25 stable in the studies that we've done, while they

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1 continue to drop in the placebo groups.

2 So while there's a four percent difference
3 at two years, that may not be -- and probably isn't --
4 the minimal difference that we'll be seeing with
5 longer term therapy. That's one point.

6 The other point let me address from a purely
7 clinical perspective, as one who sees patients in his
8 clinic and compares those patients we saw in the EPIC
9 study with regard to the dose.

10 We're all aware that bisphosphonates are
11 poorly absorbed from the GI tract and that modest
12 changes in the dosing regimen can impact the absorp-
13 tion efficiency. The patients in the EPIC study were
14 women who were very motivated to be in a clinical
15 trial. They were seen every three months, were
16 educated and cajoled and encouraged each time they
17 were seen, to take the medication correctly -- in the
18 right way.

19 In clinical practice that's not the way
20 things are done. Although two-and-a-half milligrams
21 shows an effect, the buffer if you will, between the
22 dose that's given and the one milligram dose which is
23 clearly ineffective, is a whole lot less than with a
24 dose of five milligrams a day.

25 And from the standpoint again, of effective-

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1 ness, the average change in bone density is less
2 important from a clinical standpoint, from those of us
3 who see one patient at a time than the proportion of
4 patients who are protected from bone loss.

5 And so in the total body for example,
6 although at the two-and-a-half milligram dose the
7 average bone density changes little over the course of
8 time, the majority of patients lose bone and a
9 substantially smaller proportion of patients lose bone
10 on the higher dose.

11 So with that consideration -- and particu-
12 larly since at least in the studies that were present-
13 ed, that there seems not to be a difference in side
14 effects or tolerability rate or experiences -- there
15 is an appeal from a clinical standpoint where again,
16 taking care of patients is not quite the same as it is
17 in clinical trials, to have a dose that we know is
18 effective in the larger proportion of patients.

19 ACTING CHAIR CRITCHLOW: Maybe Dr. Yates or
20 someone can address this. What was the -- I mean, in
21 other words, an issue of compliance with dosing, is
22 that true? Or what were some of the problems with
23 compliance that might translate into what you would
24 expect to see in clinical practice?

25 DR. YATES: Actually, compliance with dosing

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1 was very good. The major reason for drop-off of
2 patients in the studies was patients who no longer
3 wanted to be involved in a long-term clinical trial.

4 But those patients who remained in the
5 study, the vast majority -- over 95 percent -- were at
6 least 90 percent compliant with the medication. And
7 compliance rates were similar for the patients who
8 were receiving alendronate to the patients on placebo.

9 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

10 DR. KREISBERG: I have a question about the
11 GI side effects. Maybe Dr. McGuigan would share with
12 us his thoughts about that. It seems to me that in
13 these studies we're comparing placebo with the active
14 drug, but the placebo is formulated in exactly the
15 same way as the active drug is except that it doesn't
16 have the active drug in it.

17 And so if this is really pill esophagitis,
18 is it due to the pill itself or is it due to some
19 ingredient that's in the pill? And I wonder whether
20 Dr. McGuigan has any information about the types of
21 endoscopic abnormalities that might be seen if he were
22 to take 20 normal people off the street and look at
23 them relative to the incidence that occurs in the
24 placebo group and in the alendronate group.

25 DR. MCGUIGAN: I'm Jim McGuigan, University

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1 of Florida, Gastroenterologist. I think the questions
2 are good ones, and certainly when one is using a
3 placebo in any kind of a prospective study you want it
4 to be as similar to the test drug as possible with the
5 exception of the test agent, and that was done.

6 So when one looks at this, I think one is
7 struck in the data by how many abnormalities were seen
8 in the placebo group. It was not a null set of
9 observations. This is very consistent, however, with
10 all of the other endoscopic studies.

11 Over the last 10 to 15 years there has been
12 a plethora of endoscopic studies looking at drugs --
13 whether they be non-steroidal, anti-inflammatory
14 drugs, H2 receptor antagonists, or proton pump
15 inhibitors. So I think we have a good framework for
16 the expectation.

17 So without being able to say for sure, a
18 complete answer to which you said -- what you asked --
19 it's very clear that the set of observations of the
20 control population is very similar to a large number
21 of studies -- our expectations of what we anticipate
22 in a normal, controlled population receiving placebos
23 that were formulated differently than this. So I
24 think this is very, very consistent.

25 So I think that the endoscopic studies

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1 really did not bear out any specific, significant,
2 endoscopic lesions in the stomach or duodenum beyond
3 those that would be anticipated. And this is in
4 conformity with the clinical observations on a couple
5 of thousand people that were referenced, and the 1.3
6 million people who have taken the drug. So I think
7 they're consistent.

8 In terms of the esophageal lesions, there
9 was knowledge before the drug was made available that
10 there were esophageal problems in relation to this,
11 and the kind of observations -- though in a very small
12 number of patients -- were really consistent with
13 that.

14 When queried, the problems were almost
15 universally related to patients who either had well
16 documented history of reflux disease -- which we now
17 appreciate far more than 20 years ago; it's enormously
18 common in our population -- that these patients had
19 underlying reflux disease and/or reclined after taking
20 the agent.

21 And the kind of abnormalities are consistent
22 with reflux of an agent, which in a low gastric pH --
23 that is, a high hydrogen ion concentration -- one
24 experiences inflammatory changes and with concurrence
25 with the recommendations for treatment, one would not

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1 see that.

2 So I think that, as has been presented, the
3 incidence is very low, recognizing that there is a GI
4 intolerance if the drug is taken in a way other than
5 that which is recommended.

6 DR. KREISBERG: Can I ask Dr. McGuigan one
7 more question? If I recall some of the data that was
8 shown, it appears that the problem related to adverse,
9 gastrointestinal effects increases with age.

10 DR. MCGUIGAN: Yes.

11 DR. KREISBERG: And do you believe that age
12 and gastroesophageal reflux go hand-in-hand and that
13 is the reason why the older patient is more likely to
14 have the complication?

15 DR. MCGUIGAN: Interesting question and a
16 very good one. I think years ago we were under the
17 belief that peptic ulcer disease, duodenal ulcer
18 disease, was a disease of a young, middle-aged, or not
19 as much in terms of the elderly population.

20 The epidemiological studies now indicate
21 that peptic ulcer disease and the reflux problems --
22 independent of the agent under discussion -- increase
23 progressively with age. And it is very clear that
24 this increase is also associated with increase in the
25 incidence and the clinical manifestations of reflux

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1 disease, coupled with the use of non-steroidal anti-
2 inflammatory drugs in these populations of patients.

3 So from a clinical point of view, both
4 reflux disease and peptic ulcer disease, morbidity and
5 mortality, increase with age. So this is very
6 parallel in its observations.

7 DR. KREISBERG: A lot of the patients who,
8 in my state, are being placed on this, are actually
9 nursing home patients. And it would seem to me that
10 this whole issue of proper dosing -- not the size of
11 the dose but the position that the patient has to be
12 in and whatever -- would actually encourage adverse
13 gastrointestinal effects, because most of them are
14 lying down.

15 DR. McGUIGAN: I think your observation in
16 general, in terms of the need for this among patients
17 in nursing home, is certainly an important item and I
18 think it requires education of the patients and those
19 who are the caretakers of the patient. I think this
20 is a very important consideration.

21 DR. HIRSCH: Are they giving it with
22 propulsid or -- has this become a practice anywhere?

23 DR. McGUIGAN: Giving it with propulsid?

24 DR. HIRSCH: Or with you know, ranitidine or
25 whatever.

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1 DR. MCGUIGAN: Not in general. It is
2 recommended that the patient sit up 30 minutes -- or
3 not recline 30 minutes -- after taking the agent. And
4 that seems to be sufficient.

5 DR. DAIFOTIS: Actually, I was one of the
6 authors of the New England Journal paper where we did
7 do the analysis, okay. I want to really clarify.
8 When you look at epidemiology studies and you look at
9 gastric and duodenal, you see an increase in the older
10 age group, particularly of complications of ulcers.

11 When you look in our actual fracture
12 intervention study, for example, we don't see that
13 increase with age due to, let's say alendronate, more
14 of it than placebo. We just see that with placebo
15 with age it goes up; with alendronate with age it goes
16 up. But we don't see that difference. And I want to
17 sort of clarify that.

18 With esophageal adverse experiences as well,
19 importantly, we don't see that same increase within
20 our studies at the higher age group. I want to
21 clarify that for you to know that.

22 Do you have any more specific questions for
23 me?

24 ACTING CHAIR CRITCHLOW: To what extent
25 where -- I mean, I know the exclusion criteria for the

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1 endoscopy study was patients with major GI disease.
2 To what extent were people queried or excluded based
3 on either mild reflux disease or -- I mean, I'm
4 commenting specifically on --

5 DR. DAIFOTIS: You mean any clinical
6 studies?

7 ACTING CHAIR CRITCHLOW: Right. In the
8 clinical studies. I mean, it seems if these are in
9 fact, relatively low risk patients with respect to
10 probability of that type of an adverse event.

11 DR. DAIFOTIS: In the fracture intervention
12 trial as I showed in my talk, actually what we went
13 for was really major GI. People had to have had
14 ulcers where they were bleeding, and they had to be
15 transfused and hospitalized. Or they had to have
16 recurrent ulcers -- not just one ulcer -- but they had
17 to have had two or three -- you know, you had to have
18 had more than one time. Or they had to be on therapy
19 to meet that -- to be excluded.

20 And in fact, 16 percent of the patients that
21 were admitted to the trial had some upper gastrointes-
22 tinal, adverse experience. They included some
23 patients who had a history of ulcers but hadn't had a
24 bleed in the past year, or they included patients as
25 well with dyspepsia -- very common in that age group

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1 -- as well as well as with reflux esophagitis.

2 As well in the prevention studies where
3 patients were excluded if they had major gastrointes-
4 tinal disease. Again, approximately ten percent of
5 the patients that went in, in fact, had some upper
6 gastrointestinal prior history.

7 ACTING CHAIR CRITCHLOW: And were you able
8 then, to compare -- perhaps you weren't -- adverse
9 events in those patients with some sort of GI --

10 DR. DAIFOTIS: Yes. We looked at patients
11 in our fracture intervention trial, and we looked at
12 them in the osteoporosis prevention and treatment. We
13 combined those to get more events.

14 And when you look at that relative to their
15 upper GI history, if you are in the placebo group and
16 you have a history of having had an upper GI history,
17 guess what, you're more likely to have an ulcer.

18 Same thing is true of alendronate. But more
19 importantly, we were not able -- and what we were
20 looking for was a further increase -- we did not see
21 that.

22 ACTING CHAIR CRITCHLOW: Among those
23 patients with some sort of GI disease?

24 DR. DAIFOTIS: That's right, that's right.
25 But we were able to -- the studies, you know, the

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1 studies have the power to see what we do know. They
2 had the power to see that if you take a non-steroidal,
3 anti-inflammatory drug you're more likely to get an
4 ulcer. They had the power to see that if you were
5 older, you were more likely to have an upper GI
6 adverse experience.

7 But no difference was detectable between the
8 alendronate and the placebo. So we specifically --
9 exactly for all the issues you arranged -- we specifi-
10 cally looked at all of these subpopulations. You
11 know, same question I was asking: What about the risk
12 groups? But even though I looked I couldn't really
13 find or demonstrate that difference. Just couldn't
14 see it.

15 ACTING CHAIR CRITCHLOW: Looking at our
16 questions, perhaps are there comments from the
17 committee with respect to question 1 having to do with
18 results of the clinical trials showing evidence that
19 alendronate prevents post-menopausal osteoporosis?
20 Dr. Kreisberg.

21 DR. KREISBERG: I don't want to be a
22 nitpicker, but I don't think the trials demonstrate
23 that it prevents osteoporosis. It prevents bone loss,
24 to be semantically correct. These were only 3-year
25 trials. The implication is that it would prevent

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1 osteoporosis.

2 If none of these patients had been treated
3 they would have lost two percent of their bone
4 mineral. They still would not be osteoporotic,
5 perhaps by definition. So I think that there's a
6 semantic issue here, and I think what it does is, it
7 prevents bone loss.

8 ACTING CHAIR CRITCHLOW: Any comment to
9 that?

10 DR. NEW: That's the very question that Dr.
11 Hirsch has been addressing. When is it significant?
12 And that's the question I asked you, Bob. It seems
13 like a mystery.

14 DR. KREISBERG: Well, I think osteoporosis
15 has a definition. Dr. Marcus has told us approximate-
16 ly what the definition is. And I don't know what the
17 bone mineral densities were of the patients that were
18 enrolled in the prevention study, but most of these
19 women, or many of these women, were close to the onset
20 of menopause. So relatively small -- 16 percent of
21 those patients would have osteoporosis by definition,
22 at the age of 50, isn't that what you said, Bob?
23 Roughly?

24 DR. MARCUS: What percent?

25 DR. KREISBERG: Sixteen.

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1 DR. MARCUS: Sixteen percent is one standard
2 deviation down. That would qualify for a diagnosis of
3 osteopenia, but if you're going to say it's going to
4 have to be two-and-a-half standard deviations down
5 then -- which is problematic as I've already explained
6 -- but then we're talking about, you know, less than
7 two percent.

8 DR. KREISBERG: So we're talking -- that the
9 study population in the prevention trials were not
10 osteoporotic, they by definition, had relatively
11 normal or acceptable, post-menopausal bone mineral
12 density values. And what the drug did is, it prevent-
13 ed loss of mineral from the skeleton. But they were
14 not osteoporotic by definition, and therefore it
15 didn't prevent osteoporosis.

16 ACTING CHAIR CRITCHLOW: You mean, there
17 were osteogenic patients -- I mean, approximately half
18 or so were less than -1.

19 DR. KREISBERG: Right. But I mean, we have
20 never demonstrated -- because it would take a longer
21 study, I believe -- to demonstrate that they would
22 have become osteoporotic by definition. All we can
23 demonstrate is that it prevents bone loss.

24 DR. HIRSCH: Exactly. Why get into those
25 arbitrary definitions? I mean, I can see other

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1 reasons for it, but in the context of this question we
2 ought to just say what the plain truth is, and there
3 was less bone loss and fewer fractures in people who
4 use it -- the other studies.

5 ACTING CHAIR CRITCHLOW: Perhaps I could ask
6 Dr. Sobel for the Agency perspective on this question
7 in terms of whether, in our subsequent discussion we
8 could change that to loss of bone, or bone loss, or
9 leave it at --

10 DR. SOBEL: You mean in the context of
11 prevention of osteoporosis?

12 ACTING CHAIR CRITCHLOW: Yes.

13 DR. SOBEL: Well, I think what we're really
14 dealing with here is going back to our guidelines.
15 This has followed what we considered a logical
16 algorithm. That first, the company demonstrated bone
17 mineral density changes in osteoporosis, and with the
18 FIT trial moved on to a definitive fracture study.

19 Then when we have nailed that part of it
20 down, we go into the prevention arm and we make
21 certain logical assumptions that, since we have
22 demonstrated its effect in established osteoporosis,
23 if we can achieve a good effect in bone mineral
24 density as was done in the prevention study, we can
25 follow that line of thought through to the osteoporot-

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1 ic population.

2 I agree with Dr. Kreisberg that he's not
3 nitpicking, but I wanted to tell you what logic we
4 built into our guidelines. I mean, theoretically you
5 might ask, do our prevention studies have to eventual-
6 ly go on to a fracture endpoint? And we say no.

7 Once we've established the efficacy in a
8 treatment mode, we can then go back to a preventive
9 mode and rely on bone mineral density as interfering
10 with a continuum that leads to osteoporosis and
11 fracture.

12 So I don't disagree with what Dr. Kreisberg
13 is saying semantically, but I want to tell you what
14 the logic of the wording in our question is. That our
15 ultimate goal is to tie into what we saw in osteoporo-
16 sis and say, by substantially effective bone mineral
17 density, we are interrupting that continuum. It's
18 words.

19 DR. KREISBERG: Well, I know the Agency
20 seems to be a little bit schizophrenic about some
21 things. Maybe that's not news to anybody. But it
22 seems to me that we --

23 DR. SOBEL: In what way are we schizophren-
24 ic? And other things, perhaps.

25 DR. KREISBERG: Okay, let me give you an

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1 example. Dr. Illingworth and I were talking about the
2 parallelism between coronary artery disease and
3 osteoporosis, and there's primary prevention and
4 secondary prevention.

5 We're talking about primary prevention right
6 now. We couldn't claim for a cholesterol-lowering
7 drug that it prevented coronary artery disease until
8 you showed it.

9 DR. SOBEL: That is right.

10 DR. KREISBERG: Okay.

11 DR. SOBEL: And that's what we've done here.

12 DR. KREISBERG: No --

13 DR. SOBEL: You cannot claim --

14 DR. KREISBERG: Well, you've shown in a
15 second intervention study that you can prevent another
16 complication, but you haven't shown in a primary
17 prevention study --

18 DR. HIRSCH: This is lowering cholesterol is
19 what you -- this is the first step. They lessened the
20 degree of bone loss with the drug, period.

21 DR. KREISBERG: Right.

22 DR. HIRSCH: That's all you can say. I
23 don't know what you want --

24 DR. KREISBERG: That's right; we're prevent-
25 ing bone loss. It seems to me that we haven't

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1 demonstrated that primary prevention will prevent
2 fractures, even though I happen to believe that. I
3 also happen to believe that lowering the cholesterol
4 would prevent first heart attacks, but you wouldn't
5 have taken my word on that. You had to have the data
6 for that. So this is the same type of thing.

7 DR. NEW: But Bob, they did do a FIT study.

8 DR. HIRSCH: But that was secondary.

9 DR. KREISBERG: That's secondary prevention.

10 ACTING CHAIR CRITCHLOW: Dr. Troendle.

11 DR. TROENDLE: I'd like to ask Dr. Kreisberg

12 --

13 MS. REEDY: Use the microphone please, Dr.
14 Troendle.

15 DR. TROENDLE: The proposed indication says,
16 for the prevention of osteoporosis, Fosamax™ should
17 be considered, and so forth. Would that be something
18 you're recommending? That it say, for the prevention
19 of bone loss Fosamax™ should be considered in post-
20 menopausal women?

21 DR. KREISBERG: Right. Now, I happen to
22 believe that what it says is correct. But I think
23 technically it doesn't show that. The study does not
24 show that.

25 DR. TROENDLE: That may not distinguish it

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1 adequately from those who have not completed the
2 studies. That it would be too similar to what we had
3 before. What the company is allowed to say before the
4 date of the --

5 ACTING CHAIR CRITCHLOW: I'm sorry, I don't
6 understand the distinction you were making.

7 DR. TROENDLE: Well, I --

8 DR. MARCUS: That microphone is not working,
9 Dr. Troendle.

10 DR. SOBEL: I would like to just take some
11 issue with your interpretation of the progress of
12 coronary disease in the Agency. As you know, origi-
13 nally we allowed drugs on the market based on lipid
14 altering effect, and then we did say we would want to
15 have a demonstration in a population that it prevented
16 heart attack, but not specify primary or secondary
17 prevention. We said prevention.

18 Subsequently, we did get a secondary
19 prevention endpoint -- a 4S study or whatever, and
20 other studies -- but the primary prevention was an
21 issue which the companies themselves pursued in a mode
22 of clearly demonstrating that in a primary population.

23 But the genesis of our approval of these
24 agents was not based on the need to demonstrate either
25 in a primary or secondary population. It isn't

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1 schizophrenic. We never specified that that eventual,
2 Phase IV commitment would require either primary or
3 secondary.

4 DR. KREISBERG: Let me withdraw my word
5 "schizophrenic" and say "inconsistent"

6 DR. SOBEL: I don't think it's inconsistent
7 or schizophrenic.

8 DR. KREISBERG: Well Sol, let me just say
9 that no drug company can claim that their cholesterol-
10 lowering drug prevents coronary heart disease until
11 they prove it --

12 DR. SOBEL: Well, that --

13 DR. KREISBERG: -- and a drug company has
14 just gotten that indication. So it seems to me that
15 no other drug company can claim that they prevent
16 osteoporotic fractures until they prove it. Now, am
17 I making a -- is that an incorrect parallelism?

18 DR. GOLDMANN: I think there's some confu-
19 sion. First of all, if you remember the definition of
20 osteoporosis -- and a lot of work went into the
21 guidelines that the Agency -- actually this committee,
22 different members -- put together. But osteoporosis
23 is not defined by fractures as you well know.
24 Osteoporosis is defined by loss of bone and microarch-
25 itecture.

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1 But there is a consistency. Sol is abso-
2 lutely right. As one of the companies that have done
3 the prevention they did not make the distinction. But
4 we have made the connection. There are two different
5 pieces of data that make the connection.

6 There was a predefined pooled analysis from
7 phase III which had non-patients who -- only 20
8 percent had prevalent fractures and those were pooled
9 and predefined as such so that they would meet the
10 guidelines, and there we clearly showed fracture
11 reduction.

12 And you now have the FIT study in which the
13 patient population had prevalent fractures and that
14 too, shows. The whole idea behind the osteoporosis
15 guidelines was that you had to show and validate for
16 your particular drug, BMD -- the change in BMD
17 translating into fracture reduction.

18 But because of the difficulties in doing
19 prevention -- that would be the second part of it --
20 and by showing that again, you reduce BMD, it trans-
21 lates -- you already know it translates into fracture
22 reduction. So we actually have shown that in two
23 separate situations.

24 ACTING CHAIR CRITCHLOW: In the prevention
25 study you said 20 percent had prevalent fractures --

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1 DR. GOLDMANN: No, no, in the --

2 ACTING CHAIR CRITCHLOW: I mean the --

3 DR. GOLDMANN: We've got treatment data and
4 prevention data. The prevention data, as required by
5 the guidelines, show BMD changes.

6 ACTING CHAIR CRITCHLOW: Right.

7 DR. GOLDMANN: There are two pieces of
8 information that show the fracture.

9 ACTING CHAIR CRITCHLOW: The FIT. And the
10 other?

11 DR. GOLDMANN: The phase III studies were
12 done in a treatment population, but only 20 percent of
13 those patients actually had prevalent fracture.

14 ACTING CHAIR CRITCHLOW: And were most of
15 the fractures occurring in that group, in that 20
16 percent?

17 DR. GOLDMANN: No. We have looked at that.
18 And the other piece of information that we've just
19 completed the puzzle with is the first arm of the FIT
20 study in which those patients did have prevalent
21 fracture. And those patients, clearly we showed that
22 they have an effect in reducing fracture risk.

23 MR. MARTICELLO: It might be worth stepping
24 back for a minute and relating question 1 with Merck's
25 proposed label, which is in their looseleaf document.

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1 It's the second-from-last tab -- Proposed Label -- on
2 page 10.

3 And if you look at the third paragraph under
4 Indications and Usage it says, for the prevention of
5 osteoporosis, Fosamax™ should be considered in post-
6 menopausal women who are at risk of developing
7 osteoporosis and for whom the desired clinical outcome
8 is to maintain bone mass and to reduce the risk of
9 future fracture.

10 You might want to relate that to the wording
11 of question 1, and actually what is being claimed in
12 the proposed label.

13 ACTING CHAIR CRITCHLOW: Do you have a
14 comment on what's in the label?

15 DR. KREISBERG: I believe that the implica-
16 tion is clear. I believe that the data show that it
17 prevents bone loss. That's all that the data shows.

18 That all of the other data that has been
19 presented by Merck -- which is fine data -- have been
20 studies in women with established osteoporosis, either
21 by bone mineral density measurements -- that is, the
22 study population for which the approval of the ten
23 milligram dose was initially given.

24 And it prevents fractures in those women who
25 by definition, have osteoporosis, and it prevents

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1 fractures in those women who by definition, have
2 osteoporosis because they've had previous fractures --
3 the FIT data. The five milligram dose data simply
4 demonstrates that it prevents bone loss.

5 ACTING CHAIR CRITCHLOW: Other comments on
6 this?

7 DR. HIRSCH: It all hangs on the definition
8 of osteoporosis, and someone -- I can say osteoporosis
9 is a clinical entity on which there's a complicated
10 set of events that occurred -- osteoblasts and osteo
11 -- that we don't understand, and blah-blah-blah-blah.

12 All you know here is that a drug was given
13 and one of the most important manifestations of this
14 disease is ameliorated, and there's less bone loss,
15 and that's the clear truth. And to argue about what
16 osteoporosis is brings up another thing.

17 I would say actually, that probably what you
18 measure in the DEXA and everything is another manifes-
19 tation and is probably not osteoporosis either.
20 There's more to it than that that we don't know about.
21 So why get into trouble by bringing all this in? Just
22 put down what was seen. We gave the drug and there
23 was less bone loss, that's all.

24 DR. TROENDLE: If we only allow the claim
25 for lost bone then we also would -- I'm trying to

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1 figure out how we would word this. Fosamax™ is
2 indicated for treatment and prevention of osteoporosis
3 in post-menopausal women. Then that would have to
4 become, Fosamax™ is indicated for the treatment of
5 osteoporosis and for prevention of bone loss in --

6 DR. HIRSCH: No, for the reduction of bone
7 loss that accompanies osteoporosis, or is so defined
8 or whatever you want to say. I mean, what you saw was
9 the bone loss. I don't know. It's not my expertise
10 but it seems logically to be the --

11 ACTING CHAIR CRITCHLOW: It seems like we're
12 getting to defining what the appropriate target
13 population is in the study of the second question in
14 terms of the role of either bone mineral density in
15 predicting osteoporosis and/or other risk factors.

16 Would the members of the committee, particu-
17 larly those who treat these patients, are there
18 comments in terms of what in your minds, would be, at
19 least guidelines for defining an appropriate target
20 population? Dr. Marcus?

21 DR. MARCUS: I just wanted -- I'm very
22 nervous about responding to these questions, particu-
23 larly the last few minutes -- because I'm not permit-
24 ted to weigh in on a vote, and any comment I would
25 make was going to be sounding too much like a vote.

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1 DR. KREISBERG: I want to be swayed. I want
2 to hear what you have to say.

3 DR. HIRSCH: We'll take it into consider-
4 ation, but I do want -- your views are important.

5 ACTING CHAIR CRITCHLOW: I think we're --
6 I'm at this point, just wanting to get into some
7 general considerations rather than specific --

8 DR. MARCUS: I think the target population
9 are estrogen-deprived women who, regardless of whether
10 they are immediately post-menopausal or substantially
11 later, are in need of skeletal protection. That's as
12 liberal a term as I can put it.

13 And that would be predicated on some
14 evidence for a low bone mass, or evidence of bone
15 loss, either by serial densitometry examinations over
16 time, or by a bone density measurement that is of
17 concern and accompanied by some biochemical influence
18 of increased bone turnover, which would be some
19 indication that there was bone loss going on.

20 ACTING CHAIR CRITCHLOW: Dr. New.

21 DR. NEW: So Bob, are you saying that you
22 would exclude any woman on estrogen treatment?

23 DR. MARCUS: No. I've already said before
24 that there may be -- I mean, I have personal guide-
25 lines, even though it's off-label -- that I have added

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1 -- I have added Fosamax™ to women who were already on
2 estrogen or continuing to fracture despite being on
3 adequate replacement of estrogen.

4 And in particular older women -- that is,
5 I'll define as women above the age of 70 -- who are
6 not tolerating standard replacement doses of the
7 estrogen I know best, which is Premarin. If they're
8 on some other agent which I have reason to believe may
9 not be as adequate for protection at the hip, or they
10 need to be on a dose lower than the equivalent of .625
11 milligrams of Premarin, then I have added alendronate
12 to that.

13 DR. NEW: Therefore, I don't understand your
14 statement that the target population should be
15 estrogen-deprived when --

16 DR. MARCUS: I said that only because I
17 don't want to focus only on women within the first six
18 months of menopause. That is, I think that there's
19 benefit to be had from shutting down bone turnover,
20 essentially regardless of age.

21 And the focus of this study, by virtue of
22 the prevention studies that have been shown us, has
23 been on women within a, you know, reasonably short
24 period of menopause -- six years on average, let us
25 say.

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1 But there are many women let's say, in their
2 seventies, who have not seen estrogen for a long time,
3 who do not satisfy criteria for osteoporosis. There-
4 fore, it would not be appropriate to think of them as
5 a treatment, but still are heading that way, and so I
6 would consider that prevention. And I would like to
7 feel that I had the Agency's blessing to use a
8 preventive strategy in those women as well.

9 DR. HIRSCH: Why would you not then just say
10 the target population should be those who are at high
11 risk for the development of osteoporosis? The
12 following are the factors which --

13 DR. MARCUS: I would love to --

14 DR. HIRSCH: -- to that --

15 DR. MARCUS: -- I would love to. Absolute-
16 ly. I would love to consider women who are pre-
17 menopausal who have extremely low bone mass, and
18 people on corticosteroids and all the other things.
19 Unfortunately we're confined in a submission like
20 this, to think narrowly rather than broadly. But I'm
21 perfectly happy to broaden the stakes.

22 DR. HIRSCH: Because here if it becomes
23 proper to use the clinical term, it seems to me --

24 DR. MARCUS: Right.

25 DR. HIRSCH: -- rather than to list what you

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1 consider to be the risk factors for the development of
2 that -- which includes low bone density or whatever --
3 A, B, C.

4 DR. MARCUS: Yes, yes.

5 ACTING CHAIR CRITCHLOW: Dr. Hirsch, do you
6 have other comments?

7 DR. HIRSCH: The other risk factors. I
8 think low bone density, the post-menopausal individu-
9 als not on estrogen replacements, family history -- I
10 mean, I think all the things that you listed here are
11 appropriate, but they ought to be just sort of sorted
12 out. I consider the bone density to be one of those
13 risk factors rather than the only one, or --

14 ACTING CHAIR CRITCHLOW: I mean, there was
15 some discussion -- maybe Mr. Marticello brought it up
16 -- in terms of whether the goal -- and I guess Dr.
17 Marcus did as well -- to maintain what is there as
18 opposed to optimizing for that patient, some level of
19 bone density.

20 I mean, is that still -- I would think that
21 would still be within the paradigm of prevention now,
22 given that the claim here is for at least maintenance
23 of bone mass. But in practice I can see where
24 individual decisions would come into play as to what
25 would be best for that particular women.

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1 DR. HIRSCH: Sure, I'm just trying to be
2 physicianly and not, you know, say we're treating a
3 laboratory finding. We're treating a patient and the
4 bone density is just a thing about -- it's one among
5 other considerations.

6 ACTING CHAIR CRITCHLOW: Dr. Kreisberg, do
7 you have --

8 DR. KREISBERG: Well, I like the broad
9 approach to deciding who's a candidate for it. It
10 seems to me -- and I'd have to ask Dr. Marcus this --
11 would you consider treating any woman to prevent bone
12 mineral loss, without having a bone mineral density,
13 even if she had other factors such as she was thin and
14 she came from a family that had a history of osteoporo-
15 sis and she was white or Asian. Would you initiate
16 therapy without having a bone mineral density measure-
17 ment?

18 DR. MARCUS: For me personally, in practice?
19 The answer is no, I would not. I have not, I will
20 not.

21 DR. KREISBERG: So it seems to me then, that
22 no matter what factors we list, a requirement in order
23 to enter a woman onto -- or even a man for that matter
24 -- onto alendronate therapy for the prevention of bone
25 loss, is going to have to require a bone mineral

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1 density in order to make that decision.

2 DR. MARCUS: I have to clarify just a point
3 of information on behalf of the Asian women in this
4 country. It is true that they have a low bone mass,
5 but they have about 50 percent of the -- particularly
6 with hip fracture -- much lower incidence of hip
7 fracture than their Caucasian counterparts for any
8 given bone density.

9 So I'm not sure how this got into the
10 submission and what we were talking about here. I
11 don't consider that, certainly for hip fracture, as
12 being a particular risk.

13 ACTING CHAIR CRITCHLOW: Dr. Siris.

14 DR. SIRIS: I just wanted to make a couple
15 of comments because I thought a great deal about how
16 in the world are we going to decide which people are
17 the candidates for prevention? We know that by the
18 age of 80, probably two-thirds or more women have the
19 criteria for being called osteoporotic, and a fair
20 number of them fracture.

21 We know that if you're 50 years old and you
22 bring to menopause a bone density, for example, of --
23 a T-score of -1 -- your value is one standard devia-
24 tion below 30-year-olds. And if you lose a percentage
25 per year -- which is what the placebo patients were

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1 losing -- for ten years, between 50 and 60 you could
2 lose ten percent, and at 60 you have a -2 and in fact,
3 you could be a candidate for treatment. I mean, you'd
4 have the disease by some criteria.

5 So with this background in mind it makes a
6 decision to have a bone density measurement very
7 appealing. The problem is that right now in the
8 United States there is no way we can do bone mineral
9 density measurements on all of the women who are at
10 risk of osteoporosis. I hope that in the future we
11 will be able to do this.

12 But until that time I think we have to -- in
13 the best of worlds -- if we have bone mass measurement
14 available, make a bone mass measurement. A value of
15 -1 at 50 isn't the same thing as a value of -1 at 60.
16 You have to take this into consideration and you have
17 to view the bone density, if you have it, in terms of
18 the other factors -- the age and other considerations:
19 her weight, her family history, etc.

20 But if you can't do bone mass measurement
21 and you have a woman in your practice who has a strong
22 family history, who's pitifully thin, perhaps who's
23 had an early menopause, you have to take those factors
24 into consideration.

25 And hopefully the physician will balance

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1 bone mass measurement when it's available -- which
2 would be optimal -- with the other risk factors, put
3 it all together, and use your judgment and make a
4 clinical decision. Because we know that when we give
5 the drug, we stop the loss of bone. And by doing
6 that, we prevent osteoporosis in those women who are
7 low to begin with.

8 ACTING CHAIR CRITCHLOW: Dr. Illingworth, do
9 you have comments on this?

10 DR. ILLINGWORTH: Just one comment in terms
11 of broadening the description. I would favor putting
12 something into the effect that patients with either
13 low bone mineral density or women with factors present
14 which are known to accelerate bone resorption.

15 And that would widen the spectrum to include
16 drugs such as corticosteroids, and other things that
17 may be not written down in these defined guidelines.
18 And that would enable the physician to give, hopefully
19 a wider spectrum to patients who may receive treatment
20 -- who may be appropriate to receive treatment.

21 DR. MARCUS: There's something very appeal-
22 ing about that and I can assure you that if we had
23 that guideline and I saw a man with corticosteroid-
24 induced osteoporosis and applied to Blue Shield of
25 California for payment of Fosamax™, that it would be

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1 turned down.

2 So I think if we're going to broaden the
3 stakes we need to think in much larger terms, and I
4 don't know that this hearing is necessarily the place
5 to do that. I would not want to see the only attempt
6 at getting reference to corticosteroids, you know, be
7 now, because then it's going to close out a large
8 segment of people who would benefit.

9 ACTING CHAIR CRITCHLOW: So in terms of any
10 nature of guidelines that we could come up with here,
11 I mean, that seems like I -- like you said, this is
12 really not the place to do that -- but in terms of
13 what specifically can go into a label in terms of
14 indication, you would go to what you originally said
15 in terms of -- well --

16 DR. MARCUS: I mean, this is a tough
17 problem. I just think that we need to be aware that
18 the HMOs and insurance industry today is trying to
19 minimize what it pays for support of healthcare. And
20 they will be strict constructionists in terms of
21 looking at FDA guidelines to find any possibility of
22 a window of escape.

23 And if they say for the post-menopausal
24 woman, than by God, that's the only person who's going
25 to get this drug paid for, until something comes along

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1 to open up the gate a little bit more.

2 So I would welcome the opportunity to
3 consider a much broader indication, but unfortunately,
4 we don't really have data at hand to make that kind of
5 a judgment.

6 DR. HIRSCH: Including the absence of a
7 measurement of bone density. I mean, that would be
8 part of the --

9 DR. MARCUS: Certainly, I agree. Absolute-
10 ly.

11 DR. HIRSCH: Why shouldn't we do that, then,
12 if that's the correct thing to do?

13 ACTING CHAIR CRITCHLOW: Dr. Molitch.

14 DR. MOLITCH: I'll comment on both aspects.
15 I think the aspect of whether preventing bone loss or
16 osteoporosis, I think is nitpicking a little bit more
17 than I would like. And I think the chain of events of
18 losing bone and then preventing fractures is so tight
19 that I think that I'd be willing to accept it if we're
20 preventing bone loss that we're also then preventing
21 osteoporosis a few years after that.

22 That will be clinically significant in a
23 large number of people that will cause fractures.
24 Then I'm willing to accept that and I'm willing to
25 accept the language of osteoporosis as opposed to bone

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1 loss.

2 On the other hand, coming to the second
3 question, I'm not happy about treating somebody with
4 a drug like this where I don't have a diagnosis at
5 all, and I'm willing to make a diagnosis of signifi-
6 cant osteopenia -- that's a risk -- based on a
7 measurement that shows me the patient has osteopenia.

8 If we're just talking about somebody who has
9 lots of risk factors I can show you a 75-year-old,
10 Hispanic, overweight women who has got a family
11 history of diabetes, who's got a risk of 50 percent of
12 having diabetes who doesn't have diabetes. And that
13 happens.

14 And so that we can show people who are thin,
15 white, and who have not had any milk since they were
16 children, who are at high risk for osteoporosis and
17 you do a bone mineral density and they don't have
18 osteopenia. And so that I think that all the risk
19 factors in the world don't establish a disease. So I
20 think that those are the people that you would send
21 for bone mineral density to see whether they are
22 candidates.

23 On the other hand, that woman at menopause
24 is certainly someone that I would encourage to use
25 estrogens because it seems like the so-called natural

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1 thing to do to replace estrogen in an estrogen-
2 deficient woman -- both for bone mineral density and
3 for cardiovascular reasons. But to start them on
4 another specific bone directive medication, I think I
5 would like to actually show that there's actually a
6 bone mineral decrease.

7 DR. HIRSCH: Well, I'd like to argue that,
8 because I think that this is -- I mean, with no great
9 knowledge but at least this is something that is being
10 touted as possibly a preventive, and therefore it
11 seems to me a woman, even whom you measured and has
12 absolutely normal bone mass but is at high risk for
13 developing -- and can't take estrogens or won't for
14 some reason, but has all the other criteria for high
15 risk of this family history or whatever it is -- maybe
16 such a person should be put on this drug, and there-
17 fore the measurement of bone mass is not a very
18 interesting thing to do altogether.

19 If it either is there or isn't there, but it
20 doesn't matter -- you would use it anyhow in such a
21 person. I think it may be very useful in monitoring
22 treatment or that kind of thing, or establishing maybe
23 the dosage or whatever else you want to do.

24 But whether the drug is used or not, if it's
25 truly a preventive, then you might do it in someone

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1 who is absolutely normal and has no disease at that
2 moment. Why not, if it can be shown to do these
3 things, as it has?

4 ACTING CHAIR CRITCHLOW: Dr. Marcus, did you
5 have a comment?

6 DR. MARCUS: I was just going to ask Dr.
7 Hirsch how he would decide which dose of medication --
8 suppose he had available 2.5 through 20 milligrams; a
9 wide spectrum like with synthroid, multiple different
10 -- how would you know what to use unless you had some
11 sense for whether you wanted to restore a deficit that
12 existed or are just content to leave things the way
13 they were?

14 DR. HIRSCH: The point you made before is
15 excellent. That maybe in such a person the lowest
16 dosage range, 2.5, would be what -- otherwise I would
17 have said, use estrogens and if you can't use estro-
18 gens use the one thing that's been shown to stop
19 breaking of bones to some degree, which is five
20 milligrams. But maybe in this other circumstances you
21 would be well advised to use 2.5; I don't know.

22 But I don't see why in essence, you have to
23 prove abnormality in order to do something that's
24 preventive when you know that the abnormalities are
25 going to be likely to be forthcoming and you have to

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1 act on the likelihood of that possibility.

2 ACTING CHAIR CRITCHLOW: I mean, given the
3 adequate safety profile.

4 DR. HIRSCH: Correct. I mean, at least --
5 I'm not stating that --

6 ACTING CHAIR CRITCHLOW: No, I know.

7 DR. HIRSCH: -- I'm just asking the question
8 really -- of why that is not a reasonable thing to do.

9 ACTING CHAIR CRITCHLOW: Other than it
10 wasn't specifically tested. Dr. Kreisberg.

11 DR. KREISBERG: Well, I was going to say, by
12 analogy in most women who are menopausal who are
13 offered estrogens, they're offered estrogens for the
14 prevention of skeletal disease and the prevention of
15 heart disease and the prevention of other things --
16 but we don't do angiograms on them to determine
17 whether they're eligible candidates and we often don't
18 do bone mineral density measurements, particularly if
19 they're willing to take estrogen.

20 So it seems to me that the analogy between
21 recommending estrogen and recommending a small dose of
22 alendronate for the woman who's not a candidate for
23 estrogen, or other types of patients who would not be
24 candidates for estrogen, seems eminently reasonable to
25 me.

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1 DR. MARCUS: Well, I agree that it's
2 eminently reasonable, but let's look now at the
3 experience of estrogen in this country. First of all,
4 no more than 35 percent of American women have ever
5 agreed to take estrogen, and marketing data that I've
6 seen indicate that the half-life of staying on
7 estrogen is actually very low -- that only about half
8 of women who get that initial prescription are still
9 on as much as six to nine months later.

10 And it has been shown -- in defense of bone
11 density measurements -- that knowledge of bone density
12 is an inducement for both taking and complying with
13 estrogen therapy. So although I certainly agree on
14 it, on a desert island if you're practicing medicine
15 and you don't have access to this inexpensive, non-
16 invasive technique, fine -- you can fly by the seat of
17 your pants and not use it. But we do have it and it
18 should be used.

19 DR. KREISBERG: Well, I'm not sure we do
20 have it. Because some of the people that I relate to
21 actually do practice on a desert island. I mean,
22 they're very remote and they don't have access to
23 these types of things and when we go out to talk about
24 the general problem of osteoporosis it doesn't mean
25 anything because they can't make the measurement that

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1 would allow them to make the decision to use a drug.
2 DR. MARCUS: Certainly, everyone in the bone
3 community is sensitive to that question, and there are
4 all sorts of approaches that are being developed.
5 I've alluded to some of them. The one that I forgot
6 even to mention is, anybody who has access to a hand
7 x-ray, you can put that aluminum step-wedge and go and
8 get a, you know, a centrally-read estimate of, this is
9 someone who needs to have a more formal assessment.
10 So they send them up to you in Birmingham and you can
11 do it properly.

12 DR. HIRSCH: Sometimes.

13 ACTING CHAIR CRITCHLOW: Aside from risk of
14 GI or other risks such as that, are there women for
15 whom you would not recommend alendronate? I mean, I
16 assume that if they are willing to take estrogen then,
17 you would --

18 DR. MARCUS: Yes.

19 ACTING CHAIR CRITCHLOW: But are there other
20 situations where you would not --

21 DR. MARCUS: Well, I think there is a
22 problem with woman who have had -- or men -- who have
23 had a disruption of their intestine. For example,
24 people who have had gastrojejunostomies -- which are,
25 you know, not that uncommon, although fewer now than

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1 before, nonetheless we see them -- and they often have
2 terrible bone disease and I feel saddened that we
3 don't have a parenteral form of alendronate to use in
4 those patients.

5 ACTING CHAIR CRITCHLOW: With respect to
6 question 2, are there other -- I mean, as we have been
7 given it, our five parts -- are there other issues
8 surrounding any of those questions that anyone would
9 like to address?

10 DR. NEW: Cathy, I would like "d" addressed.
11 I'm still not clear as to whether the committee feels
12 that the first line of treatment in a post-menopausal
13 woman is hormonal therapy, and then only if that is
14 not tolerated or refused -- for whatever reasons -- do
15 we recommend alendronate as a preventive? Without any
16 tests, just do it -- like pediatricians give vaccina-
17 tions.

18 But I think -- I'm confused about this
19 because at the moment, probably as a preventive, most
20 women are taking hormonal therapy. Do we then say to
21 them, stop taking them and take alendronate? You
22 don't. But this question confuses me, then.

23 DR. HIRSCH: But most women are not taking
24 hormones -- that's the point you're making --

25 DR. NEW: Well, you're saying 35 percent --

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1 DR. HIRSCH: Thirty-five percent.

2 DR. NEW: Okay, so take that 35 percent.

3 DR. MARCUS: It's actually only about 30
4 now. The 35 percent was the peak value before the
5 endometrial cancer revelations came out in the early
6 1970s.

7 ACTING CHAIR CRITCHLOW: So now it's --

8 DR. NEW: Why do you think, Bob, that only
9 35 percent of women take it?

10 DR. MARCUS: Thirty-five percent have agreed
11 to take it, and it seems to be highly related to
12 socio-economic status areas like the Palo Alto -- you
13 know, the San Francisco peninsula area with all the
14 university communities nearby, it's actually up to
15 about 45 or 50 percent. So it's patchy throughout the
16 country.

17 I think that the -- certainly concerns about
18 the risk for breast cancer is a major player. Most
19 women don't know about coronary heart disease risk.

20 And I don't really think that endometrial
21 cancer -- although it's something that's cited a lot
22 -- I don't think that it really makes a blip on the
23 graph in terms of -- I mean, women who know about that
24 also know about the use of progestins to protect the
25 endometrium. So it's largely a breast cancer concern

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1 I think, more than anything else.

2 ACTING CHAIR CRITCHLOW: I mean, would in
3 practice, you explain the risks and benefits of either
4 estrogen and alendronate and, I mean, one would
5 proceed from there?

6 DR. MARCUS: That's why Endocrinologists are
7 lost leaders. We explain all this stuff -- it takes
8 about 40 minutes -- and we lose money every time we do
9 it. I think that Kreisberg and Molitch recognize
10 that.

11 ACTING CHAIR CRITCHLOW: Does anyone see a
12 role -- or, what role do those on the committee see
13 for the use of the biochemical markers of bone
14 turnover? Is that something that's even less likely
15 to be used than the bone mineral density ascertain-
16 ment? Dr. Illingworth.

17 DR. ILLINGWORTH: Well, the data we heard
18 this morning, the basic suggestion is that they don't
19 give you a reliable indication of -- do you have rapid
20 bone loss or osteopenia? Hopefully it will get
21 better, and I think that's the thing that we can hope
22 for.

23 But it looks like to me that, my impression
24 was there's a poor correlation between the metabolic
25 parameters in bone turnover and present parameters of

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1 osteopenia or osteoporosis. And so perhaps in
2 selective patients they may be worthwhile to use, but
3 as a screening test my impression is they're not very
4 helpful.

5 ACTING CHAIR CRITCHLOW: I don't if one --
6 I mean, given that they're measuring different things,
7 I mean, you're looking at different points in natural
8 history of the disease, it would be difficult to know
9 whether someone with adequate bone density but
10 supposedly high bone turnover -- I mean, I would
11 assume that those women would be at greater risk than
12 somebody with the similar bone density --

13 DR. MARCUS: Well, actually they are
14 fracture data from a very large European study called
15 EPIDOSE, which is economic for something -- I can't
16 remember. It's a big multi-national European study of
17 fracture -- largely hip fractures.

18 And it turns out that as evidenced by bone
19 turnover markers, that bone turnover itself emerges as
20 an independent predictor of hip fracture, even once
21 corrections have been made for bone mass.

22 It's a mixed story. Certainly the data this
23 morning were not impressive for a specific role for
24 bone -- at least the two markers that were shown.
25 There are other data that have been published; Dr.

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1 Chestnut's group looking at patients in whom an
2 estrogen intervention was made, in which the use of
3 resorption markers actually performed considerably
4 better.

5 And you know, I think the jury is still out
6 on those. In my own experience I have tried to see
7 whether a patient had an adequate response to a
8 therapy by looking at a marker within six to eight
9 weeks of starting a therapy, rather than having only
10 to wait for a year and a half or so for a bone density
11 response.

12 And there's no question, at least in the
13 limited experience I have in clinic patients, they
14 respond the same way to administration of alendronate
15 as the patients in these various studies. You know,
16 they suppress down to low levels of cross laps or NTX,
17 deoxypyridinoline, within the first period of, you
18 know, the follow-up measurement. I don't know yet
19 exactly how that will presage the change in bone
20 density.

21 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

22 DR. KREISBERG: Could I follow up on that?
23 It seems to me then, that it is not good -- it's not
24 a good test to help you make the decision about
25 whether a woman ought to be -- whether a patient ought

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1 to be placed on alendronate, but it may tell you the
2 response that the patient gets after being placed on
3 it. That is --

4 DR. MARCUS: I think that's reasonably
5 accurate, yes.

6 ACTING CHAIR CRITCHLOW: I'm looking at
7 question 2b, and questions that have "all" and "never"
8 and words like that in it tend to make me nervous.
9 What are the committee's thought on that question:
10 Should all women who are postmenopausal, younger than
11 60 years of age and have low bone density, be treated
12 prophylactically? I mean, I don't know if there's any
13 way to answer that.

14 DR. KREISBERG: Prophylactically with what?

15 ACTING CHAIR CRITCHLOW: Well, I'm assuming
16 that this question is pertaining specifically to
17 alendronate.

18 DR. SOBEL: The question is worded in a
19 deliberately provocative way.

20 ACTING CHAIR CRITCHLOW: My first thought on
21 reading on the questions was, you know, if we were
22 talking about in the general sense, you would have to
23 answer these with respect to whatever specific product
24 you were considering because it would, in my mind,
25 depend on the mode of action or some other issues. So

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1 presuming that this is specific to alendronate, are
2 there thoughts on that?

3 DR. KREISBERG: I don't think the question
4 works, because the term prophylactically, I think,
5 makes a lot of sense. We're talking about preventive
6 medicine. But which drug you choose -- in other
7 words, if it's in the context of, are we recommending
8 that alendronate be used prophylactically, sure,
9 that's an option.

10 But that is not the only option, and I
11 wouldn't want someone to come away from this feeling
12 that we're recommending that that's the option. And
13 I don't know what low bone mass is. I mean, you want
14 to say osteopenia or do you want to say more than one
15 standard deviation -- low bone mass just is a catch-
16 all.

17 And in fact, we've already heard that you
18 don't even need low bone mass to consider preventive
19 therapy, so I'm not even sure that that's the right
20 term to use.

21 ACTING CHAIR CRITCHLOW: I mean, in my naive
22 way of thinking it would seem, if I were someone, even
23 at say, -1, why in my own mind would I want my bone
24 mass to go lower than that, even though that may or
25 may not be particularly detrimental for me at that

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1 particular point in time. But again, some of these
2 issues I think, are extremely complicated.

3 Are there other comments on question 2 at
4 all?

5 DR. HIRSCH: I mean, the only way to really
6 diagnosis this is by bone biopsy. No one would say
7 that obviously, that when the bone biopsy shows
8 changes then you start with this. But you know, all
9 these other things are sort of levels of hazard that
10 we're talking about. So the biggest hazard is post-
11 menopausal women who do not take estrogen replacement
12 have X likelihood -- there's some p-value -- probably
13 that they're going to get this disease.

14 That's sort of the opening statement. Here
15 are some more things that make it much more likely:
16 if there's a family history, if they already show
17 evidence of it by bone density, whatever. It seems to
18 me that's the truth of the thing. And then a decision
19 is made whether you do want to use this thing or not.

20 You give a recommended dose and the hazards
21 and that's -- isn't that what we do with all drugs?
22 Why do we have to get into such a, sort of philosoph-
23 ic, genetic kind of excursus here?

24 ACTING CHAIR CRITCHLOW: Any comments from
25 the Agency?

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1 DR. TROENDLE: Well, what we're trying to
2 get out of course, in this is, how should we word the
3 indication? We don't know that everybody who is post-
4 menopausal needs to get treated and we need some
5 guidance on how this can be put in the package insert
6 so that it can be used. We don't want to be too
7 specific, like what is low bone density, because we
8 want the ability for the physician to interpret this
9 depending on the actual patient he's faced with.

10 ACTING CHAIR CRITCHLOW: I mean, would it be
11 more useful for us to comment on the specific label as
12 it is, the indication paragraph, or not?

13 DR. TROENDLE: Certainly. There are four
14 paragraphs in the indications as proposed by the
15 sponsor, and we'd like to know your reaction to that,
16 or if you want to write an indication for us to let us
17 know what you think it should be, we'd be glad to
18 evaluate that.

19 ACTING CHAIR CRITCHLOW: I mean, what's
20 difficult here is, everyone has indicated some desire
21 or need to treat each case on an individual basis, and
22 I think in terms of deciding who are targets for
23 primary prevention -- I mean, in other fields anyone
24 who has even any degree of risk for something is a
25 candidate for primary prevention of some sort.

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1 DR. MARCUS: Well, first of all, half this
2 population are going to have a bone density which is
3 at the median or higher, and I would not be moved to
4 use any pharmacologic agent to prevent bone loss in
5 that population. I would certainly use hormone
6 replacement therapy because there's other indications
7 for that. But if a woman came to my office and had a
8 bone mass which was down only, let us say, $-.25$ of a
9 standard deviation, she's not somebody I'm particular-
10 ly worried about.

11 But we are talking about making an informed
12 decision with our patients, and if she says look, my
13 high priority is I don't want to look curved like the
14 woman across the hall and I don't want to have a hip
15 fracture like the woman in the next house; I want
16 effective therapy and I can't take estrogen. Then I
17 would have no opposition to putting that woman on two-
18 and-a-half milligrams of alendronate, long-term.

19 ACTING CHAIR CRITCHLOW: And what if she --

20 DR. MARCUS: Because she's losing; she's
21 predictably going to lose over the next few years.

22 DR. MOLITCH: What if you did the bone
23 mineral density and it was $+1$?

24 DR. MARCUS: No, I really wouldn't. I'd say
25 your risk for having fragility-related fractures is

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