

1 UNITED STATES OF AMERICA

2 + + + + +

3 DEPARTMENT OF HEALTH AND HUMAN SERVICES

4 PUBLIC HEALTH SERVICE

5 + + + + +

6 FOOD AND DRUG ADMINISTRATION

7 CENTER FOR DRUG EVALUATION AND RESEARCH

8 + + + + +

9 ENDOCRINOLOGIC AND METABOLIC

10 DRUGS ADVISORY COMMITTEE

11 MEETING #66

12 + + + + +

13 THURSDAY, FEBRUARY 20, 1997

0870 97 MAR 20 10:36

ORIGINAL

14  
15 The meeting took place in Versailles Rooms  
16 I, II, and III, Bethesda Holiday Inn, 8120 Wisconsin  
17 Avenue, Bethesda, Maryland, at 8:00 a.m., Cathy W.  
18 Critchlow, Ph.D., Acting Chair, presiding.

19  
20 PRESENT:

- 21 CATHY W. CRITCHLOW, Ph.D. Acting Chair
- 22 KATHLEEN R. REEDY Exec. Secretary
- 23 COLLEEN A. COLLEY, PharmD Member
- 24 JULES HIRSCH, M.D. Member
- 25 D. ROGER ILLINGWORTH, M.D., Ph.D. Member

1	ROBERT A. KREISBERG, M.D.	Member
2	ROBERT MARCUS, M.D.	Member
3	MARK E. MOLITCH, M.D.	Member
4	MARIA I. NEW, M.D.	Member
5	SAMARENDRA DUTTA, M.D.	FDA Rep.
6	DAN MARTICELLO, M.D.	FDA Rep.
7	SOLOMON SOBEL, M.D.	FDA Rep.
8	GLORIA TROENDLE, M.D.	FDA Rep.
9	LINDA JOHNSON	Public Comment
10	CINDY PEARSON	Public Comment
11	SANDRA C. RAYMOND	Public Comment
12	ANASTASIA DAIFOTIS, M.D.	Sponsor Rep.
13	BONNIE GOLDMANN, M.D.	Sponsor Rep.
14	EDWIN HEMWALL, Ph.D.	Sponsor Rep.
15	A. JOHN YATES, M.D.	Sponsor Rep.

16 ALSO PRESENT:

17	MICHAEL McCLUNG, M.D.	
18	JAMES McGUIGAN M.D.	
19	MICHAEL ROSENBLATT, M.D.	
20	ETHEL SIRIS, M.D.	

21  
22  
23  
24  
25

C O N T E N T S

	<u>PAGE</u>
1	
2	
3	Call to Order, Introductions, Open Comments 4
4	Meeting Statement - Ms. Reedy 6
5	Open Public Hearing
6	Ms. Sandra Raymond 8
7	Ms. Cindy Pearson 12
8	Ms. Linda Johnson 16
9	Introduction - Dr. Troendle 20
10	Merck Presentation
11	Dr. Hemwall 22
12	Dr. Yates 31
13	Dr. Daifotis 57
14	Dr. Goldmann 77
15	FDA Presentation
16	Dr. Dutta 110
17	Dr. Marticello 115
18	
19	LUNCHEON RECESS
20	
21	Discussion and Questions 140
22	
23	
24	
25	

P R O C E E D I N G S1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25

8:08 a.m.

ACTING CHAIR CRITCHLOW: Good morning. I'd like to call the 66th Meeting of the Endocrinologic and Metabolic Diseases Advisory Committee to Order. If I may first ask those of us at the table to introduce ourselves, starting with FDA Representatives.

MR. MARTICELLO: Dan Marticello, Biometrics, FDA.

DR. DUTTA: Sam Dutta, Medical Officer, FDA.

DR. SOBEL: Sol Sobel, Director, Division of Endocrine and Metabolic Drug Products, FDA.

DR. MOLITCH: Mark Molitch, Northwestern University.

ACTING CHAIR CRITCHLOW: Cathy Critchlow, University of Washington, Seattle.

MS. REEDY: Kathleen Reedy, FDA.

DR. KREISBERG: Bob Kreisberg, Birmingham, Alabama.

DR. COLLEY: Colleen Colley, VA Medical Center in Portland, Oregon.

DR. HIRSCH: Jules Hirsch, Rockefeller University, New York.

DR. MARCUS: Robert Marcus, Stanford University.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 DR. ILLINGWORTH: Good morning. Roger  
2 Illingworth, Portland, Oregon.

3 ACTING CHAIR CRITCHLOW: And I've heard that Dr.  
4 New will be here in about one hour.

5 Today we're going to be discussing alendron-  
6 ate for the prevention -- the indication being the  
7 prevention of post-menopausal osteoporosis. That will  
8 be a, I'm sure, interesting discussion.

9 If I could now have Ms. Reedy read the  
10 meeting statement.

11 MS. REEDY: The following announcement  
12 addresses the issue of conflict of interest with  
13 regard to this meeting and is made a part of the  
14 record to preclude even the appearance of such at this  
15 meeting.

16 Based on the submitted agenda and informa-  
17 tion provided by the participants the Agency has  
18 determined that all reported interests in firms  
19 regulated by Center for Drug Evaluation and Research  
20 present no potential for a conflict of interest at  
21 this meeting with the following exceptions.

22 In according with 18 United States Code  
23 Section 208(b)(3), full waivers have been granted to  
24 Dr. D. Roger Illingworth and Dr. Mark Molitch. Dr.  
25 Robert Marcus has been granted a limited waiver that

**SAG, CORP**

4218 LENORE LANE, N W.  
WASHINGTON, D C. 20008

1 will allow him to participate in the committee's  
2 discussions without voting privileges.

3 A copy of these waiver statements may be  
4 obtained by submitting a written request to FDA's  
5 Freedom of Information Office, Room 12A30 of the  
6 Parklawn Building.

7 Dr. Henry Bone has been excluded from  
8 participation in all matters regarding Fosamax™  
9 because of his consultant and research involvements  
10 with respect to Merck and Company, and Fosamax™. Dr.  
11 Critchlow will serve as Acting Chair in Dr. Bone's  
12 stead during this portion of the meeting.

13 In the event that the discussions involve  
14 any other products or firms not already on the agenda  
15 for which an FDA participant has a financial interest,  
16 the participants are aware of the need to exclude  
17 themselves from such involvement and their exclusion  
18 will be noted for the record.

19 With respect to all other participants, we  
20 ask in the interest of fairness that they address any  
21 current or previous financial involvement with any  
22 firm whose products they may wish to comment upon.

23 ACTING CHAIR CRITCHLOW: Thank you. The  
24 first item on the agenda is, of course, the Open  
25 Public Hearing. On our program there are five persons

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 that are indicated. Fortunately Judy Simon has  
2 submitted a written statement which is included in our  
3 folders and is available I believe, out on the table.  
4 And Ms. Smolkin was unable to be here.

5 So we'll now start with Sandra Raymond.

6 MS. RAYMOND: Good morning. It's a pleasure  
7 to stand before you again to comment on yet another  
8 therapy to fight osteoporosis. As you know, I'm  
9 Sandra Raymond. I'm the founding Executive Director  
10 of the National Osteoporosis Foundation, the only  
11 national, non-profit, voluntary health organization  
12 solely dedicated to reducing the wide spread of  
13 osteoporosis through programs of research -- public  
14 and professional -- and patient education.

15 The Foundation, which celebrated its 10th  
16 anniversary last year, is comprised of more than  
17 100,000 members and donors. Its broad-based support  
18 is derived from: federated campaigns, grants from  
19 philanthropic foundations, federal and state grants  
20 such as a major NIH grant to support the Osteoporosis  
21 and Related Bone Diseases National Resource Center,  
22 major individual gifts and membership dues, special  
23 events, and general operating and programmatic support  
24 -- from not only pharmaceutical companies but from  
25 non-pharmaceutical companies as well.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 Merck is among more than the 20 pharmaceuti-  
2 cal companies and the 50 non-pharmaceutical companies  
3 that support the work of the foundation. NOF prides  
4 itself in always presenting a balanced perspective  
5 based on the most currently available, scientific  
6 findings.

7 In the few minutes allotted to my testimony  
8 I would like to focus on the human and economic impact  
9 of osteoporosis and the importance of prevention. The  
10 human toll of this disease, as you know, is stagger-  
11 ing. NOF has issued new prevalence data based on the  
12 work of Drs. Ann Looker and Joseph Melton, and we  
13 estimate that ten million women and men have osteopo-  
14 rosis in 1996, and another 18 million have low bone  
15 mass, placing them at risk for osteoporosis.

16 This number, 28 million, is predicted to  
17 increase to 41 million by the year 2015 if nothing is  
18 done to intervene. Women, as you know, are at the  
19 highest risk for developing this silent bone-weakening  
20 disease and its associated fractures, typically of the  
21 hips, spine, and wrist.

22 A woman's risk of developing a hip fracture  
23 is equal to her combined risk of developing breast,  
24 uterine, and ovarian cancer. Each year there are more  
25 than 1.5 million osteoporotic fractures, including

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 more than 300,000 hip fractures, more than 500,000  
2 spinal fractures, and hundreds of thousands of  
3 fractures at other bone sites.

4 As you know again, osteoporosis causes pain,  
5 disability, deformity, loss of independence. During  
6 their lifetime one of every two women and one in eight  
7 men over the age of 50 will develop a fracture caused  
8 by osteoporosis.

9 The economic impact is equally dramatic.  
10 The Centers for Disease Control and Prevention  
11 estimate that the medical care associated with  
12 osteoporotic fractures suffered by the Medicare  
13 population add three percent to the overall cost of  
14 the Medicare program. Based on the most recent  
15 Congressional Budget Office Medicare data, in 1996  
16 osteoporosis will cost the Medicare program alone,  
17 \$5.7 billion.

18 In the year 2007 that figure will increase  
19 to almost \$14 billion, and that's just the cost to the  
20 Medicare program. That does not take into account the  
21 cost of the Medicaid program, private insurance, or  
22 the individual out-of-pocket expenditures that could  
23 as much as double these figures.

24 We do have an interest in this hearing  
25 today, because Fosamax<sup>TM</sup> plays a major role in the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 treatment of osteoporosis and the prevention of  
2 fractures. Many of our patients have experienced an  
3 increase of bone mass during the past year while  
4 taking the medication. One of our NOF members, Linda  
5 Johnson who will speak to you this morning, is an  
6 example of such a success story.

7 By far, most of the stories we hear from our  
8 patients are similar to Linda's story. However at the  
9 higher dose used for osteoporosis treatment there have  
10 been a few reported, adverse, acute, and chronic  
11 gastrointestinal experiences which we might speculate  
12 that these adverse experiences will not occur with the  
13 lower dosage required for prevention. We would  
14 however ask that if they do, it should be noted in the  
15 patient information sheet.

16 Currently, the only FDA-approved drug for  
17 the prevention of osteoporosis is estrogen replacement  
18 therapy. Since not all women are able or willing to  
19 take ERT it would be clearly beneficial for both  
20 menopausal women to have therapeutic choices for the  
21 prevention of osteoporosis.

22 NOF continues to recommend that in order to  
23 determine who should receive treatment, post-menopaus-  
24 al women with major risk factors should have a test to  
25 determine their bone density and risk of future

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 fracture.

2 It is our hope that the data presented today  
3 meet FDA safety and efficacy guidelines for an  
4 osteoporosis prevention indication. We look forward  
5 to your deliberations and stand ready to answer  
6 questions you might have. Thank you.

7 ACTING CHAIR CRITCHLOW: Thank you. I'd now  
8 like to introduce Linda Johnson. Is Linda here -- Ms.  
9 Johnson here?

10 DR. MARCUS: Did you say her's was the  
11 written --

12 ACTING CHAIR CRITCHLOW: No, that was the  
13 next -- Judy Simon was the written statement which is  
14 included in the folders, and Ms. Smolkin cannot be  
15 here. Cindy Pearson?

16 MS. PEARSON: I'm Cindy Pearson. I'm the  
17 Executive Director of the National Women's Health  
18 Network. We're a non-profit Women's Health Advocacy  
19 Group. We've testified before the panel before about  
20 both alendronate for treatment of osteoporosis and  
21 etidronate.

22 As continuing panel members know, we are  
23 primarily supported by donations from individual and  
24 organizational members around the country. The only  
25 connection we have with a group with any financial

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D.C. 20008

1 involvement in osteoporosis is small general support  
2 grants we've received from Proctor and Gamble over the  
3 last two years.

4 Those grants never have amounted to more  
5 than three percent for a total budget, and to Proctor  
6 and Gamble's credit, they were both made after we  
7 testified against etidronate.

8 Turning to the topic today, I want to begin  
9 by saying that we support the availability of non-  
10 hormonal options for both the prevention and treatment  
11 of osteoporosis, and concur with the Foundation in its  
12 description of osteoporosis as an important public  
13 health concern of women.

14 We have not seen the data that you'll be  
15 seeing in the next few minutes and so can't comment  
16 specifically on that, although have heard, as probably  
17 many people have through the media, about an interim  
18 analysis of the data that was presented at a meeting  
19 several months ago.

20 And we also hadn't seen the questions that  
21 the committee was given, before today. But assuming  
22 that the data that you see are good, you the commit-  
23 tee, will be asked to advise the FDA as to the  
24 specifics of the approval, whether or not the drug  
25 should be approved for prevention, how it should be

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 labeled, and indirectly, the advice you give will  
2 guide the FDA on what sort of promotion and advising  
3 the manufacturer will be able to do.

4 And this is the area on which we want to  
5 comment today. When I spoke before the Advisory  
6 Committee meeting in 1995 I expressed a similar point  
7 of view: we hadn't seen the data, we assumed it was  
8 going to be good, and if it were to be good we, like  
9 others, would support the approval of the first non-  
10 hormonal option for treatment.

11 But we expressed some concern about the  
12 possible overuse of a treatment drug for osteoporosis,  
13 and talked about our basic philosophy that no drug, no  
14 matter how safe, is safe enough if it wasn't needed in  
15 the first place.

16 Based on your recommendation, the FDA  
17 approved Fosamax™ for the treatment of osteoporosis  
18 in post-menopausal women based on a pivotal trial  
19 which enrolled women, all of whom have been tested for  
20 bone mineral density and had been demonstrated to have  
21 bone mineral density that was low.

22 Although Merck's ads about osteoporosis  
23 included information to that effect at the beginning,  
24 it quickly left that behind, and by mid-1996, running  
25 ads such as this -- which is from the Journal of

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 Women's Health and has run in other medical journals,  
2 saying no matter what her degree of osteoporotic bone  
3 loss.

4 Now, Merck may well have felt that it had  
5 the data to back that statement up at the time it ran  
6 that ad. Unfortunately, the data hadn't been reviewed  
7 in an open process like this, and the indication for  
8 approval after use of the drug, didn't reflect this.

9 Now it may be that the data are going to be  
10 presented today that after the fact, make this ad  
11 accurate. But as a consumer group, I think it's  
12 reasonable for us to express some concern to you about  
13 what kind of advertising we'll see next.

14 And taking a quick look at the questions you  
15 were asked to answer, it looks like there's some very  
16 good questions as to how broad should the recommenda-  
17 tion for use be. Should it be for all post-menopausal  
18 women? Should it be for all post-menopausal women who  
19 have some risk factors for osteoporosis? Should it be  
20 for all post-menopausal women who have low bone  
21 density?

22 Without having heard the data yet we can't,  
23 as a consumer group, give you very specific advice  
24 about how you should craft your recommendation to the  
25 Agency so that the Agency has some details on which to

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C 20008

1 make its recommendation for approval.

2 But I would just say that our general advice  
3 would be to make the recommendation for approval  
4 closely near the entry criteria to the study, to also  
5 recommend that in the materials that are used to  
6 advertise, both to the profession and to the general  
7 public, that the length of time of the pivotal trials  
8 be highlighted in bold.

9 Peri-menopausal women or newly post-meno-  
10 pausal women who start Fosamax™ for prevention are  
11 facing 20 to 30 years on the drug, and even though the  
12 data may be very good as to its short term safety and  
13 effectiveness, women who are making the decision to  
14 start a decade's long treatment program at least  
15 deserve to know that they'll always be just a few  
16 year's more data before them, not decade's worth of  
17 experience and data.

18 I know that our testimony has been primarily  
19 raising concerns and possible criticisms about the  
20 over-promotion of Fosamax™ for treatment, but I'd  
21 like to just finish by restating something that I said  
22 at the beginning; that we do agree that osteoporosis  
23 is a significant health problem; that more drug  
24 options for women, and specifically non-hormonal drug  
25 options are a good step forward.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           And if the drug seems to have performed well  
2           in these new studies that you're going to look at, we  
3           believe it is reasonable to approve it for prevention  
4           as long as you do everything you can to give the FDA  
5           some good guidance on how to craft the language  
6           carefully so that we don't get into a problem of over-  
7           promotion.

8           Thank you.

9           ACTING CHAIR CRITCHLOW: Thank you. Linda  
10          Johnson has arrived and will be our last speaker in  
11          the open public hearing.

12          MS. JOHNSON: Good morning. I didn't mean  
13          to make such a grand entrance but I couldn't find this  
14          place. I have been outside on Wisconsin Avenue for  
15          the last 15 minutes looking for Holiday Inns. But I  
16          did want to speak today because I did have an interest  
17          in Fosamax<sup>TM</sup> as a medicine for osteoporosis.

18          And as I said, my name is Linda Johnson, and  
19          the reason I have this interest is because in 1991, at  
20          the young age I think, of 43, I fractured my ankle  
21          when I stepped down from a curb. Now, this was the  
22          sixth fracture in my feet, or my foot, in six years,  
23          and I had been going to the doctor after each fracture  
24          and asking after the first three, why am I breaking my  
25          bones so quickly, or so easily?

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 I was told that I was clumsy. I was also  
2 told that I might be accident-prone. Finally, when  
3 the ankle fractured I had a different orthopedist, and  
4 when he looked at my x-ray he gave me a different  
5 answer. He told me I had osteoporosis. I asked him  
6 what should I do about that; he said he really didn't  
7 know much about the disease. So he told me to call  
8 NIH.

9 So I did, and NIH told me to call the  
10 Osteoporosis Foundation and gave me the number. And  
11 I did. The Osteoporosis Foundation helped me find a  
12 doctor who specialized in osteoporosis. When I first  
13 went to the doctor, we had our consultation in his  
14 office. He asked me if I was a smoker; I said no.  
15 Was I a drinker? No. Did I have a history of  
16 osteoporosis in my family? I said no.

17 And then when he found out that I was pre-  
18 menopausal he lighted up like a candle and said, well,  
19 you can't have osteoporosis, you probably have  
20 osteomyelitis because osteoporosis starts in women  
21 after menopause. And he says, and that's curable. So  
22 I left there feeling pretty good.

23 He ordered some tests: a bone density test,  
24 a blood work, 24-hour urinalysis, and some x-rays.  
25 When the tests finally came back, I indeed, had

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 osteoporosis. I had lost 35 to 40 percent of the bone  
2 density in my bones, I had lost an inch in height due  
3 to a collapsed vertebrae in my spine, and I had lost  
4 another inch in my height because I was curved at the  
5 neck; I was beginning the dowager's hump.

6 Now, if that wasn't bad enough, the next  
7 thing he told me was worse. He said there was no  
8 treatment for me. He said the treatment that they had  
9 on the market at that time was for post-menopausal  
10 women. They didn't know what the drugs would do to  
11 someone who was pre-menopausal.

12 All he could tell me to do was take calcium  
13 supplements. He told me I had the bones of a 70-year-  
14 old, which I already realized because my 70-year-old  
15 mother was in much better shape than I was. My  
16 children used to go and visit their grandmother and  
17 come back and say, Grand-mom acts your age and you act  
18 her age. They even started to say, don't touch Mom  
19 because she'll break.

20 And it wasn't being funny, it was true. My  
21 husband picked me up one day and my rib cracked. I  
22 couldn't understand what was wrong. At least now I  
23 did know that there was something wrong, but there was  
24 nothing that they could do for me. I was told to  
25 exercise, that maybe the calcium supplements would

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C 20008

1 help my bones to stay the same, but they would not get  
2 better.

3 In the subsequent years I had more bone  
4 density tests and true to their words, I really didn't  
5 get better. I got a little bit better but not  
6 significantly. But I didn't get worse. I started my  
7 own exercise program 3-1/2 years ago because there was  
8 no one out there how could give me one.

9 I would ask and they couldn't tell me what  
10 to do or what not to do, except not to bend at the  
11 waist and not to do high-intensity aerobics. After 3-  
12 1/2 years I stand an inch taller. My spine is still  
13 curved but my muscles stand straight. I've gotten a  
14 lot better in that way and I'm glad.

15 But then I heard about a drug called  
16 Fosamax™, and when I heard that it might be something  
17 that could help me I was very, very interested. I  
18 told my doctor about it, I kept up on it, and I  
19 couldn't wait until it came on the market.

20 Last March I started taking Fosamax™. I  
21 had a bone density test this past January. When the  
22 doctor told me that my hips had improved a great deal,  
23 I was ecstatic. My spine hasn't improved yet, but he  
24 believes that in another year that my spine will also  
25 improve.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           And I can't tell you what it feels like to  
2 wake up in the morning now, and have hope. For so  
3 many years I had no hope of ever getting any better,  
4 and now I wake up and know that my bones are getting  
5 stronger, and it's a wonderful feeling.

6           And what I would like is for Fosamax™ to be  
7 available to as many people as can take it so that  
8 they would be able to share in my hope now, instead of  
9 having to share in my pain. Thank you.

10           ACTING CHAIR CRITCHLOW: Thank you. As we  
11 do have a few more minutes available to us in the open  
12 public hearing, are there any other speakers who might  
13 wish to make a brief statement?

14           If not, we have a slight change in the  
15 agenda. Dr. Gloria Troendle will make an introduction  
16 to the proceedings and then we will proceed to the  
17 sponsor presentation.

18           DR. TROENDLE: We thought there might be a  
19 little confusion about the two indications that we're  
20 talking about today. There are two issues for the  
21 committee consideration today: the claims that  
22 alendronate reduces fractures, and claims that it  
23 reduces bone loss in post-menopausal women who do not  
24 have established osteoporosis, thus preventing  
25 osteoporosis from developing.

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D.C. 20008

1           Although any treatment for osteoporosis is  
2 ultimately intended to reduce the risk of fractures,  
3 claims are limited to what has actually been shown in  
4 adequate and well-controlled trials. Alendronate was  
5 reviewed by this Advisory Committee in July 1995, and  
6 approved by the Agency in September 1995 for treatment  
7 of Paget's Disease and for treatment of post-menopaus-  
8 al osteoporosis.

9           The osteoporosis claims were based on our  
10 draft guidelines which provide for approving a drug on  
11 the basis of an increase in bone mineral density of  
12 the lumbar spine. A drug so approved may claim to  
13 treat osteoporosis and to increase bone mineral  
14 density but not to reduce fractures or fracture risks.

15           Two pending supplements to the alendronate  
16 NDA seek to extend the osteoporosis indication. They  
17 are the subject of discussion today.

18           One of the supplements presents data showing  
19 reduction of vertebral, hip, and wrist fractures by  
20 Fosamax™ in women with established osteoporosis,  
21 affirming that Fosamax™-induced increase in bone  
22 mineral density is associated with a decreased risk of  
23 these fractures.

24           We request your evaluation of the adequacy  
25 of this fracture data for including a fracture claim

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 in the Indications Section of the package insert.  
2 Questions five and six relate to this change in the  
3 indications for Fosamax™.

4 Another supplement presents information on  
5 Fosamax™ for prevention of osteoporosis based on  
6 Fosamax™-induced changes in bone mineral density in  
7 women who do not have established osteoporosis. The  
8 proposed change in indications for this supplemental  
9 application means that the drug will be recommended  
10 for what is potentially a very big expansion of the  
11 population to be treated.

12 The new indication will suggest treating  
13 women with a much smaller risk of fractures than the  
14 population presently described in package labeling.  
15 The definition of this population is deserving of  
16 careful consideration, and we have asked for your  
17 response to several questions, numbered a to e in  
18 question 2, and one question about the appropriate  
19 dose for preventing bone loss in women with only  
20 moderately-reduced bone density, which is question 3.

21 Are there questions about that?

22 ACTING CHAIR CRITCHLOW: Thank you, Dr.  
23 Troendle. I'd now like to introduce Dr. Hemwall who  
24 will introduce the presentation of Merck.

25 DR. HEMWALL: Good morning Dr. Critchlow,

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D C. 20008

1 committee members, FDA staff, and guests. I am Dr. Ed  
2 Hemwall representing Merck Research Labs where I'm  
3 senior director of Regulatory Affairs. We are here  
4 today to present data from our development program in  
5 support of the use of Fosamax™, the trade name for  
6 alendronate sodium, for the prevention of osteoporosis  
7 in post-menopausal women.

8 I'll begin by orienting you to the main  
9 elements of this program and today's presentation.  
10 First, I will briefly review the regulatory history of  
11 Fosamax™, and as you heard from Dr. Troendle, in  
12 September of 1995, the original, new drug application  
13 was approved by FDA for the treatment of post-meno-  
14 pausal osteoporosis at a dose of ten milligrams per  
15 day, and for the treatment of Paget's Disease of bone  
16 at a dose of 40 milligrams per day.

17 This approval followed upon the unanimous  
18 recommendation of this committee. Today the Agency  
19 has asked the committee to review our pending supple-  
20 mental application which supports an expansion of the  
21 Fosamax™ indication to include prevention at a dose  
22 of five milligrams per day.

23 The committee has also been asked to assess  
24 the results of studies which demonstrate a reduction  
25 in fracture risk associated with Fosamax™ in the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 treatment of osteoporosis. The key distinction  
2 between prevention and treatment is based on the  
3 differing therapeutic objectives.

4 For prevention, the patient is at increased  
5 risk of losing bone mass but is not yet osteoporotic.  
6 Therefore, the therapeutic goal is to slightly  
7 increase or maintain bone mass in order to prevent  
8 further loss which can lead to osteoporosis.

9 In contrast, for treatment the patient has  
10 already lost significant bone mass and the goal is to  
11 maximally increase or restore bone mass, thereby  
12 reducing fracture risk.

13 As many are aware from the last time we  
14 appeared before this committee, the approval of  
15 Fosamax™ for treatment of osteoporosis was based on  
16 several key factors: demonstration of increased bone  
17 density and strength while retaining normal bone  
18 structure and biomechanical qualities in a number of  
19 animal models; two 3-year clinical trials demonstrat-  
20 ing progressive increases in bone marrow density;  
21 normal bone histology in clinical trial patients; and  
22 significant reductions in vertebral fracture incidents  
23 based upon a pre-defined analysis of combined data  
24 from the two primary, phase III studies.

25 In addition to the compelling therapeutic

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 benefit demonstrated by these findings, approval was  
2 based on Fosamax™ program meeting all criteria of the  
3 draft FDA guidelines for evaluation of agents used in  
4 the treatment of post-menopausal osteoporosis.

5 These same guidelines also provide for  
6 development of agents aimed at prevention of post-  
7 menopausal osteoporosis with these key criteria: the  
8 requirement that the agent has been approved for  
9 treatment of osteoporosis; demonstration of normal  
10 bone quality in a prevention setting through animal  
11 models and appropriate clinical measures; demonstra-  
12 tion of fracture risk reduction in a large-scale  
13 fracture endpoint trial in a treatment population; and  
14 the need for clinical studies of at least two year's  
15 duration employing multiple doses to assess the  
16 optimally effective dose in a post-menopausal popula-  
17 tion at risk of developing osteoporosis.

18 Use of bone marrow density as an endpoint is  
19 a key factor for these prevention studies, as the  
20 Agency's guidelines recognize that demonstrating risk  
21 reduction in a prevention population would not be  
22 achievable on a practical timeframe. Therefore, it is  
23 required that fracture risk reduction be demonstrated  
24 in the treatment population, thus validating the BMD  
25 endpoint for that particular drug.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 I'll now briefly review how the Fosamax™  
2 development program has successfully fulfilled all the  
3 criteria required for approval for prevention.

4 First, normal bone quality -- that is,  
5 normal structure, histology, and biomechanical  
6 strength -- has been demonstrated in animals for both  
7 the treatment and prevention paradigms, including two  
8 separate studies in prevention models.

9 Normal bone quality has also been demon-  
10 strated through an extensive bone biopsy program  
11 incorporated into our clinical trials. This program  
12 -- which was reviewed extensively when we last  
13 appeared before this committee, involved histomor-  
14 phometric analysis of bone biopsy specimens from over  
15 500 patients and has now been supplemented with data  
16 from another 55 patients enrolled in prevention  
17 studies.

18 The results continue to confirm that  
19 alendronate is associated with a partial suppression  
20 of bone turnover which does not progress over long-  
21 term use, and has no negative effects on bone struc-  
22 ture or mineralization.

23 The ultimate evidence of normal bone quality  
24 is demonstrated by the approximately 50 percent  
25 reduction in osteoporotic fractures observed in long-

SAG, CORP

4218 LENORE LANE, N W  
WASHINGTON, D C. 20008

1 term studies of alendronate-treated patients.

2 With regard to fracture risk reduction, a  
3 brief overview is called for at this point. As  
4 previously noted, the Agency and this committee  
5 recommended approval of Fosamax<sup>TM</sup> for treatment of  
6 osteoporosis based upon the predefined, combined  
7 analysis of the fracture data from our two phase III  
8 treatment studies in a population of which the  
9 majority of patients had no vertebral fractures at  
10 baseline.

11 Since that time, Merck has submitted to the  
12 FDA and published the results of the vertebral  
13 fracture arm of our fracture intervention trial, known  
14 by its acronym FIT. In this 3-year study, over 2,000  
15 patients were enrolled: half receiving placebo and  
16 half receiving alendronate, five milligrams for years-  
17 1 and -2, and ten milligrams for year-3.

18 In this population of women with at least  
19 one pre-existing vertebral fracture at baseline,  
20 Fosamax<sup>TM</sup> was associated with significant, 50 percent  
21 reductions in new fractures of the spine, hip, and  
22 wrist. Therefore, fracture risk reduction first  
23 demonstrated in the phase III studies has been  
24 confirmed by FIT, thus validating bone mineral density  
25 as an endpoint for clinical trials in the prevention

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C 20008

1 of osteoporosis.

2 In addition, these data support an expansion  
3 of the treatment indication to reflect this reduction  
4 in fracture risk.

5 The new information which we will review  
6 today supporting the use of Fosamax™ in the preven-  
7 tion of osteoporosis will focus primary on the  
8 clinical and post-marketing experience, including a  
9 full accounting of the fracture intervention trial  
10 results just mentioned.

11 Results of three clinical studies of 2- to  
12 3-year's duration which enrolled over 2300 women --  
13 nearly 1600 on Fosamax™ -- a younger, post-menopausal  
14 population which, left untreated, undergoes rapid bone  
15 loss as represented by the placebo groups.

16 And, very importantly, we will review the  
17 excellent safety and tolerability profile of the five  
18 milligram dose, augmented by long-term clinical trial  
19 data up to five years and post-market experience in  
20 over one million patients with the ten milligram dose.

21 I'd now like to introduce you to the  
22 proposed wording of our prevention indication which  
23 has been integrated, where appropriate, with the  
24 treatment indication beginning with Fosamax™ as  
25 indicated for the treatment and prevention of osteopo-

SAG, CORP

4218 LENORE LANE, N.W  
WASHINGTON, D C 20008

1           rosis in post-menopausal women.

2                       But as was done for the treatment indica-  
3           tion, we have developed additional language to help  
4           guide the physician when considering potential  
5           patients who may benefit from prevention therapy.  
6           Therefore, the following guidance is proposed as part  
7           of the indication.

8                       For the prevention of osteoporosis, Fosa-  
9           max™ should be considered in post-menopausal women  
10          who are at risk of developing osteoporosis and for  
11          whom the desired clinical outcome is to maintain bone  
12          mass and to reduce the risk of future fracture.

13                      Additional language not shown here, also  
14          lists some of the risk factors such as low bone mass  
15          and early menopause, which may be assessed when  
16          considering use of Fosamax™ in a particular patient.

17                      Also, because it is a focus of today's  
18          meeting, it may be helpful for the committee to see  
19          our proposed wording to expand the treatment indica-  
20          tion as follows.

21                      When used for the treatment of osteoporosis,  
22          Fosamax™ increases bone mass and prevents fractures,  
23          including those of the hip, wrist, and spine. And as  
24          already noted, the treatment indication is currently  
25          accompanied by additional language which provides

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 guidance in identifying appropriate patients through  
2 bone mass assessment or history of previous fracture.

3 Our presentation this morning is organized  
4 as I show it here. Following my own remarks, Dr. John  
5 Yates will provide an overview of the efficacy data  
6 supporting this application and he'll be followed by  
7 Dr. Anastasia Daifotis who will provide a comprehen-  
8 sive overview of the Fosamax<sup>TM</sup> safety profile. Dr.  
9 Bonnie Goldmann will finish our formal presentation  
10 with concluding remarks.

11 We will be pleased to address the commit-  
12 tee's questions after we have completed our entire  
13 presentation, but members should feel free to inter-  
14 rupt if immediate clarification is required at any  
15 point during the course of our review.

16 To aid the committee in their deliberations  
17 we have with us today a number of outside consultants  
18 who may provide their perspective on certain topics as  
19 needed. Dr. Ethel Siris from Columbia University, an  
20 internationally recognized expert in bone metabolic  
21 disease, and has also served at one time as a member  
22 of this committee.

23 Dr. Michael Rosenblatt from Harvard Univer-  
24 sity who was involved in the inception of the alendro-  
25 nate development program. Dr. Michael McClung from

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 Portland, Oregon, also an internationally known expert  
2 and a key investigator in two of the main prevention  
3 studies to be presented today.

4 Dr. James McGuigan is here from the Univer-  
5 sity of Florida, an expert Gastroenterologist, who is  
6 prepared to provide his perspective on the upper  
7 gastrointestinal safety profile of alendronate. And  
8 finally, Dr. Janet Wittes is here from the Washington  
9 area, an authority in biostatistics and large-scale,  
10 clinical trial design.

11 That concludes my opening remarks, and at  
12 this time I would like to turn the podium over to Dr.  
13 John Yates. Thank you.

14 DR. YATES: Dr. Critchlow, Advisory Commit-  
15 tee members, FDA Staff, and guests, good morning. I'm  
16 Dr. John Yates. I'm senior director of Clinical  
17 Research at Merck Research Laboratories. This morning  
18 I want to review with you the efficacy data supporting  
19 the use of alendronate in the prevention of osteoporo-  
20 sis in post-menopausal women.

21 I have three objectives in my presentation.  
22 First, as stated by Dr. Hemwall, the FDA draft  
23 guidelines require that anti-fracture efficacy must be  
24 clearly demonstrated for any non-estrogenic agent  
25 prior to approval for prevention of osteoporosis. In

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C 20008

1 accordance with these requirements I will summarize  
2 the anti-fracture efficacy data that come from studies  
3 of patients who already have osteoporosis.

4 Next, I will briefly review the rationale  
5 for prevention of osteoporosis and discuss how  
6 appropriate candidates for preventative therapy may be  
7 identified.

8 Finally, the major focus of my talk will be  
9 a review of the extensive database supporting the  
10 efficacy of alendronate for prevention of osteoporosis  
11 in post-menopausal women.

12 To assess the anti-fracture efficacy of  
13 alendronate we not only looked at the fractures in our  
14 phase III osteoporosis treatment program, but more  
15 recently, also conducted the fracture intervention  
16 trial, or FIT, which was specifically powered to  
17 evaluate fracture risk reduction.

18 In our phase III studies the primary  
19 endpoint was bone mineral density, or BMD. However,  
20 we did pre-specify fractures to be an important  
21 secondary endpoint in those studies. Also important-  
22 ly, the women recruited into the phase III studies  
23 were not required to have evidence of a previous  
24 vertebral fracture.

25 In contrast, all of the women in the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 vertebral fracture arm of the fracture intervention  
2 trial had x-ray evidence of a previous vertebral  
3 fracture. This arm of FIT enrolled over 2,000 women  
4 who were randomized either to placebo for three years,  
5 or to alendronate for five milligrams for the first  
6 two years, followed by ten milligrams in year-3.

7 This dose increase was in response to data  
8 that became available from the phase III clinical  
9 trials that clearly demonstrated greater efficacy of  
10 the ten milligram dose versus five milligrams, to  
11 increased bone mass.

12 The primary efficacy endpoint in FIT was the  
13 incidence of new vertebral fractures, and the second-  
14 ary endpoint was clinical fractures, meaning any  
15 painful fracture that came to clinical attention.

16 In FIT, 15 percent of patients on placebo  
17 were documented by x-ray to have a new vertebral  
18 fracture during the three years of the study, compared  
19 to eight percent of patients taking alendronate. This  
20 represents a 47 percent risk reduction.

21 Similarly, five percent of patients on  
22 placebo experienced a painful vertebral fracture that  
23 came to clinical attention, as compared to only 2.3  
24 percent of those on alendronate treatment, which  
25 represents a 55 percent reduction in clinical verte-

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1       bral fracture risk.

2               This slide shows the anti-fracture efficacy  
3       of alendronate for patients in FIT who are younger or  
4       older than 65. As expected, the younger women have  
5       fewer vertebral fractures than those over age 65.  
6       However, relative to placebo, the percent risk  
7       reduction with alendronate is similar in younger and  
8       older patients in this study.

9               This slide shows the vertebral fracture  
10       incidents in the FIT population separated into  
11       tertiles of baseline spine BMD. You can see that  
12       there is the expected risk gradient -- those with the  
13       lowest BMD having the highest incidence of fractures.  
14       However, the percent risk reduction with alendronate  
15       was similar, irrespective of the baseline BMD.

16               We also looked in FIT at the effect on other  
17       fracture types, in particular hip and forearm frac-  
18       tures, since together with vertebral fractures, these  
19       are the most common sites of osteoporotic fracture.

20               The time of fracture was available for these  
21       clinical fractures and therefore it is possible to  
22       present these data in terms of cumulative fractures  
23       incidence over time. As you can see, at both sites  
24       there was a progressive separation between the placebo  
25       and alendronate incidence curves over the 3-year

SAG, CORP

4218 LENORE LANE, N W  
WASHINGTON, D C 20008

1 duration of the study.

2 The relative risk reduction was 51 percent  
3 for hip fractures, and 48 percent for fractures of the  
4 forearm. These data clearly indicate that alendronate  
5 reduces the incidents of vertebral, hip, and forearm  
6 fractures, which represent the three fracture types  
7 that are most characteristic for osteoporosis.

8 In this slide I'm showing you a comparison  
9 of the fracture risk reductions between FIT and our  
10 phase III treatment program. You will recall that the  
11 patients in FIT all had evidence of previous vertebral  
12 fractures at baseline. However in contrast, only 20  
13 percent of the patients in the phase III osteoporosis  
14 treatment studies had a prior vertebral fracture.

15 Despite this difference, we observed very  
16 similar fracture risk reductions in the two study  
17 populations. These reductions were seen at the spine,  
18 hip, and forearm, and in each case, the fracture  
19 incidence on alendronate was approximately half that  
20 seen in patients on placebo.

21 Each of these reductions was statistically  
22 significant with the exception of hip fractures in the  
23 phase III program where the p-value is .15 due to the  
24 relatively small number of events. Therefore, the  
25 efficacy of alendronate to reduce the incidence of

SAG, CORP

4218 LENORE LANE, N.W  
WASHINGTON, D C 20008

1 these three types of fracture is independent of  
2 fracture status at the start of treatment.

3 So to conclude on this section of my  
4 presentation, in post-menopausal women with osteoporosis,  
5 alendronate has clearly been demonstrated to  
6 reduce the incidence of fractures of the spine, hip,  
7 and forearm, consistent with its effects to increase  
8 BMD at these sites. The anti-fractures efficacy is  
9 independent of age, baseline BMD, and baseline  
10 fracture status; therefore maintaining or increasing  
11 bone base with alendronate is associated with a  
12 decrease in fracture risk.

13 I now want to move to the next part of my  
14 presentation which is to discuss the rationale for  
15 prevention of osteoporosis. In order to distinguish  
16 between treatment and prevention of osteoporosis, it  
17 is helpful to start with the definition of the  
18 disease.

19 Osteoporosis is defined as a systemic,  
20 skeletal disease characterized by low bone mass and  
21 microarchitectural deterioration of bone tissue with  
22 a consequent increase in bone fragility and suscepti-  
23 bility to fracture.

24 We can understand this relationship between  
25 bone mass, bone architecture, and bone fragility much

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 more easily when we look at the 3-dimensional,  
2 microscopic structure of bone. Normal cancellous bone  
3 is shown on the left. There are abundant cross-  
4 connections in the trabecular network, giving this  
5 bone its near-optimal mechanical resistance to stress.

6 Bone loss leads to osteoporosis. The  
7 typical picture of severe osteoporosis is shown here  
8 on the right. Note that not only is there less bone,  
9 but that its structure has also been severely compro-  
10 mised. Thus you can see that the trabeculae have been  
11 reduced to thin spicules, and in addition, many  
12 trabeculae have been removed entirely, resulting in a  
13 major loss of trabecular connectivity.

14 These factors together are responsible for  
15 the almost eggshell-like fragility of severely  
16 osteoporotic bone. Importantly, once these trabecular  
17 connections are lost they can never be regained, so  
18 even if we could fully restore bone mass, this would  
19 not entirely restore bone strength.

20 The irreversibility of the loss of normal  
21 bone microarchitecture provides a compelling rationale  
22 for osteoporosis prevention since by preventing bone  
23 loss we can maintain both normal bone mass and normal  
24 bone microarchitecture.

25 By doing so, we can prevent the progressive

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D C 20008

1 increase in fracture risk that otherwise occurs, and  
2 have a far greater impact to reduce the lifetime risk  
3 of fracture than is attainable with treatment once  
4 osteoporosis is already present.

5 In practical terms, we define osteoporosis  
6 as a bone mass below the range seen in young, adult  
7 women, shown here as the blue area. Here, the solid  
8 black line represents the mean value for BMD for each  
9 age, and the dashed lines represent values two  
10 standard deviations above or below that mean.

11 Bone mass is often reported in terms of T-  
12 score which is the number of standard deviations above  
13 or below the mean for young, normal women. You can  
14 see that with increasing age, a progressively higher  
15 proportion of women have osteoporosis, including a  
16 clear majority of those over age 80.

17 As a result of the high prevalence of  
18 osteoporosis in later life, approximately one in six  
19 women will develop a vertebral fracture, with similar  
20 proportions experiencing a hip or forearm fracture.  
21 Fractures at other sites also occur as a result of  
22 osteoporosis and it has been estimated that approxi-  
23 mately half of all post-menopausal women will develop  
24 at least one fracture during their remaining lifetime.

25 Since history of fracture is itself a major

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C 20008

1 risk factor for further fracture, many of the women  
2 who do fracture go on to have multiple fractures.

3 One important question before this committee  
4 today is, how can physicians identify women who are at  
5 even greater-than-average risk for developing osteopo-  
6 rosis?

7 The risk factors for developing osteoporosis  
8 in later life include: early menopause, a moderately  
9 low bone mass, thin body build, maternal history of  
10 osteoporosis, and Asian or Caucasian race. I would  
11 like to point out that although current bone mass is  
12 important, several of these other risk factors  
13 increase the lifetime risk of osteoporosis and  
14 fracture independent of the current level of bone  
15 mass.

16 Thus for example, a woman experiencing a  
17 premature menopause at age 40 can be expected to have  
18 rapid bone loss and is also likely to have a long,  
19 remaining life expectancy. The value of preventing  
20 osteoporosis in her would be considerably greater than  
21 for a 60-year-old woman with the same bone mass.

22 Also, risk factors such as thin body build  
23 and maternal history of osteoporosis increase lifetime  
24 fracture risk by mechanisms that cannot be fully  
25 explained by bone mass alone. Therefore, there is

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 clearly no single level of BMD below which all women  
2 should be treated, and above which treatment should  
3 not be considered.

4 Rather, physicians should consider all of  
5 the available information for each woman individually  
6 when making therapeutic decision regarding the need  
7 for preventive therapy for osteoporosis.

8 To summarize then on the rationale for  
9 prevention of osteoporosis, in the absence of preven-  
10 tive therapy, progressive bone loss occurs following  
11 menopause, and this is accompanied by irreversible  
12 loss of the normal microarchitecture of bone.

13 As many as half of all women will develop  
14 fractures due to osteoporosis, and even higher risk  
15 can be identified by the finding of a moderately low  
16 bone mass or the presence of others factors that are  
17 known to increase the risk for development of osteopo-  
18 rosis.

19 Since we now have effective therapies for  
20 prevention of osteoporosis, it is appropriate to  
21 consider these in women who are at risk for osteoporo-  
22 sis and resulting fractures during later life.

23 I now want to move on to discuss the  
24 efficacy data from the osteoporosis prevention  
25 studies. First, it is helpful to compare the thera-

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 peutic objectives of treatment versus prevention of  
2 osteoporosis.

3 In treatment of osteoporosis we aim to  
4 maximally increase bone mass and thereby maximally  
5 reduce the current excess in fracture risk. In  
6 contrast, our objective in prevention, where bone mass  
7 is currently normal or only moderately decreased, is  
8 to prevent post-menopausal bone loss in a substantial  
9 majority of women, and thereby prevent the progressive  
10 increase in fracture risk that otherwise ensues.

11 This slide compares the mean age and BMD in  
12 the prevention population with that in our osteoporo-  
13 sis treatment populations. The mean values for the  
14 largest of our three prevention studies, the early  
15 post-menopausal interventional cohort study, or EPIC,  
16 are shown by the yellow dot, whereas the phase III  
17 osteoporosis treatment studies and the fracture  
18 intervention trial are shown as the green and red  
19 dots.

20 You can see that the average BMD in the EPIC  
21 study was approximately one standard deviation below  
22 the mean for young, normal women. These women were  
23 substantially younger -- average age 53 -- than those  
24 in our osteoporosis treatment populations. Given the  
25 current level of BMD, this represents a decrease in

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 bone mass relative to the mean in the middle of the  
2 young, normal range of approximately 10 to 15 percent.

3 The main characteristics of the population  
4 recruited into the prevention studies are shown here.  
5 All women were at least six months post-menopause and  
6 were up to 60 years old.

7 We excluded women with a history of frac-  
8 tures due to osteoporosis and those with vitamin D  
9 deficiency or other disorders of bone. We also  
10 excluded women who are currently taking estrogen or  
11 other medications known to act on both.

12 We conducted three studies for osteoporosis  
13 prevention. The first study referred to in your  
14 background package as protocol 029, I will refer to in  
15 my presentation as the dose range finding, or DRF  
16 study. This had a total of 447 patients who we  
17 studied over three years.

18 The smallest of the three studies, protocol  
19 038, recruited 291 patients and was conducted to  
20 investigate the effects of treatment discontinuation  
21 after short-term dosing with alendronate. Finally, in  
22 our largest study, EPIC or protocol 055, we randomized  
23 a total of 1,609 women.

24 In both the dose range finding study and  
25 EPIC, we recruited half the subjects at sites in the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 U.S. and half in other countries, whereas protocol 038  
2 was conducted primarily at sites in Italy with a  
3 single site in the U.K.

4 Data from all three studies are provided in  
5 the background package, but for my presentation this  
6 morning I will focus on our two larger studies; that  
7 is, the DRF and EPIC studies.

8 In the DRF study we recruited women age 40  
9 to 59, whereas in EPIC they were between 45 and 59  
10 years old. In the DRF study we recruited women within  
11 the first three years of menopause and excluded those  
12 with either marked osteoporosis, a T-score below -2.6  
13 standard deviations, or particularly high bone mass,  
14 more than .7 standard deviations above the young,  
15 adult mean.

16 In contrast, in EPIC we elected to study all  
17 post-menopausal women within the target age range with  
18 no upper limit on their time since menopause.  
19 Similarly, in EPIC we did not exclude women on the  
20 basis of either high or low baseline spine BMD, except  
21 that we did ensure that no more than ten percent of  
22 the total study cohort at BMD values indicative of  
23 osteoporosis.

24 Mean baseline values for the women enrolled  
25 in these studies are shown here. On average, the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 women in these studies were in their early 50's. In  
2 the DRF study all women were around two years post-  
3 menopause, whereas in EPIC the average was six years.

4 Spine and hip BMD hip T-scores averaged  
5 about minus-one standard deviations in both study  
6 populations, reflecting a current bone mass that was  
7 already 10 to 15 percent lower than the mean in young  
8 women.

9 We performed very careful dose ranging in  
10 our clinical trials. In the dose range finding study  
11 we investigated alendronate doses of one, five, ten,  
12 and twenty milligrams per day in comparison to  
13 placebo. Each of these treatments was given continu-  
14 ously for the three years of the study, except for the  
15 20 milligram group which was switched to blinded  
16 placebo for year-3.

17 Based upon a planned, one year interim  
18 analysis of the DRF study, we determined that the one  
19 milligram dose was clearly sub-optimal, whereas all  
20 three higher doses -- five, ten, and twenty milligrams  
21 -- effectively prevented bone loss. Therefore, we  
22 selected the lowest effective dose, five milligrams,  
23 for inclusion into EPIC, and also included a 2.5  
24 milligram dose in that study.

25 In evaluating the most appropriate dose for

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C 20008

1 osteoporosis prevention, we considered the mean  
2 changes in BMD from baseline, and also the proportion  
3 of women within each treatment group who had bone  
4 loss. We also sought to define a dose of alendronate  
5 with effects approximately comparable to those of  
6 estrogen.

7 In addition to these general approaches,  
8 prior to the unblinding of the EPIC study, the optimum  
9 dose for osteoporosis prevention was defined as the  
10 lowest dose that preserves BMD at the spine, hip, and  
11 total body in a substantial majority of women.

12 I will now show you the data for percent  
13 change in BMD over time. The next several slides each  
14 have the same format. The dose range finding study is  
15 shown on the left and the EPIC study on the right.  
16 Note that in the placebo group shown as the white  
17 circles, there was a loss of approximately one percent  
18 per year in both studies.

19 In the DRF study, the one milligram dose,  
20 shown as the red triangles, significantly attenuated  
21 bone loss. The five milligram dose, shown as the  
22 yellow squares, increased bone mass by about three  
23 percent in the first year, and this was maintained  
24 over the entire duration of both studies.

25 The 2.5 milligram dose, shown in green,

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 induced a somewhat smaller mean increase of about two  
2 percent. Similar data are shown on this slide for the  
3 total hip. There was attenuation of loss with one  
4 milligram, and small but significant gains at the  
5 higher doses. Once again, the increases were greater  
6 with five milligrams relative to 2.5 milligram dose.

7 The third key site is the total body. It is  
8 key because as noted in the definition, osteoporosis  
9 is a systemic disease of low bone mass. Also, even  
10 though hip and vertebral fractures are the two most  
11 characteristics sites of osteoporotic fracture,  
12 patients with osteoporosis have an increased risk of  
13 almost every type of fracture, therefore it is  
14 critically important that we should strive to prevent  
15 bone loss from the skeleton as a whole.

16 Maintenance of total body BMD also provides  
17 assurance that the increases in BMD that we observed  
18 at the spine and hip are not simply the result of  
19 redistribution of bone mass from other parts of the  
20 skeleton, but instead reflect a generalized, positive  
21 effect to maintain overall bone balance.

22 Here again, one milligram attenuated bone  
23 loss and the five milligram dose resulted in modest  
24 gains. However, there was no increase from baseline  
25 with a 2.5 milligram dose. Indeed, 53 percent of the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C 20008

1 women in the 2.5 milligram group experienced some loss  
2 in total body BMD, and thus this dose clearly failed  
3 to meet our pre-defined objective of preventing bone  
4 loss in a substantial majority of women.

5 The effects on forearm BMD are shown on this  
6 slide. The dose response relationship differed from  
7 the other sites measured in that here, one milligram  
8 was without significant effect, and five milligrams  
9 attenuated the rate of loss by about half, rather than  
10 resulting in a mean increase in forearm BMD.

11 Here, the 2.5 milligram dose had only  
12 marginal effects to prevent forearm bone mass, and the  
13 ten milligram dose resulted in greater attenuation of  
14 loss than seen with five milligrams.

15 Although sub-optimal, the effects of the  
16 five milligram dose of the forearm are nonetheless  
17 likely to be clinically meaningful. However, since  
18 the 2.5 milligram dose reduced the loss of forearm BMD  
19 by only about 25 percent, the protective effect for  
20 forearm fractures is expected to be correspondingly  
21 less.

22 This provides further reason to consider the  
23 five milligram dose as the most appropriate dose for  
24 prevention of osteoporosis.

25 The last approach we employed to assess the

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 most appropriate dose for osteoporosis prevention was  
2 to compare the effects of alendronate with those of  
3 estrogen, which is currently the only approved therapy  
4 for this indication.

5 Estrogen has been clearly demonstrated to  
6 prevent bone loss and we consider that the dose we  
7 selected for osteoporosis prevention should have  
8 effects that are approximately comparable to those  
9 standard doses of estrogen.

10 In the EPIC study women were preferentially  
11 entered into stratum 1, which entailed randomization  
12 to either blinded therapy with placebo, alendronate  
13 2.5, or alendronate five milligrams a day, or to open  
14 label therapy with estrogen and progestin.

15 However, women who either had a contraindi-  
16 cation to the use of estrogen and progestin or who  
17 indicated a clear preference to avoid possible  
18 randomization to hormonal therapy, were permitted to  
19 enter into stratum 2 which did not include an estrogen  
20 arm.

21 Of the 1,609 women in this study, just over  
22 one-quarter entered stratum 1, and 110 of these were  
23 randomized to receive estrogen and progestin.

24 The study sites in the U.S. used Premarin,  
25 0.625 milligrams, and Provera, five milligrams, as a

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 continuous daily regimen; whereas the European study  
2 sites used a cyclical formulation containing 17 beta  
3 estradiol and norethisterone acetate, an androgenic  
4 progestin which is known to have independent effects  
5 on bone density. The European formulation is not  
6 approved for use in the U.S.

7 For comparison to estrogen we assessed  
8 changes in BMD within stratum 1 only. The data I will  
9 show you are those from the U.S. cohort since this is  
10 the most relevant comparison for consideration at this  
11 meeting -- although the results for the European  
12 cohort are also included in your background materials.

13 The effects on BMD of the spine and total  
14 hip are shown here. You can see that the mean  
15 increases in BMD with estrogen/progestin -- shown in  
16 pink -- were slightly greater than those of alendron-  
17 ate -- shown in yellow. And this difference reached  
18 borderline significance at the spine.

19 Note however, that the 2.5 milligram dose  
20 was clearly outperformed by estrogen/progestin.  
21 Furthermore, estrogen/progestin had comparable effects  
22 on total body BMD to those seen with alendronate five  
23 milligrams -- both treatments achieving a target  
24 effect of a modest increase in BMD at this site.

25 In contrast, the 2.5 milligram dose was

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 associated with a small, mean decrease in total body  
2 BMD in this cohort of women. Estrogen/progestin was  
3 more effective than alendronate five milligrams in  
4 preventing bone loss of the forearm, although as we  
5 saw previously, alendronate five milligrams had more  
6 marked effect than 2.5 to attenuate loss of forearm  
7 BMD.

8 We also compared the effects of alendronate  
9 versus those of estrogen/progestin, to decrease the  
10 rate of bone turnover. This plot shows the changes in  
11 urine excretion of NTX which is a breakdown product of  
12 bone collagen that acts as a highly specific marker of  
13 bone resorption.

14 The blue line represents the mean value for  
15 young, pre-menopausal. As expected, due to their  
16 post-menopausal status, the women in the EPIC study  
17 started off with high rates of bone resorption, and it  
18 is this that is responsible, both for the progressive  
19 bone loss and progressive deterioration in bone  
20 microarchitecture.

21 In response to either alendronate or  
22 estrogen/progestin, there are substantial decreases in  
23 NTX with turnover reaching a new steady state after  
24 about six months of treatment, without evidence of  
25 progressive suppression thereafter.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           Of interest, the degree of reduction in the  
2 rate of bone turnover with alendronate, five milli-  
3 grams, was identical to that achieved with estro-  
4 gen/progestin, and in either case, the values came  
5 close to the middle of the pre-menopausal, reference  
6 range.

7           So to summarize the rationale for selection  
8 of the five milligram dose, the mean increases in BMD  
9 were consistently greater with five versus 2.5  
10 milligrams and as a result, fewer women experienced  
11 bone loss at each skeletal site. Indeed, the five  
12 milligram dose met the predefined target to maintain  
13 total body BMD in a substantial majority of women;  
14 whereas the 2.5 milligram dose clearly failed to do  
15 so.

16           The effects of the alendronate five milli-  
17 grams, of the spine, hip, and total body, were close  
18 to those of Premarin and Provera; whereas hormonal  
19 treatment clearly outperformed the 2.5 milligram dose  
20 at all sites of bone mass measurement.

21           In addition, the effects of alendronate five  
22 milligrams, and those of estrogen/progestin to reduce  
23 the rate of bone turnover, were highly comparable.  
24 Finally, as will be discussed by Dr. Daifotis in her  
25 presentation, alendronate five milligrams also appears

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 to be very safe and well tolerated.

2 For these reasons we believe that five  
3 milligrams is the most appropriate dose for prevention  
4 of osteoporosis.

5 I'll now move to review the data concerning  
6 the long-term effects of alendronate on bone. The  
7 questions I propose to address are: firstly, what are  
8 the long-term effects on bone turnover; second, is  
9 efficacy maintained over a total of five years of  
10 therapy; and third, what happens to bone mass and bone  
11 turnover once therapy with alendronate is discontin-  
12 ued?

13 To answer the first of these questions,  
14 namely the long-term effects on bone turnover, we  
15 looked in our U.S. osteoporosis treatment study at the  
16 effects of alendronate on bone turnover, over five  
17 years.

18 In this plot, we show the rates of bone  
19 turnover as assessed by NTX. The blue diamonds  
20 represent alendronate ten milligrams, given continu-  
21 ously for the entire five years of the study, and the  
22 white circles indicate placebo treatment.

23 Women who completed three years on placebo  
24 were subsequently given alendronate, ten milligrams  
25 per day, shown as the dashed blue line. Note that in

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 the group previously treated with placebo, the degree  
2 of reduction in the rate of turnover at 48 and 60  
3 months -- that is, after only 12 and 24 months of  
4 alendronate, ten milligrams in this group -- was  
5 identical to that seen in the continuous alendronate  
6 ten milligrams group, over the five years of these  
7 time points.

8 Therefore, these results clearly demonstrate  
9 that the reduction in the rate of bone turnover does  
10 not become greater following long-term therapy, even  
11 at the ten milligram dose.

12 To address the questions regarding long-term  
13 efficacy and osteoporosis prevention, as well as the  
14 effects of discontinuation of therapy, we extended our  
15 dose range finding study out to five years. As  
16 illustrated here, the placebo group was discontinued  
17 at the end of year-3, whereas the group receiving  
18 alendronate five milligrams was maintained on that  
19 dose for a total of five years.

20 Also of interest, the group that received  
21 alendronate 20 milligrams a day for the first two  
22 years, received placebo in year-3, and then we  
23 followed these women off all therapy in years four and  
24 five.

25 Note that since the 20 milligram dose is

**SAG, CORP**

4218 LENORE LANE, N.W.

WASHINGTON, D C. 20008

1 four times the proposed five milligrams osteoporosis  
2 prevention dose, the cumulative amount of alendronate  
3 taken over these two years is equivalent to that  
4 administered over eight years of alendronate, five  
5 milligrams per day.

6 This slide shows the changes in spine BMD in  
7 these groups. Note that the increase in spine BMD  
8 seen in the five milligram group, was maintained  
9 throughout the entire five years of therapy, indicat-  
10 ing that we can prevent bone loss over the long-term  
11 with continued administration of alendronate.

12 Over the first two years the increases in  
13 the 20 milligrams group -- shown in purple -- were  
14 somewhat greater than those seen with five milligrams.  
15 However, following discontinuation of alendronate 20  
16 milligrams at 24 months, there was a resumption in  
17 bone loss at a rate similar to that seen with placebo,  
18 over the initial three years of the study.

19 An important question is whether there could  
20 be accelerated or catch-up bone loss after stopping  
21 treatment. This is of relevance since that if there  
22 was accelerated loss, the advantages of prior therapy  
23 may be expected to gradually disappear after withdraw-  
24 al from treatment.

25 To investigate this we compared the bone

SAG, CORP

4218 LENORE LANE, N W.  
WASHINGTON, D C. 20008

1 loss in the placebo group over the first three years  
2 of the study with the loss seen in the 20 milligram  
3 group in the three years following treatment discon-  
4 tinuation. These losses in BMD are shown for the  
5 different sites: the spine, femoral neck, trochanter,  
6 and total body.

7 You can see that in each case, the loss in  
8 BMD over the three years following discontinuation of  
9 alendronate 20 milligrams -- shown as the purple bars  
10 -- was either similar to or less than, that seen over  
11 the first three years in the placebo group -- shown in  
12 white. Plus these data indicate that there is no  
13 catch-up bone loss.

14 In addition to looking at the effects of  
15 treatment discontinuation on bone mass, we also  
16 evaluated the effects on bone turnover -- in this case  
17 looking at urine deoxypyridinoline, another specific  
18 marker of bone resorption.

19 There was little change over three years in  
20 the placebo group -- shown in white -- whereas both  
21 alendronate five milligrams -- in yellow -- and 20  
22 milligrams -- in purple -- decreased this marker by  
23 approximately 40 percent. However, interestingly,  
24 once the 20 milligram dose was discontinued, urine  
25 deoxypyridinoline increased back towards pretreatment

**SAG, CORP**

4218 LENORE LANE, N W.  
WASHINGTON, D.C 20008

1 baseline values.

2 Therefore, taken together, these BMD and  
3 biochemical marker data confirmed that it has been  
4 recently administered alendronate rather than the  
5 cumulative dose that is responsible for effects on  
6 both bone mass and bone turnover.

7 Thus, to summarize the long-term data,  
8 following the initial decrease the rate of bone  
9 turnover is maintained at a constant, steady state  
10 similar to that seen with estrogen, even with very  
11 long-term therapy.

12 Continued daily therapy with alendronate  
13 five milligrams, continues to prevent bone loss over  
14 at least five years. However, bone loss resumes after  
15 treatment discontinuation although there is no catch-  
16 up bone loss. Also, the rate of bone turnover returns  
17 back towards baseline after discontinuation of  
18 therapy.

19 In summary, the data I've shown you today  
20 demonstrate that alendronate five milligrams, prevents  
21 bone loss at the spine, hip, and total body, and  
22 attenuates loss at the forearm. Five milligrams is  
23 more effective than 2.5 milligrams at all skeletal  
24 sites. Based upon predefined criteria, five milli-  
25 grams was selected as the most appropriate dose for

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 prevention of osteoporosis.

2 The efficacy of alendronate five milligrams  
3 is maintained over at least five years of continuous  
4 therapy, and there is no accelerated loss after  
5 treatment discontinuation.

6 Therefore, in conclusion, these data show  
7 that alendronate five milligrams is an effective, non-  
8 hormonal therapy for prevention of post-menopausal  
9 osteoporosis. Thank you for your attention.

10 I'd now like to hand over to Dr. Anastasia  
11 Daifotis, who will discuss our extensive experience  
12 concerning safety and tolerability of alendronate.

13 ACTING CHAIR CRITCHLOW: Thank you, but  
14 first I'd like to ask the committee if there are any  
15 questions for Dr. Yates.

16 DR. KREISBERG: Do you really want to know?

17 ACTING CHAIR CRITCHLOW: Well, questions of  
18 clarification.

19 Dr. Daifotis.

20 DR. DAIFOTIS: Good morning, ladies and  
21 gentlemen. I'm Dr. Anastasia Daifotis, Director of  
22 Clinical Research at Merck Research Laboratories. As  
23 you know, in the phase III osteoporosis treatment  
24 studies, alendronate ten milligrams was shown to be  
25 safe and well tolerated for the treatment of osteopo-

SAG, CORP

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           rosis in post-menopausal women.

2                   Today, I'm going to show you new data from  
3           the osteoporosis prevention studies that will demon-  
4           strate that alendronate five milligrams is safe and  
5           well tolerated for the prevention of osteoporosis in  
6           post-menopausal women.

7                   Let's look at the extent of clinical data  
8           available for you to use in assessing the safety of  
9           alendronate. To begin with, we have the prevention  
10          population and this consists of the three osteoporosis  
11          prevention studies that Dr. Yates showed you earlier.

12                   Fifteen hundred and ninety-seven women with  
13          a mean age of 53 years were randomized to receive  
14          alendronate. This safety experience is supplemented  
15          by data from the phase III treatment studies previous-  
16          ly reviewed by this Advisory Committee which included  
17          a group of 202 women who received alendronate five  
18          milligrams.

19                   In addition, new data is available from the  
20          fracture intervention trial which enrolled over 2,000  
21          women, half of whom received alendronate. So we have  
22          a total of 5,371 women enrolled in clinical studies.

23                   We also now have experience with approxi-  
24          mately 1.3 million patients who have received alend-  
25          ronate in the marketed use in the United States.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D. C. 20008

1 These women are on average, slightly older than the  
2 women in the fracture intervention trial with an  
3 estimated mean age of 72 years.

4 Before we begin to actually review the  
5 clinical safety data, let's review the key character-  
6 istic, pharmacologic properties of alendronate since  
7 this information is germane to understanding the  
8 excellent safety profile of alendronate.

9 Alendronate has very low systemic exposure  
10 because of both low, but consistent bioavailability,  
11 as well as minimal, extraskeletal deposition. Because  
12 food, when taken with alendronate greatly decreases  
13 its bioavailability, alendronate must be taken on an  
14 empty stomach. Alendronate is rapidly distributed  
15 from plasma directly to bone, or excreted by the  
16 kidneys in an unmetabolized form.

17 These pharmacologic properties appear to  
18 explain why alendronate has such an excellent safety  
19 profile. Apart from the bone, the target tissue, only  
20 the upper GI tract is exposed to a biologically  
21 significant amount of alendronate, and this explains  
22 why our entire experience appears to indicate that  
23 side effects of alendronate occur predominantly in the  
24 upper GI tract.

25 Today, we will begin our review with a brief

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 summary of the safety profile seen in the phase III  
2 osteoporosis treatment studies. Then we will review  
3 the clinical safety data with specific regard to the  
4 gastrointestinal tract. I will spend quite a bit of  
5 time reviewing this upper gastrointestinal safety data  
6 because it's important for you to fully understand the  
7 information currently available.

8 This comprehensive review will enable you to  
9 assess the safety of alendronate five milligrams from  
10 the prevention of osteoporosis in the context of our  
11 entire alendronate experience.

12 We will review individual upper gastrointes-  
13 tinal tract adverse experiences as well as looking at  
14 adverse experiences based on location, including the  
15 esophagus where we know alendronate has potential to  
16 cause irritation, and the remaining upper GI tract:  
17 the stomach and duodenum.

18 This will include a review of the marketed  
19 use experience followed by data from a recent endosco-  
20 py study which specifically addresses erosions in the  
21 upper GI tract. Lastly, I will review the upper GI  
22 experience in the larger study -- the fracture  
23 intervention trial. Then we will focus on the safety  
24 of alendronate in the osteoporosis prevention studies.

25 In the phase III osteoporosis prevention

SAG, CORP

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 studies, the following upper GI drug-related adverse  
2 experiences were seen with alendronate ten milligrams:  
3 abdominal pain or distention, dysphagia, and esophage-  
4 al ulcer.

5 As expected, small, asymptomatic, transient  
6 decreases in serum calcium and phosphate were observed  
7 and are consistent with the antiresorptive property of  
8 alendronate. These adverse experiences, as well as a  
9 few non-gastrointestinal adverse experiences, are  
10 already reflected in the current alendronate label.  
11 Overall, the clinical and laboratory adverse experi-  
12 ences reveal no detectable difference from placebo.

13 Now let's go on and review the marketed use  
14 experience with alendronate. Alendronate was launched  
15 in the United States in October 1995, and since then,  
16 approximately 1.3 million patients have received  
17 alendronate ten milligrams for osteoporosis and  
18 another 8,000 have received alendronate 40 milligrams  
19 for Paget's Disease.

20 The greatest value of marketed use experi-  
21 ence is the potential to identify rare, adverse  
22 experiences that cannot be detected in clinical  
23 studies, even those as large as were conducted in the  
24 alendronate program. Although we saw esophageal  
25 ulcers in the original osteoporosis treatment studies,

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 it was the marketed use experience that confirmed the  
2 association with alendronate therapy.

3 The limitation of the marketed use experi-  
4 ence, however, is the lack of a placebo control group  
5 and this can make causality assessment very difficult  
6 when considering more common adverse experiences.

7 Several months after alendronate was  
8 launched in the United States we received some reports  
9 of esophagitis and esophageal erosions for ulcers that  
10 were more serious than those seen in the clinical  
11 trials.

12 We reviewed our experience in an article  
13 that appeared in the New England Journal of Medicine  
14 this past October. As discuss in that article, we  
15 reviewed 51 reports that had been received as of March  
16 5th, 1996, at which time the estimated worldwide  
17 exposure of alendronate was 470,000 people.

18 Several of these cases had characteristic,  
19 clinical and endoscopic features that enabled us to  
20 confirm that they were associated with the use of  
21 alendronate. In a majority of cases where information  
22 was available, improper dosing -- specifically dosing  
23 with insufficient water, lying down shortly after  
24 dosing, or continuing to take alendronate after the  
25 onset of symptoms -- was noted.

SAG, CORP

4218 LENORE LANE, N.W.  
WASHINGTON, D.C 20008

1           Since in pre-clinical studies we found that  
2           alendronate is only irritating to the esophagus at a  
3           pH below 3.5, it seems that the most likely mechanism  
4           for esophageal irritation is the contact of acidic  
5           stomach contents containing alendronate with esophage-  
6           al mucosa.

7           Merck was able to quickly act upon this new  
8           information, providing letters to physicians and  
9           pharmacists, as well as supporting other educational  
10          initiatives, and by changing the Fosamax™ label to  
11          reinforce proper dosing. In updating the label to  
12          reflect post-marketing, adverse experiences we added  
13          the gastrointestinal adverse experiences seen in the  
14          post-marketed use, as well as reports of rare,  
15          allergic events.

16          Since we had evidence of GI irritation in  
17          the esophagus with post-marketed use, we undertook a  
18          review of reports of GI irritation below the esophagus  
19          as well. We reviewed a number of reports describing  
20          gastric or duodenal ulcers or erosion, perforations,  
21          or upper GI hemorrhage.

22          Unlike the reports for the esophagus  
23          however, there had been no characteristic, clinical,  
24          or endoscopic features to definitively suggest causal  
25          relationship. Interestingly, there have been no

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 confirmed reports of gastric or duodenal ulcers with  
2 the 40 milligram dose for Paget's in the over 8,000  
3 estimated users.

4 In summary, the marketed use experience  
5 demonstrates that esophageal ulcers or erosions are  
6 uncommon events with alendronate therapy. Their  
7 incidence may be reduced by proper dosing and avoid-  
8 ance of behavior known to exacerbate reflux of acidic  
9 stomach contents into the esophagus.

10 The current Fosamax™ label already cautions  
11 use in patients with active upper GI disease. No  
12 other adverse experiences that appear to be causally  
13 related to the use of alendronate had been identified  
14 from the marketed use experience.

15 As part of an assessment of the potential  
16 for gastric irritation with alendronate, we designed  
17 a short-term endoscopy study to rule out a major  
18 effect of alendronate on the stomach and duodenum  
19 which I will now review.

20 The objective of this study was to look at  
21 gastric of duodenal erosions in post-menopausal women  
22 receiving alendronate therapy. This study enrolled  
23 post-menopausal women with a mean age of 51, so this  
24 cohort is particularly relevant to the prevention  
25 population.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           None of these women had a recent history of  
2 a major GI disease or took non-steroidal, anti-  
3 inflammatory drugs -- including aspirin -- within a  
4 month of participating in the study. Patients were  
5 randomized to receive either daily placebo, alendron-  
6 ate five milligrams, alendronate ten milligrams, or  
7 aspirin, 650 milligrams four times a day -- a standard  
8 dose for endoscopy studies.

9           And all patients and investigators remained  
10 blinded to treatment. The primary endpoint in this  
11 study is the incidence of gastric or duodenal erosions  
12 seen after one or two weeks of therapy.

13           Ninety-five healthy, post-menopausal women  
14 met the initial criteria -- including no GI disease or  
15 use of irritants -- and were endoscoped for the study.  
16 Of those 95 women, 17 percent were excluded from the  
17 study because they had abnormalities on initial  
18 endoscopy. These included three subjects with gastric  
19 or duodenal ulcers as well as two subjects with  
20 esophageal erosions; 79 women were randomized.

21           A standardized, 5-point scoring system is  
22 used to assess the degree of irritation in the stomach  
23 or duodenum. Zero denotes a normal mucosa. Score of  
24 two, three, or four represent increasing numbers of  
25 grossly visible, mucosal breaks or erosions and were

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C 20008

1 the endpoint of this study.

2 An ulcer was defined as a white-based  
3 lesion, three or more millimeters in diameter with  
4 unequivocal depth, and received a score of four.

5 This slide shows the number of women within  
6 the study that had a gastric or duodenal mucosal  
7 erosion or ulcer at either day-8, day-15, or at either  
8 time point. As expected, overwhelmingly numbers of  
9 aspirin-users developed erosions; however, there is no  
10 apparent difference between the placebo and alendron-  
11 ate subjects in terms of individuals with erosions.

12 Although this study was not powered for  
13 other endpoints we also looked specifically at the  
14 incidents of either esophageal ulcer, esophageal  
15 erosions, or gastric ulcers. Remember that in the  
16 screening population we saw two women with esophageal  
17 erosions. Here we see three in the placebo group and  
18 two and one in the alendronate five and ten milligram  
19 groups, respectively.

20 There were no subjects with esophageal  
21 ulcers. This is not unexpected because they are  
22 uncommon events. We also saw three women with gastric  
23 ulcers in the screening population for the study.  
24 During the study, gastric ulcers were seen in approxi-  
25 mately five and ten percent of alendronate -- five and

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 ten milligram, respectively -- compared to 21 percent  
2 of women with aspirin.

3 All of the ulcers were small. One of the  
4 ten milligram subjects had an ulcer at day-8 that  
5 completely resolved by day-15 even though alendronate  
6 therapy was continued.

7 The conclusions from this endoscopy study  
8 were that as anticipated, aspirin induced a high  
9 incidence of multiple gastric erosions. Gastric  
10 erosions were not increased with alendronate five or  
11 ten milligrams relative to placebo. Based on this  
12 small study, endoscopic gastric ulcers were uncommon.  
13 It's not possible to detect a relationship to alend-  
14 ronate therapy.

15 Although this cannot be ruled out, these  
16 data suggest that alendronate five or ten milligrams  
17 is not associated with a detectable increase in  
18 gastric or duodenal erosive disease.

19 Now I would like to review safety data from  
20 the largest clinical study, the fracture intervention  
21 trial. The fracture intervention trial enrolled over  
22 2,000 women, half of which received alendronate,  
23 representing 3,000 patient-years experience on  
24 alendronate. On average, these women are 71 years of  
25 age. They're nearly two decades older than the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 prevention population and might be more likely to  
2 exhibit side effects were they to occur.

3 As well, these women received five milli-  
4 grams of alendronate for the first two years of the  
5 study followed by alendronate ten milligrams for an  
6 additional year.

7 Because the study was designed to be more  
8 real-world, we used minimal exclusion criteria for  
9 gastrointestinal disease prior to study. Patients  
10 were only excluded if they had a recent history of an  
11 upper GI bleed requiring hospitalization and transfu-  
12 sion, recurring ulcer disease, or dyspepsia treated on  
13 a daily basis.

14 It's important to realize that of approxi-  
15 mately 40,000 women who were screened by phone calls  
16 for entry into the fracture intervention trial, fewer  
17 than five percent were excluded because of one of  
18 these criteria. Patients had a variety of concurrent  
19 conditions and medications. In fact, 16 percent had  
20 a history of upper gastrointestinal diseases, and  
21 these included prior ulcer and reflex esophagitis.

22 As well, approximately 75 percent used non-  
23 steroidal, anti-inflammatory drugs including aspirin,  
24 for at least 30 days during the study.

25 This slide shows you the clinical adverse

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 experiences from the fracture intervention trial. As  
2 you can see, there is no appreciable difference in  
3 drug-related adverse experiences.

4 Now, these are those described by the  
5 investigator as being possibly, probably, or definite-  
6 ly related to drug therapy while they remain blinded  
7 to therapies. That's why you'd have on the placebo or  
8 alendronate. And there was no difference in with-  
9 drawals.

10 However, interestingly, serious adverse  
11 experiences are significantly decreased in the  
12 alendronate group. Part of this decrease is due to a  
13 decrease in serious fractures.

14 Now, let's look at upper gastrointestinal  
15 adverse experiences in the fracture intervention  
16 trial. The two most common upper GI adverse experi-  
17 ences were abdominal pain and dyspepsia. No differ-  
18 ence was detected.

19 We then looked at the esophageal adverse  
20 experiences that might be associated with esophageal  
21 irritation, including esophageal ulcer and esophagi-  
22 tis, and gastric and duodenal adverse experiences that  
23 might suggest irritation at these sites, including  
24 gastric and duodenal ulcers, gastritis and duodenitis.

25 While a slight numerical increase is seen

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 for esophageal lesions, there is clearly no excess of  
2 either gastric or duodenal adverse experiences in the  
3 alendronate-treated patients relative to placebo.

4 One might ask the question, well this is  
5 what you see at the end of the study, but what happens  
6 during the study and what happens when women go from  
7 five to ten milligrams? So let's look at this graph  
8 of cumulative, upper GI, adverse experiences in the  
9 FIT study.

10 Three important points are illustrated here.  
11 Time to first event is shown on the X-axis and percent  
12 with an upper GI adverse experience is shown on the Y-  
13 axis. Placebo is shown in white, five milligrams in  
14 yellow and ten milligrams in blue.

15 Now, the first thing that you notice is that  
16 the lines for placebo events and alendronate events  
17 are identical; that is, one superimposed on the other.  
18 The second thing you notice is that by six months, 20  
19 percent of the patients have already experienced an  
20 upper GI event, whether they're on placebo or alend-  
21 ronate. The last thing you notice is that there is no  
22 increase in events when patients go to the higher ten  
23 milligram dose.

24 With no obvious, detectable difference in  
25 upper GI adverse experiences we asked the following

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 question: What about the risk factors that we know  
2 exist for ulcer disease in general? We know that as  
3 people age they get more ulcers and associated  
4 complications.

5 It's known that if you have a history of  
6 upper GI disease you are more likely to have an ulcer.  
7 We know that if you take non-steroidal, anti-inflamma-  
8 tory drugs you are more likely to have an ulcer.

9 Within the clinical studies -- that's the  
10 fracture intervention trial as well as the prevention  
11 and the treatment studies -- we saw the expected  
12 higher incidence of ulcers among older patients, those  
13 with a history of upper GI disease, and during periods  
14 of NSAID use. However, no excess incidence was  
15 detected in alendronate versus placebo patients. This  
16 can best be illustrated by an example.

17 Let's look at what happens to the incidence  
18 of ulcers with aging. The patients have been divided  
19 into three tertiles: those under 67, 67 to 74, and  
20 those over the age of 74, in yellow. There is a  
21 general trend in both treatment groups for the oldest  
22 patients to have the highest incidence of ulcers.  
23 However, in comparing between treatments there does  
24 not appear to be any excess in such events on alend-  
25 ronate relative to placebo.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           In summary, in the fracture intervention  
2 trial, alendronate was demonstrated to be safe and  
3 well tolerated, with a safety profile consistent with  
4 the treatment population. No new adverse experiences  
5 were identified.

6           In summary, based on the post-marketed  
7 experience, the endoscopy studies, and clinical trial  
8 experience, esophagitis and ulcers are uncommon events  
9 with alendronate therapy that may be reduced with  
10 proper dosing.

11           No increase in endoscopic erosive events  
12 were detected with short-term alendronate therapy.  
13 More importantly, no increases in ulcers was observed  
14 clinically. However, caution must be used in patients  
15 with active, upper GI disease.

16           Having completed a review of upper GI  
17 adverse experiences with alendronate, let's now focus  
18 on the safety of alendronate in the osteoporosis  
19 prevention studies.

20           The osteoporosis prevention studies enrolled  
21 2,347 women, of which 1597 received alendronate, 648  
22 the five milligram dose. This study represents  
23 approximately 2800 patient-years on alendronate. The  
24 mean age of the study of 53 with a range of 40 to 60.

25           Exclusion criteria with regards specifically

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D.C. 20008

1 to the GI tract included recent, major gastrointesti-  
2 nal disease, regular use of non-steroidal, anti-  
3 inflammatory drugs or aspirin, and the recent use of  
4 a drug to inhibit gastric acid secretion.

5 Shown here are the three individual preven-  
6 tion studies: protocol 029, the dose range finding  
7 study; protocol 038; and protocol 055, the EPIC study  
8 -- the largest of the three studies.

9 Dr. Yates has discussed that five milligrams  
10 is the optimal dose for the prevention of osteoporo-  
11 sis. This was also the only dose common to all three  
12 studies. My talk will focus on the safety of this  
13 dose. Information on higher and lower doses has been  
14 provided in the background document.

15 This is a summary of the clinical adverse  
16 experiences in the osteoporosis prevention studies.  
17 There are no apparent differences between alendronate  
18 five milligrams, and placebo, for the drug-related --  
19 remember, those were the ones that were rated by the  
20 investigators possibly, probably, or definitely drug-  
21 related, while they were still blinded -- serious  
22 adverse experiences or withdrawals due to adverse  
23 experiences in the osteoporosis prevention studies.

24 Now let's look at the drug-related events.  
25 Remember, these are the events that investigators

**SAG, CORP**

4218 LENORE LANE, N W.  
WASHINGTON, D.C. 20008

1 rated as drug-related while they were still blinded.  
2 There were only five adverse experiences that occurred  
3 in an incidence of one percent or higher in either  
4 group.

5 All five were gastrointestinal terms. They  
6 included abdominal pain, acid regurgitation, diarrhea,  
7 dyspepsia, and nausea. As you can see when you  
8 compare these numbers, no apparent difference was seen  
9 between alendronate five milligrams and placebo.

10 I'd now like to focus specifically on the  
11 upper GI adverse experiences. This slide shows a  
12 summary of the upper GI adverse experiences reported  
13 in the osteoporosis prevention studies. Once again,  
14 no apparent difference was seen between the alendron-  
15 ate five milligrams and placebo groups, and withdraw-  
16 als occurred in only ten patients from each group.

17 The two most common upper GI adverse  
18 experiences were abdominal pain and dyspepsia, as seen  
19 in the fracture intervention trial and the phase III  
20 treatment studies. The adverse experiences were then  
21 also subgrouped by their location, looking at esopha-  
22 geal adverse experiences that might denote irritation  
23 as well as gastric or duodenal adverse experiences  
24 that might denote irritation of the stomach or duodenum.

25 And as you can see from the data, there's no

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D C 20008

1           And as you can see from the data, there's no  
2 appreciable difference between alendronate five  
3 milligrams and placebo for these events.

4           We wanted to look at a comparison of 2.5 and  
5 five milligram doses to see if we could detect a  
6 difference. Now, this is possible in the EPIC study.  
7 And shown here is the upper GI adverse experiences  
8 from that study in placebo, two-and-a-half, and five  
9 milligrams.

10           There was no difference in any upper GI  
11 adverse experience, not were there differences in  
12 those considered drug related, serious, or leading to  
13 withdrawal. When we look at individual upper GI  
14 adverse experiences shown here, including those  
15 suggestive of esophageal or gastric or duodenal  
16 irritation, there is no appreciable difference between  
17 alendronate five milligrams and 2.5 milligrams --  
18 either esophageal or for gastric or duodenal -- or  
19 either alendronate groups or placebo.

20           We also performed extensive laboratory  
21 analyses. Consistent with the mechanism of action of  
22 alendronate and as seen in the treatment studies, we  
23 saw small, transient, asymptomatic decreases in serum  
24 calcium, and phosphate. No effects were observed on  
25 the hemic, hepatic, or renal parameters.

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C 20008

1           In addition to the 500 bone biopsies that  
2           were done in the osteoporosis treatment and Paget's  
3           Disease studies, 55 additional biopsies were taken in  
4           the prevention population. These biopsies were all  
5           consistent with our previous data and demonstrated  
6           that mineralization was not impaired and that bone  
7           quality was normal with continued bone turnover  
8           present in all patients.

9           Long-term safety data is now also available  
10          in the osteoporosis prevention population from the  
11          dose range finding study, protocol 029. This is an  
12          open label extension and data is available through  
13          five years, and confirms the safety profile seen in  
14          the previous three years of the study. No new adverse  
15          experiences have been identified.

16          Today, we have extensively reviewed the  
17          safety experiences with alendronate five milligrams in  
18          the prevention studies. There was no apparent in-  
19          creased incidence in overall or serious adverse  
20          experiences with alendronate five milligrams compared  
21          to placebo. But let's balance that with the addition-  
22          al experience from the older treatment, as well as the  
23          fracture intervention populations.

24          All three populations consistently demon-  
25          strate that alendronate five milligrams is safe.

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D.C. 20008

1 Withdrawals occurred at less than seven-and-a-half  
2 percent in all alendronate groups, speaking to the  
3 excellent tolerability of the five milligram dose.

4 Therefore in summary, alendronate five  
5 milligrams is safe and well tolerated. Esophagitis  
6 and esophageal ulcers are uncommon events associated  
7 with alendronate that may be reduced with attention to  
8 proper dosing. Bone biopsy studies in both prevention  
9 and treatment populations confirm normal bone quality.

10 The continued follow-up now available to  
11 five years in clinical trials reveals no new safety  
12 concerns and supports the excellent safety profile of  
13 alendronate.

14 In conclusion, alendronate five milligrams  
15 is a safe and well-tolerated, non-hormonal therapy for  
16 the prevention of osteoporosis. Thank you for your  
17 attention.

18 ACTING CHAIR CRITCHLOW: Thank you. Are  
19 there questions from the committee for Dr. Daifotis?

20 DR. MARCUS: Just clarification -- no  
21 questions?

22 ACTING CHAIR CRITCHLOW: At the moment. Dr.  
23 Goldmann.

24 DR. GOLDMANN: Good morning Dr. Critchlow,  
25 members of the Advisory Committee, FDA ladies and

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D C 20008

1 gentlemen. My name is Dr. Bonnie Goldmann, Vice  
2 President of Regulatory Affairs, and I'd like to spend  
3 the next few minutes providing some concluding  
4 remarks.

5 In today's deliberations it's important to  
6 consider that bone loss after menopause is a continu-  
7 ous process, and the distinction of treatment and  
8 prevention -- although essential from a regulatory  
9 paradigm -- is somewhat obscured since the goal of  
10 intervention regardless, is to preserve or build bone  
11 mass to reduce fracture risk.

12 The issue clinically is deciding the  
13 appropriate patient and the appropriate time to  
14 intervene. I will come back to this shortly.

15 The data discussed today provide the  
16 necessary support as defined by the FDA guidelines for  
17 the approval of the use of alendronate for the  
18 prevention of fractures and the prevention of post-  
19 menopausal osteoporosis.

20 We have discussed the results of approxi-  
21 mately ten years of pre-clinical and clinical research  
22 which resulted in approval in 1995 for the treatment  
23 of osteoporosis in post-menopausal women, and which  
24 now supports modifying the treatment indication to  
25 include that Fosamax™ prevents fractures based on the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 pooled phase III data and the completion of the  
2 fracture intervention trial, or FIT.

3 Further, the data from the three prevention  
4 trials support the approval of Fosamax™ for the  
5 prevention of osteoporosis in post-menopausal women.  
6 It is clear that alendronate maintains normal bone  
7 quality, produces significant increases or preserves  
8 bone mineral density of the spine, hip, and total body  
9 in both treatment and prevention populations, and that  
10 this positive effect on BMD translates into signifi-  
11 cant reductions in fracture risk in post-menopausal  
12 women.

13 Further, it is apparent that the fracture  
14 reduction resulting from treatment with alendronate is  
15 consistent across studies and study populations  
16 regardless of the patient's baseline fracture risk.

17 The objective of therapy and prevention is  
18 to maintain or slightly increase bone mass. As has  
19 been discussed today, five milligrams of alendronate  
20 achieves this goal. The five milligram dose is the  
21 lowest dose that met the predefined clinical objective  
22 or preventing bone loss at the spine, hip, and total  
23 body.

24 Five milligrams resulted in a 50 percent  
25 attenuation of loss of bone BMD at the forearm, and

**SAG, CORP**

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 since the first two years of treatment and FIT was  
2 with the five milligram dose, it is clear that the  
3 dose attributed to the dramatic reductions in the  
4 incidence of vertebral, hip, and even forearm frac-  
5 tures.

6           Importantly, the degree of suppression of  
7 bone resorption seen with the five milligram dose, was  
8 comparable to that seen with estrogen/progestin, both  
9 returning the rate of bone turnover to the normal,  
10 pre-menopausal range.

11           Further, in the prevention trials there was  
12 no detectable difference in safety between the five  
13 milligram dose and placebo. In today's discussions of  
14 safety we focus a great deal on upper GI adverse  
15 experiences since this is an area that has previously  
16 been identified for bisphosphonates as the predominant  
17 body system of interest.

18           Based on the extensive database, including  
19 marketed experience in over a million patients who  
20 have received two to five times the proposed five  
21 milligram prevention dose, Fosamax™ has been shown to  
22 be well tolerated.

23           Therefore, the efficacy and safety of data  
24 support five milligrams of alendronate as an appropri-  
25 ate treatment for the prevention of post-menopausal

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 osteoporosis.

2 The need to have a safe and effective  
3 intervention such as alendronate to prevent osteoporo-  
4 sis is clear. Progressive bone loss occurs following  
5 menopause. In our three clinical trials for example,  
6 the placebo-treated women -- many of whom were  
7 receiving calcium supplementation -- had a significant  
8 decrease in spine, head, and total body BMD at a rate  
9 of approximately one percent a year.

10 This bone loss is accompanied by deteriora-  
11 tion of the bone's microarchitecture which further  
12 increases the risk of fracture. Unfortunately,  
13 neither the bone loss nor the disrupted microarchitec-  
14 ture can be restored to normal even with effective  
15 treatment once osteoporosis has developed.

16 For example, an effective treatment such as  
17 alendronate results in a marked, 50 percent reduction  
18 in incidents of new vertebral fractures. However,  
19 bone mass does not return to normal and fracture risk  
20 is not completely eliminated.

21 Thus, although treatment of osteoporosis  
22 with alendronate is clearly effective, earlier  
23 intervention to stop bone loss prior to the develop-  
24 ment of osteoporosis offers the prospect of better  
25 maintaining skeletal microarchitecture as well as

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 retaining bone mass at levels seen in young, healthy  
2 women, and substantially further reducing fracture  
3 risk.

4 As I stated at the beginning of my discus-  
5 sions, the issue clinically is deciding the appropri-  
6 ate patient and the appropriate time to intervene. It  
7 is clear that all post-menopausal women will experi-  
8 ence bone loss, most will develop osteoporosis, and  
9 many will develop a fracture. The state-of-the-art is  
10 such that medical consensus on exactly how to identify  
11 the appropriate patient at risk and when to intervene  
12 is evolving.

13 As indicated in the proposed package  
14 circular, it's Merck's intention that Fosamax™ be  
15 used in women at risk to develop osteoporosis. As Dr.  
16 Yates previously discussed, there are several risk  
17 factors for osteoporosis such as: early menopause,  
18 moderately-low bone mass, thin body build, a maternal  
19 history, and being of Asian or Caucasian racial  
20 background.

21 As part of the suggested labeling we've  
22 included several of the risk factors associated with  
23 the development of osteoporosis as an aid in identify-  
24 ing those patients at increased risk. The decision  
25 for therapy is multifactorial and must involve the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C 20008

1 physician and the individual patient.

2 Presently, this decision process occurs with  
3 only one approved therapeutic option available:  
4 estrogen replacement therapy. Once the physician and  
5 the woman have made a decision that intervention is  
6 appropriate, there needs to be therapeutic options  
7 available to ensure that the patient gets the treat-  
8 ment most suited to her.

9 The data presented today certainly support  
10 the approval of Fosamax™ as a therapeutic option to  
11 prevent post-menopausal osteoporosis. Thank you.

12 ACTING CHAIR CRITCHLOW: Thank you. Now,  
13 we'll have questions from the committee for any of the  
14 sponsor presenters. Dr. Molitch.

15 DR. MOLITCH: Yes. I have actually several  
16 questions and they can be grouped into several  
17 categories, starting with the long-term effects of  
18 this drug. We know that it's clearly going to have  
19 long-term effects.

20 I have this vague recollection from long-  
21 term studies with etidronate that osteomalacia some-  
22 times occurred as a very late finding with prolonged  
23 studies, and I was wondering if there are plans for  
24 long-term biopsy studies -- to be done at perhaps five  
25 years, ten years, 15 and 20 years -- for long-term

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 surveillance for this type of medication.

2 We're trying to presumably have this drug  
3 being treated for patients for many, many years and I  
4 would hope that there would be a leading edge of  
5 surveillance of patients for that 5-, 10-, 20-year  
6 type of period, ahead of any clinical use that we're  
7 going to have for that. So that's my first question.

8 DR. YATES: The major issue with etidronate  
9 and the reason why biopsies are being required long-  
10 term is because, at doses the same as, or similar to  
11 those used clinically, there is a defect that develops  
12 in mineralization.

13 We have looked in our pre-clinical studies  
14 at alendronate and have seen that the dose that is  
15 required to -- the lowest dose that you see, any  
16 defect in mineralization is about 6,000 times higher  
17 than the lowest dose that inhibits bone resorption,  
18 and in fact, amounts to about 20- to 40,000 times  
19 higher than the dose that we're giving clinically.

20 So based upon the fact that we see normal  
21 bone turnover assessed by biochemical markers, over  
22 the long term we have extensive biopsy data in over  
23 500 patients out to three years. We do not believe  
24 that it's necessary at this point in time to go on  
25 beyond that to collect further bone biopsies.

SAG, CORP

4218 LENORE LANE, N W  
WASHINGTON, D C 20008

1 DR. MARCUS: Are there going to be perhaps,  
2 without biopsies, will there be surveillance data at  
3 five, ten, 15, 20 years --

4 DR. YATES: Yes.

5 DR. MOLITCH: -- in some of the cohorts that  
6 you're now studying?

7 DR. YATES: Absolutely. Our intent -- and  
8 we are doing this in our clinical trials -- is to  
9 continue to follow the women in our clinical trials.  
10 We've shown you data today on 5-year extensions --  
11 which were 2-year extensions to our original 3-year  
12 studies -- both for prevention and treatment.

13 Those studies have been extended now to  
14 seven years. We are going to go beyond that. The  
15 EPIC clinical study with 1,600 patients is a pre-  
16 planned -- there's a 6-year study -- and I'm sure  
17 we're going to be looking at extending that study as  
18 well. So we're very committed to looking at these  
19 patients over the long term.

20 DR. MOLITCH: Thank you.

21 ACTING CHAIR CRITCHLOW: Dr. Marcus?

22 DR. MARCUS: I have one question about  
23 toxicity and one about efficacy that I'd like to ask  
24 you at this point. I'll ask the toxicity one first,  
25 just a point of clarification.

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1           It was stated that really nothing other than  
2 the gastrointestinal effects have come to light in all  
3 the post-marketing survey. That comes as a surprise  
4 to me. In my clinical practice using Fosamax™ I have  
5 seen two patients with a musculoskeletal syndrome  
6 which is quite disabling, involving diffuse muscle  
7 aches.

8           And in discussing this with colleagues of  
9 mine in the bone community around the country, I think  
10 most others have seen at least a few patients with  
11 that as well. Some have the experience that that  
12 occurs in patients who are either vitamin D deficient  
13 or not getting enough calcium intake.

14           In my own clinic population that is not the  
15 case. This is an effect which is clearly related to  
16 the drug; it stops when the drug is discontinued and  
17 begins again when the drug is reinstated. And I  
18 just wonder whether this has only happened in so few  
19 patients that it has not hit Merck's threshold for  
20 actually counting it as something that they see.  
21 Perhaps you could just address that.

22           DR. DAIFOTIS: Yes, actually Dr. Marcus, let  
23 me try a clarification. We actually already had  
24 information in the label about musculoskeletal pain  
25 and musculoskeletal pain actually was a common,

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D C. 20008

1 adverse experience seen in the clinical trials.

2 In the clinical trials themselves we didn't  
3 detect a difference straight-out between placebo and  
4 alendronate, because not surprisingly looking at the  
5 age group, many women complained both in placebo and  
6 alendronate of types of musculoskeletal pain.

7 We have gone further within the label to  
8 define it as muscle, bone pain so that people are much  
9 more clear on that information with the post-marketed  
10 use, and there have been reports of individuals that  
11 develop pain like that. We saw that actually already  
12 and put it in the label in the Paget's patients as  
13 well.

14 So my statement was rather, what was not  
15 new. It was already there and that is there and we  
16 already recognize that it's going on.

17 DR. MARCUS: Good. Thank you, very much.  
18 From my experience in the EPIC trial the use of  
19 intention-to-treat analysis -- which is certainly  
20 proper for a submission like this -- does mask a  
21 treatment effect in those patients who actually  
22 succeed in taking the drug and staying on it.

23 The dropout rate, the number of subjects who  
24 actually didn't make it to 36 months or to 24 months  
25 of trial, was actually fairly substantial in this

SAG, CORP

4218 LENORE LANE, N W  
WASHINGTON, D C 20008

1 trial, and I think the person who practices medicine  
2 and wants to know what can be achieved in patients who  
3 stay on a medication becomes a very relevant question.

4 And I wonder if there are any efficacy data,  
5 if there was a percent increases in bone mass that you  
6 can tell us about -- patients who actually were  
7 compliant with say, more than 80 percent of their  
8 assigned study drug.

9 DR. YATES: As part of our standard investi-  
10 gations we do both intention-to-treat analysis and a  
11 per protocol analysis. The per protocol differs in  
12 two ways. One is that patients who are not compliant  
13 over a certain standard are not included in the  
14 analysis. And the other is that we do not carry  
15 forward data. So if a patient drops out, say, in the  
16 second year of the study, in our intention-to-treat we  
17 take the last point available and carry that forward  
18 as the end-of-study timepoint.

19 In our per protocol analysis we simply look  
20 at the timepoint in question -- whether it's 24 months  
21 or 36 months -- of patients who are available at that  
22 timepoint, and also have a placebo measurement. And  
23 those analyses were very consistent. There was very  
24 little difference and no difference whatsoever in the  
25 conclusions between per protocol and intention-to-

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 treat analyses.

2 ACTING CHAIR CRITCHLOW: Could you please  
3 elaborate on the reasons for that rather substantial  
4 difference between the ITT and the per protocol number  
5 of subjects?

6 DR. YATES: The number of subjects -- first  
7 of all, in order to be included in the per protocol  
8 analysis the patient -- at the last study timepoint --  
9 the patient had to complete the study. There was a  
10 dropout in the prevention studies of a little under  
11 ten percent per year. And this I think, is probably  
12 a reflection of the patient populations, but in fact,  
13 is a recently high retention rate.

14 And then we did exclude some patients who  
15 were less than 75 percent compliant with the study  
16 medication or had taken other therapies which were not  
17 permitted per the protocol. And so those were the  
18 main differences between the per protocol analysis and  
19 the intention-to-treat.

20 As I say, the conclusions and the values  
21 achieved in terms of increases in bone mass on  
22 treatment and decreases on placebo, were actually very  
23 similar irrespective of which analysis we performed.

24 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

25 DR. KREISBERG: I guess this is also for Dr.

**SAG, CORP**

4218 LENORE LANE, N W.  
WASHINGTON, D C. 20008

1 Yates. When he was showing the FIT data he said that  
2 there was no difference in benefit from alendronate  
3 therapy based upon baseline bone mineral density of  
4 the participants. But I think that really is incor-  
5 rect and obscures the fact that it is not the relative  
6 risk reduction that's important; it's the absolute  
7 risk reduction. And that depends upon the baseline of  
8 bone mineral density measurements.

9 DR. YATES: I agree with you, Dr. Kreisberg.  
10 That essentially, in terms of -- the benefit in terms  
11 of the absolute fracture risk reduction over a 3-year  
12 period in a controlled clinical trial, than those with  
13 the highest risk of baseline have the greatest to gain  
14 in terms of the number of fractures saved over that  
15 period.

16 However as I stated, the relative risk  
17 reduction is similar, and I think that has an impor-  
18 tant implication when we move towards a population  
19 with more normal levels of bone mass, because it does  
20 indicate that the treatment effect to maintain  
21 skeletal integrity is there irrespective of the  
22 baseline level of bone mass.

23 DR. KREISBERG: But it gets into cost  
24 efficacy issues because the lower the baseline risk  
25 the more people you have to treat to prevent an event,

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 so it has cost implications here --

2 DR. YATES: Yes.

3 DR. KREISBERG: -- and that needs to be  
4 taken into consideration by physicians as they try to  
5 stratify risk.

6 DR. YATES: Yes.

7 ACTING CHAIR CRITCHLOW: Dr. Molitch.

8 DR. MOLITCH: A question about the GI side  
9 effects, and I understand that there was an increase  
10 in the GI side effects when NSAIDs were used for both  
11 the placebo and with drugs. And this is certainly  
12 commonly used in this patient population who are going  
13 to have back pain and what-have-you. So it's some-  
14 thing that we will face; some patients will be using  
15 these drugs concomitantly in practice.

16 Often we as physicians, if we're seeing a  
17 patient in practice and a patient does develop a side  
18 effect such as dyspepsia when they're taking medica-  
19 tion like this, if we're getting marked benefit from  
20 the medication, then we seek to reduce the side effect  
21 by perhaps altering something else, or adding yet  
22 another drug, unfortunately, to the patients regimen,  
23 such as an H2 blocker.

24 Do you have any data that use of an H2  
25 blocker under those circumstance would decrease the

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 dyspepsia? Or if you did add it, would it alter the  
2 absorption of the drug since this is certainly  
3 something that will be done? And do we have any informa-  
4 tion about concomitant use?

5 In addition, as part of this, if patients  
6 are taking other drugs -- and again, these are going  
7 to be patient population that will be taking HMG CoA  
8 reductase inhibitors that will cause some reflux  
9 sometimes -- does this increase the risk of dyspepsia  
10 as well? Can we use H2 blockers in these patients who  
11 are taking multiple drugs? Do you have any feel for  
12 this?

13 DR. DAIFOTIS: We made exclusion criteria as  
14 I showed you, where we said the patients shouldn't be  
15 using these non-steroidals, but we not surprisingly,  
16 showed you also a FIT that in fact, during a course of  
17 the studies there was quite a bit of non-steroidal,  
18 anti-inflammatory drug use. So we have experience  
19 with it that way.

20 And then tell you what we don't see is,  
21 although we see the increase in the placebo group and  
22 the alendronate group, we are not seeing a greater  
23 increase in events with alendronate. It doesn't give  
24 you an absolute answer but what I'm saying is, I'm not  
25 seeing this huge jump which is what you would be

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 looking for or what I would be looking for.

2 Clearly, physicians have to make these  
3 decisions and know and weigh the risks and benefits of  
4 every treatment that they use and be well-informed --  
5 which is what we at Merck gone really done out of our  
6 way to do -- about what things can happen, so that  
7 they can make safe decisions.

8 DR. MOLITCH: How about concomitant use of  
9 H2 blockers? Will that alter the absorption of the  
10 drug?

11 DR. DAIFOTIS: Yes, it actually improves  
12 absorption, so we do have some information on that.  
13 But not to an extent that it would have a clinical  
14 difference or that you would have to change your dose.  
15 And there are quite a few patients in all the studies  
16 that have used H2 blockers or were using them even  
17 previously.

18 But again, this is done within the whole  
19 group of the studies; it's not a specific study  
20 looking at only at that.

21 DR. MOLITCH: Thank you. Another question  
22 is, in patients that we see like this it's not at all  
23 uncommon to see a patient who will have mild, primary  
24 hyperparathyroidism that's discovered during this.  
25 Was that looked for in any of these studies? What's

SAG, CORP

4218 LENORE LANE, N W  
WASHINGTON, D.C. 20008

1 the effect of alendronate in patients who've got mild,  
2 primary hyperparathyroidism? Is there any data on  
3 that?

4 DR. YATES: As one of the exclusion criteria  
5 in our, hypocalcemia was -- patients were excluded.  
6 We therefore don't have any direct experience with  
7 alendronate in this patient population.

8 There is information from other bisphosphon-  
9 ates that you can get small decreases in calcium and  
10 there may be potential reasons why patients with mild,  
11 primary hyperparathyroidism may experience a benefit  
12 in terms of bone mass, as well as a small and usually  
13 transient, decrease in calcium. But I can't answer  
14 your question specifically from alendronate data.

15 ACTING CHAIR CRITCHLOW: Dr. Marcus.

16 DR. MARCUS: I'd like, Dr. Yates, just to  
17 clarify one point about the entylopeptide data. Just  
18 to reassure us that you're not dealing with the floor  
19 effect that everyone no matter what dose, seemed to  
20 get down to a value of 20 and over time that didn't go  
21 down further. I'd just like everybody to be reassured  
22 that in fact, one could go down further.

23 DR. YATES: Right. No, that's a very good  
24 question. We do have a slide on that showing the  
25 effects of intravenous pamidronate in a study that was

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 done to look at the specific question.

2 And what was seen in that study -- which is  
3 a non-Merck study -- was that it was possible in  
4 normal, healthy males who have relatively normal bone  
5 turnover similar to that in pre-menopausal women, to  
6 get an 85 percent reduction in the level of entylopep-  
7 tide crosslinks.

8 And that is indicative of a much greater  
9 degree of suppression of bone turnover than we see in  
10 our clinical studies. And also when we compare the  
11 level achieved with alendronate I remind you that the  
12 values were the same as that in women who received  
13 estrogen, and the same as the range seen in healthy,  
14 pre-menopausal women.

15 So from all of those perspectives we have no  
16 concern that there is a floor effect and that is any  
17 oversuppression in bone turnover.

18 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

19 DR. ILLINGWORTH: A question related to the  
20 metabolic parameters that are used. You've got  
21 obviously a huge database. Can you predict who's  
22 going to benefit most by those patients who have the  
23 greatest NTX excretion or urine pyridinoline excre-  
24 tion? Are those patients who have a more rapid rate  
25 of bone loss, and that are going to benefit more from

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 treatment?

2 DR. YATES: The question, I think relates to  
3 the issue of whether patients with higher bone  
4 turnover and potentially more rapid loss, have greater  
5 benefit from anti-resorptive therapy with alendronate.  
6 And this was, I think a basis supposition that we  
7 would be able to detect a difference between patients  
8 with high, low, or medium levels of bone turnover.

9 We looked at a number of different biochem-  
10 ical markers of bone turnover, NTX being just one of  
11 those. But we do have a slide to show you the values  
12 of NTX and osteocalcin showing the changes in bone  
13 mass that we saw in the placebo group as well as in  
14 the group that received alendronate treatment.

15 Also we're looking for that slide because I  
16 think it would be helpful to show you that. The  
17 results basically show that there was little or no  
18 difference between tertiles of either osteocalcin at  
19 baseline -- here we have the data -- osteocalcin or  
20 NTX at baseline in terms of either the loss in bone  
21 mass seen in the placebo group shown in this column  
22 here.

23 This is baseline NTX; goes from the lowest  
24 tertile, mid, and highest. You can see that the bone  
25 loss over two years in the EPIC study, was around one-

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C 20008

1 and-a-half percent irrespective of which tertile these  
2 patients fell, which is saying that what we're seeing  
3 in osteocalcin there are minor differences between the  
4 rates of bone loss seen over the 2-year period.

5 When we also looked at the five milligram  
6 dose for the change in bone mass, again we see that  
7 there are comparable increases of around three-and-a-  
8 half percent, irrespective of the baseline mean bone  
9 turnover. So while they can't give you a good  
10 explanation for why we see these data, they are  
11 actually very consistent with the data that we  
12 observed in our phase 3 osteoporosis treatment  
13 program, and it does indicate that physicians really  
14 cannot, right now, use these markers to indicate  
15 patients who will or will not respond.

16 ACTING CHAIR CRITCHLOW: Just that slide  
17 there, was that a trend? I mean, was that a signifi-  
18 cant trend in the --

19 DR. YATES: It was not significant.

20 ACTING CHAIR CRITCHLOW: -- alendronate?

21 DR. YATES: The trends for either of these  
22 biochemical markers.

23 ACTING CHAIR CRITCHLOW: Dr. New.

24 DR. NEW: Do you have information as to  
25 whether alendronate prevents the osteoporosis of

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 cortisol ingestion?

2 DR. YATES: Of cortisol? Yes.

3 DR. NEW: Of cortisol administration --

4 DR. YATES: Steroid-induced osteoporosis.

5 We excluded patients at baseline in these studies that  
6 were on corticosteroids. However, we are conducting  
7 a very large program -- which had actually come to an  
8 end in terms of the clinical phase of the study --  
9 with over 500 patients taking glucocorticoids at doses  
10 of prednisone or equivalent, of greater than 7.5  
11 milligrams a day. So sometime later this year we  
12 would anticipate to be able to answer your question.

13 DR. NEW: With that in mind, can I ask you  
14 -- do you have any information on toxicity in the  
15 young so that this could be used, for instance, in  
16 children taking glucocorticoids or in adolescents with  
17 idiopathic osteoporosis?

18 DR. YATES: At the moment we have no  
19 experience in pediatric populations. It is an  
20 important question because glucocorticoid-induced  
21 osteoporosis obviously affects people of all ages, and  
22 so children with this side effect of corticosteroids,  
23 I think there is a potential benefit to be had there  
24 but we have not yet progressed in our studies to look  
25 at that population.

SAG, CORP

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1                   ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

2                   DR. KREISBERG: I have a question and a  
3 comment. I'm intrigued in the prevention studies, by  
4 the fact that there's progressive improvement in bone  
5 mineral density in most sites over two years, and then  
6 when the drug is discontinued you come back to  
7 baseline. And it raises the possibility of intermit-  
8 tency of therapy in prevention, not in treatment, and  
9 I wondered whether you had considered that.

10                   And the comment that I have to make is that  
11 both you and I think, Dr. Goldmann -- or someone else  
12 who spoke -- indicated and quoted from your book of  
13 information that you put out for us, is that you're  
14 proposing that Fosamax™ is indicated for the treat-  
15 ment and prevention of osteoporosis in post-menopausal  
16 women.

17                   And I really would like to see that modi-  
18 fied. It should be used to prevent osteoporosis in  
19 post-menopausal women who are unwilling or unable to  
20 take estrogen. Because I don't think that what we're  
21 suggesting is that alendronate replaces estrogen.

22                   DR. YATES: To get at your second part of  
23 the question first which is, where do physicians or  
24 should physicians stand in terms of regarding alend-  
25 ronates versus estrogen. There are very important

**SAG, CORP**

4218 LENORE LANE, N.W.  
WASHINGTON, D.C. 20008

1 differences between estrogen -- obviously a hormonal  
2 therapy with widespread effects and widespread, both  
3 benefits and long-term safety concerns -- with a  
4 specific treatment, alendronate, which has specific  
5 effects on bone mass.

6 And so we believe that patients where the  
7 primary concern is for bone mass or bone loss,  
8 alendronate is a rational therapy for prevention of  
9 osteoporosis. For women who want the benefits of  
10 estrogen and who tolerate side effects and gain  
11 benefits from estrogen treatment, clearly estrogen is  
12 an appropriate choice.

13 But I think what we have to do here is to  
14 weigh the risks and benefits of both treatments for  
15 individual women and make a therapeutic decision.

16 To get at your first question which was  
17 whether or not we had considered intermittent use of  
18 alendronate, all of our clinical trials gave continu-  
19 ous alendronate administration with the exception of  
20 some of the studies I showed where we discontinued  
21 alendronate to look at the effects of treatment  
22 discontinuation.

23 The reason we selected continuous therapy is  
24 that that allows us to give the lowest dose that is  
25 effective to achieve the desired effect. And we did

**SAG, CORP**

4218 LENORE LANE, N.W  
WASHINGTON, D C 20008