1 UNITED STATES OF AMERICA

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3 DEPARTMENT OF HEALTH AND HUMAN SERVICES

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4 PUBLIC HEALTH SERVICE

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6 FOOD AND DRUG ADMINISTRATION

7 CENTER FOR DRUG EVALUATION AND RESEARCH

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9 ENDOCRINOLOGIC AND METABOLIC DRUGS

10 ADVISORY COMMITTEE

11 MEETING #67

12 + + + + +

13 WEDNESDAY, 14 MAY, 1997

14

ORIGINAL

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15 The meeting took place in Versailles Rooms

16 II and III, Bethesda Holiday Inn, 8120 Wisconsin

17 Avenue, Bethesda, Maryland, at 8:00 a.m., Robert S.

18 Sherwin, M.D., Acting Chair, presiding.

19 PRESENT:

20	HENRY G. BONE, III, M.D.	Chairman
21	KATHLEEN R. REEDY	Exec. Secretary
22	ROBERT S. SHERWIN, M.D.	Acting Chair
23	JOSE FRANCISCO CARA, M.D.	Member
24	COLLEEN A. COLLEY, PharmD	Consumer Rep.
25	CATHY W. CRITCHLOW, Ph.D.	Member

JULES HIRSCH, M.D.	Member
D. ROGER ILLINGWORTH, M.D.,Ph.D.	Member
MARK E. MOLITCH, M.D.	Member
HUGO GALLO-TORRES, M.D., Ph.D.	Consultant
JAMES H. BILSTAD, M.D.	FDA Rep.
ERIC COLMAN, M.D.	FDA Rep.
SOLOMON SOBEL, M.D.	FDA Rep.
GLORIA J. TROENDLE, M.D.	FDA Rep.
RICHARD L. ATKINSON, M.D.	Public Comment
JERRY M. EARLL, M.D.	Public Comment
DR. MICHAEL HAMILTON	Public Comment
CHARLES P. LUCAS, M.D.	Public Comment
LYNN McAFEE	
JOYCE A. RITCHEY	Public Comment
LARRY SASICH, PharmD	Public Comment
M. PATRICIA SOLBACH, Ph.D.	Public Comment
DR. JUDITH S. STERN	Public Comment
WILLIAM CANNOVATCHEL, M.D.	Sponsor Rep.
ROBERTO GUERCIOLINI, M.D.	Sponsor Rep.
JONATHAN B. HAUPTMAN, M.D.	Sponsor Rep.

ALSO PRESENT:

BESS DAWSON-HUGHES, M.D.

E. ROBERT GREENBERG, M.D.

JEROME KAMM, Ph.D.

BRUCE STADEL, M.D.

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1 P R O C E E D I N G S

2 8:15 a.m.

3 ACTING CHAIR SHERWIN: Good morning. Can
4 people hear me? I apologize for the delay. We're
5 trying to get the lights off us a little bit so that
6 we're not interrogated too much here at this meeting,
7 so I appreciate your indulgence for another minute or
8 so -- or are we ready, now?

9 I'd like to call to order this meeting of
10 the Endocrinologic and Metabolic Drugs Advisory
11 Committee of the FDA. Our task today is to review a
12 drug called Xenical™, or orlistat, and the presenta-
13 tion will be done by Hoffmann-LaRouche. But before we
14 begin we'd like to begin with an announcement, hearing
15 meeting statement by Kathleen Reedy, our Executive
16 Secretary.

17 MS. REEDY: Conflict of interest statement
18 for the Endocrinologic and Metabolic Drugs Advisory
19 Committee, May 14, 1997. The following announcement
20 addresses the issue of conflict of interest with
21 regard to this meeting and is made a part of the
22 record to preclude even the appearance of such at this
23 meeting.

24 Based on the submitted agenda for the
25 meeting and all financial interests reported by

1 committee participants, it has been determined that
2 all interests in firms regulated by the Center for
3 Drug Evaluation and Research present no potential for
4 an appearance of a conflict of interest at this
5 meeting with the following exceptions.
6 In accordance with 18 United States Code
7 208(b)(3), full waivers have been granted to Dr. Mark
8 E. Molitch and Dr. Jules Hirsch which permit them to
9 participate in all official matters concerning
10 Xenical™. Copies of the waiver statement may be
11 obtained by submitting a written request to the
12 Agency's Freedom of Information Office, Room 12A30 of
13 the Parklawn Building.
14 In the event that the discussions involve
15 any other products or firms not already on the agenda,
16 for which an FDA participant has a financial interest,
17 the participants are aware of the need to exclude
18 themselves from such involvement, and their exclusion
19 will be noted for the record.
20 With respect to all other participants, we
21 ask in the interest of fairness, that they address any
22 current or previous financial involvement with any
23 firm whose products they may wish to comment upon.
24 ACTING CHAIR SHERWIN: Okay, thank you. Now
25 what I'd like to do is have us -- each member of the

1 committee introduce themselves, as well as the FDA and
2 our advisors. Roger?
3 DR. ILLINGWORTH: Good morning. My name is
4 Roger Illingworth. I am at the College of Medicine in
5 Oregon Health Science University on Portland, Oregon,
6 member of the FDA Advisory Panel.
7 DR. CRITCHLOW: Cathy Critchlow, University
8 of Washington, Department of Epidemiology.
9 DR. HIRSCH: Jules Hirsch, Rockefeller
10 University, New York.
11 DR. MOLITCH: Mark Molitch, Northwestern
12 University Medical School in Chicago.
13 DR. COLLEY: Colleen Colley, VA Medical
14 Center, Portland, Oregon.
15 ACTING CHAIR SHERWIN: Robert Sherwin, Yale
16 University School of Medicine.
17 MS. REEDY: Kathleen Reedy, Food and Drug
18 Administration.
19 DR. CARA: Jose Cara, Henry Ford Hospital,
20 Detroit, Michigan.
21 DR. COLEMAN: Eric Coleman, Medical Officer,
22 FDA.
23 DR. TROENDLE: Gloria Troendle, Medical
24 Officer, FDA.
25 DR. BILSTAD: Jim Bilstad, FDA, Office of

1 Drug Evaluation II.

2 DR. SOBEL: Sol Sobel, FDA, Division of

3 Metabolic and Endocrine Drug Product.

4 ACTING CHAIR SHERWIN: I think you'll

5 notice, right at the end there's a little sign for our

6 Chairman, Henry Bone. Henry Bone is in Paris today,

7 and will be hooked up on speakerphone later on in the

8 morning. And so I want you to know that we treat our

9 Chairman quite well.

10 Now, I'd like to begin by asking Dr. Sobel

11 and Mr. Bilstad if they would like to comment before

12 we begin.

13 DR. SOBEL: No, I have no comments. I will

14 have, later in the day.

15 ACTING CHAIR SHERWIN: Okay. I guess we can

16 now proceed to our open hearing. Now, we have a long

17 list of speakers and consequently, I've asked each

18 speaker to limit their remarks to about a total of

19 five minutes, and we're going to keep a timer on,

20 because it should take a total of 50 minutes and we're

21 going to try to end on time and move things along

22 expeditiously.

23 I would ask each individual, when they come

24 up to the microphone, not only to give their name and

25 their affiliation, but also whether they've been

1 reimbursed for their expenses coming to this meeting.
2 Or have any financial interest in the product that's
3 being discussed today.
4 The first person on our list is Dr. Richard
5 Atkinson, President of the American Obesity Associa-
6 tion.
7 DR. ATKINSON: Good morning. I'm Dr.
8 Richard Atkinson, President of the American Obesity
9 Association. They are paying my expenses here. In
10 terms of conflicts of interest, in the past I have
11 given a CME lecture for Hoffmann-LaRouche and in the
12 very remote past received some product and placebo to
13 do a research study on vitamin supplementation, but I
14 don't think I have any other conflicts of interest.
15 The American Obesity Association is a lay
16 advocacy group representing the interests of the 70 to
17 80 million American children and adults afflicted with
18 this disease. The missions of the American Obesity
19 Association are education, promotion of research, and
20 community action in the interests of obese people.
21 I'm also a professor of Medicine and
22 Nutritional Sciences at the University of Wisconsin in
23 Madison. My area of research interest is obesity with
24 particular interest in the use of drugs for the
25 treatment of obesity, and I'm currently participating

1 in several studies that are evaluating the effects of
2 drugs for the treatment of obesity, and these studies
3 have involved more than 3,000 patients.
4 The American Obesity Association strongly
5 supports the development of new treatments for
6 obesity. The success rate of diet, exercise, and
7 behavior modification of lifestyle has been very poor
8 over the long-term. The data of Weintraub, et. al.,
9 on phentermine and fenfluramine, our data, and those
10 of a number of other investigators, demonstrate that
11 the addition of pharmacologic agents enhances weight
12 loss, the maintenance of weight loss, and reduces the
13 major risk factors associated with obesity.
14 Obesity has a strong genetic component and
15 there are compelling data to show that the biochemis-
16 try and physiology of obese people is different from
17 that of lean people. Just as with other chronic
18 diseases, drugs will be necessary to alter the
19 biochemistry of the obese towards that of lean people.
20 Dr. Claude Buchard of Lavalle University in
21 Canada has identified over 20 genes that contribute to
22 the etiology of obesity. Combinations of these genes
23 make it like that there are numerous, different types
24 of obesity. We know almost nothing about which drugs
25 will be useful for which types of obesity, but it is

1 naive to assume that all obesity will be treated with
2 one or just a few drugs.
3 There's been little research on obesity
4 drugs since 1973, and indeed, only one new drug has
5 been released to the market for the treatment of
6 obesity since 1973. The NIH devotes only about one-
7 half of one percent of its budget to obesity research
8 and at best, only about four-and-a-half percent of the
9 budget of the NIH goes to all of nutrition research.
10 Obesity affects more than one-third of the
11 entire adult population and affects over 20 percent of
12 children. About 300,000 Americans die each year of
13 obesity-related diseases, making it the second leading
14 cause of premature deaths after smoking. Clinicians
15 and investigators need additional drugs and the
16 research that will accompany the development and
17 marketing of new drugs.
18 Many obese patients respond poorly to the
19 drugs currently available. Given the diversity of
20 obesity, this is not surprising. Chronic diseases
21 require chronic treatment, and new agents, alone or in
22 combination, must be tested to determine their utility
23 for controlling obesity and its co-morbid conditions.
24 We urge the Endocrinologic and Metabolic
25 Drugs Advisory Committee to carefully consider the

1 evidence on orlistat. If approved, it will be the
2 first drug approved by the FDA for the treatment of
3 obesity that does not act through the central nervous
4 system.
5 Should the committee find this drug to be
6 safe and efficacious, and to have an acceptable risk
7 benefit profile, the American Obesity Association
8 believes that the addition of a new agent for the
9 treatment of obesity will be beneficial for Americans
10 who suffer from this serious disease.
11 Thank you.
12 ACTING CHAIR SHERWIN: Thank you. Our next
13 speaker is Lynn McAfee, Council of Size and Weight
14 Discrimination.
15 DR. McAFEE: Thank you. My trip here was
16 reimbursed by the Council, which is a non-profit
17 organization which does not accept money from weight
18 loss industry. And thank you for the opportunity to
19 speak here today.
20 Although it's wonderful that the public gets
21 a chance to voice an opinion at these meetings, I'd
22 like to put out that it's a little difficult to know
23 what to say, since I haven't yet heard any of the
24 day's presentations. While the company expressed an
25 interest in giving me a data presentation, they have

1 been unable to find the time to do so during the last
2 three months I've been trying to meet with them.
3 It would be much more helpful to be able to
4 comment after all the evidence has been presented
5 today. So frankly, I just don't have much to say
6 about this drug. There are obvious and very serious
7 concerns about gallbladder problems and nutrient
8 absorption that I'm sure will be addressed at great
9 lengths today.
10 The company seems to be positioning this, in
11 part, as a behavior modification tool for dieters.
12 some consumers are already calling Xenical™ the
13 intestinal bypass in a pill. Eating foods with a high
14 percentage of fat is supposed to become unpleasant
15 enough that we'll just act right and stop eating them.
16 The heir to the intestinal bypass, stomach stapling --
17 often called surgically enforced bulimia -- is also
18 supposed to have that effect of modifying behavior.
19 But many people have found to their dismay,
20 that their bodies just aren't that stupid. The same
21 drives now being articulated by molecular biologists
22 eventually continue relentlessly. Believe me, if
23 weight loss surgery were all that successful, we'd all
24 be walking around with the same scars on our bellies
25 and air fresheners in our pockets.

1 All behavior modification tools have thus
2 far proven spectacularly unsuccessful. Though
3 Xenical™ is deemed safe I do have major concerns
4 about its usage. Anorexic and bulimia chat lines on
5 the Internet have provided clever ways of getting
6 redux and phenfen, and these drugs have been pre-
7 scribed for people in their eighties, and even for
8 people with HIV.
9 Labeling has proved insufficient protection,
10 yet labeling seems to be the only tool we have once a
11 drug is approved. We are still waiting for definitive
12 redux neurotoxicity testing. Perhaps it should be
13 kept in mind when you consider safety and effective-
14 ness issues.
15 We're in the very beginning of the anti-
16 obesity drug revolution. Over 50 companies are now
17 involved in obesity research. As I said before, this
18 is not our last and our only hope. And please, let
19 Xenical™ stand or fall on its own merits as a drug,
20 not as a potential cure for the social discrimination
21 we suffer. It offends me deeply to hear about curing
22 the victim of social prejudice.
23 We are in danger of creating a privileged
24 class of people who can afford to escape a pervasive
25 prejudice. We need to cure the prejudice, not the

1 victim. There are good reasons to develop anti-
2 obesity drugs but this isn't one of them.
3 So do I think this drug is okay? Is it safe
4 and effective? I don't know. I'm anxiously awaiting
5 today's evidence. Thank you in advance, for your
6 efforts on our behalf.
7 ACTING CHAIR SHERWIN: Thank you. Speakers
8 can also use the center microphone if they so -- would
9 like. The next speaker is Larry Sasich from the
10 Public Citizen Public Health Research Group.
11 DR. SASICH: Thank you, Larry Sasich, Public
12 Citizen Health Research Group. I paid for my own
13 Metro ticket here and I have no conflicts of interest.
14 Public Citizen would like to thank the Food
15 and Drug Administration and the members of the
16 Advisory Committee for this opportunity to comment on
17 orlistat. Our comments will address two topics:
18 secrecy and two public studies assessing orlistat's
19 efficacy. In addition, we will pose the following
20 question: Do the data show immeasurable benefit from
21 orlistat by reducing the health risks associated with
22 obesity?
23 In preparing our comments we requested
24 summary safety and effectiveness data on orlistat from
25 the FDA. Our request was refused on the grounds that

1 this information is confidential and commercial, and
2 its release would cause Hoffmann-LaRouche competitive
3 harm, even though the Code of Federal Regulations
4 allow, at the Commissioner's discretion, disclosure of
5 -- and I will quote -- "a summary of selected portions
6 of the safety and effectiveness data that are appro-
7 priate for public consideration of a specific pending
8 issue. For example, for consideration of an open
9 session of an FDA Advisory Committee".
10 We found that some FDA staff were not aware
11 of this section of the regulation. In addition, no
12 one knew why this regulation had been written, and if
13 it had ever been used in the past to make safety and
14 efficacy data available prior to an Advisory Committee
15 Meeting.
16 It is troubling that important information
17 about orlistat has been kept secret and the time
18 allotted for public participation is in the hour
19 before any presentations will reveal what is known
20 about orlistat. Scheduling public comment later in
21 the meeting, after presentation of what we believe are
22 numerous studies involving large numbers of subjects,
23 without the time to carefully evaluate these data, is
24 little better than keeping the data secret.
25 We can only comment on two published

1 clinical trials involving this drug, neither of which
2 provide acceptable demonstration of the drug's
3 efficacy based on 1996 FDA guidelines for the clinical
4 evaluation of weight control drugs.
5 First, demonstration that the drug effect is
6 significantly greater than placebo effect in that mean
7 drug associated weight loss exceeds the mean placebo
8 weight loss by at least 5 percent. Two, demonstration
9 that proportions of subjects who reach and maintain a
10 loss of at least 5 percent of their initial body
11 weight is significantly greater in subject on drug
12 than those in placebo.
13 Both studies lasted 12 weeks and both showed
14 a statistical difference in the mean weight loss
15 between orlistat and placebo. In the first study this
16 amounted to 3.9 pounds with the highest dose of
17 orlistat, and in the other study the difference was
18 4.9 pounds. Neither study could show that mean
19 orlistat-associated weight loss exceeded mean placebo
20 weight loss by at least 5 percent, and the first study
21 at the highest does of orlistat, the only difference
22 was a meager 1.73 percent and in the other it was only
23 2.47.
24 In summary, these two studies failed to show
25 that orlistat fulfills one of the two requirements of

1 the first FDA guideline, and neither study reported
2 results applicable to the second guideline.
3 Public Citizen is fully cognizant of the
4 health threat presented by long-term obesity and the
5 importance of developing interventions, both drug and
6 non-drug, to reduce the risks associated with this
7 disease. We are also aware that few published studies
8 have evaluated the effectiveness and safety of weight
9 control drugs beyond one year, and we are not aware of
10 published studies showing that any weight loss drug
11 reduces the health risks of obesity.
12 From the public health perspective, weight-
13 control drugs have not provided the solution to
14 chronic obesity. Only drug bills that can be counted
15 in the hundreds of millions of dollars, and countless
16 reported and unreported adverse drug reactions.
17 We have no doubt that if approved, orlistat
18 will be promoted as the magic bullet and a break-
19 through treatment for the chronic management of
20 obesity, just as lipid-lowering drugs and anti-
21 hypertensive agents have been advertised.
22 In fact, Hoffmann-LaRouche's Vice President
23 for Global Development was quoted in 1996 as saying,
24 "We believe that this drug is going to be important
25 and useful in the medical management of obesity". And

1 that means you really have to look at chronic long-
2 term management, just as you would look at an anti-
3 hypertensive or lipid-lowering agent, and that is
4 exactly what we intend to do.
5 Pharmaceutical companies which generate
6 enormous profits through sales of drugs which may be
7 used for years by millions of people, must provide
8 adequate evaluation of their products. For Hoffmann-
9 LaRouche this will mean answering the question, do the
10 data show a measurable health benefit from orlistat in
11 reducing the risks associated with obesity?
12 Thank you very much for your attention.
13 ACTING CHAIR SHERWIN: Thank you. Our next
14 speaker is Joyce Ritchey.
15 MS. RITCHEY: As a patient, I have no
16 financial interest in this program. I have paid all
17 of my expenses. My name is Joyce Ritchey. I've been
18 dieting since I was a teenager, some 38 years now,
19 with little success. I've tried fasting, fad diets,
20 even diet pills that made me hyperactive. The pills
21 cut my appetite but did not teach me about calorie
22 intake or the fat intake.
23 In my younger years I had three children
24 that were very active. During the week we ate on the
25 run and much of the food came from fast food restau-

1 rants. Fortunately, a few years ago I became aware of
2 a clinical trial to test a drug for obese people. I
3 needed help. The more the people commented on my
4 extra pounds, the more I ate.
5 I hated the way that people looked at me.
6 I knew that as soon as I was out of earshot I became
7 the topic of conversation. This leaves a sensitive,
8 caring person like myself, feeling alone, abandoned,
9 sluggish, and worthless. When I entered a room I
10 gravitated to other heavy people knowing that we
11 shared the same experiences of discrimination.
12 This trial drug gave me a jumpstart on
13 learning the process of maintaining my weight. I took
14 Xenical™ along with a balanced diet and an exercise
15 program to help me to a healthier life. Under this
16 control program I became aware of my fat intake and
17 met regularly with a Menninger Foundation support
18 team. This includes doctors, nutritional counselors
19 and staff members assigned to my case.
20 With this program I went from a size 24
21 dress to a size 14. In fact, this is a 14 petite.
22 This drug helped me learn a common sense approach to
23 a healthier, happier lifestyle. While on Xenical™ my
24 friends noticed quickly that I was losing weight.
25 This was a great incentive to continue the program.

1 Another major incentive was the birth of our
2 new granddaughter. I certainly want to be around to
3 watch her grow up. Thanks to the drug Xenical™, I am
4 physically ready to have an active life because of my
5 increased energy and my positive outlook.
6 You will never know how deeply grateful I am
7 to have had the opportunity to be a part of the
8 Xenical™ study. It has changed my life and my
9 family's life. I hope that Xenical™ will soon be on
10 the market so that others who have been in the same,
11 seemingly hopeless situation, will be able to see the
12 light at the end of the tunnel.
13 Thank you.
14 ACTING CHAIR SHERWIN: Thank you. Our next
15 speaker is Barbara Moore from Shape Up America.
16 DR. STERN: My name is Dr. Judith Stern and
17 I serve as a scientific advisor to Shape Up of
18 America. I'm also professor of Nutrition and Internal
19 Medicine at the University of California at Davis.
20 The President of Shape of America, Dr. Barbara J.
21 Moore, is unable to be here today and she asked that
22 I read her testimony. And my travel expenses are
23 being reimbursed for this meeting.
24 By way of disclosure -- now, I'm reading
25 from Dr. Moore's testimony -- of any possible conflict

1 of interest, let the record reflect that two pharma-
2 ceutical companies -- Wyeth Ayerst Laboratories and
3 Hoffmann-LaRouche -- are listed among the sponsors of
4 Shape Up America.
5 This means that they provide unrestricted
6 financial support for the educational activities of
7 Shape Up America. We are not accountable to either
8 company for the educational initiatives we undertake
9 or materials we produce.
10 When former Surgeon General, Dr. C. Everett
11 Koop, Chairman of Shape Up America, first testified
12 before this committee in January of 1995, and again in
13 November of 1995, neither company was a sponsor of
14 Shape Up America, nor were we in negotiations with
15 either company to become a sponsor. Dr. Koop testi-
16 fied then as I do now, because we believe it's the
17 right thing to do.
18 Approximately five years ago the FDA
19 commissioned a national telephone survey to discover
20 the dieting practices of Americans. That survey
21 revealed that dieting was a virtual, national pastime,
22 with record numbers of people attempting to lose
23 weight. In the spring of this year, Louis Harris
24 conducted another national phone survey of people with
25 a Body Mass Index of 25 or more.

1 We were surprised to learn that 78 percent
2 of these overweight and obese people reported that
3 they were not dieting to lose weight. Only 22 percent
4 of those surveyed reported that they are attempting to
5 lose weight. This is the reverse of what we saw five
6 years ago.
7 I would urge the committee to consider the
8 fact that in America, overweight and obesity preva-
9 lence are climbing even as American people shun
10 dieting and embrace physical activity. The rate of
11 increase of obesity is alarming. It is our under-
12 standing that the Federal Government is moving towards
13 adopting the international definition of overweight;
14 that is, a of BMI of 25.
15 Using this cut point, more than half of the
16 adult American population is overweight and the burden
17 of obesity falls disproportionately on the poor and
18 less educated, a group with less access to health
19 care. Consequently, the health care costs associated
20 with the disease, disability, and loss of economic
21 productivity of this group is a problem that we as a
22 nation, must face.
23 And the costs will be staggering. We
24 predict that the $100 billion estimated by the
25 Institute of Medicine in 1995 will be considered a

1 modest figure in the year 2005. As stated earlier,
2 there is a virtual epidemic of obesity, but we cannot
3 point to a single cause responsible for that epidemic.
4 There are multiple causes of obesity and there need to
5 be multiple treatment approaches.
6 The FDA and this Advisory Committee are to
7 be congratulated for allowing fast track evaluation of
8 new agents and for considering agents with novel
9 mechanisms of action. We are gratified that the FDA
10 is fostering an environment that will stimulate
11 innovation by allowing new products to come to market
12 that pass appropriate standards of safety and long-
13 term efficacy.
14 Finally, there is no compound for the
15 treatment of obesity as yet developed that replaces
16 the need for dietary and lifestyle change. These are
17 the bedrock upon which any effective therapy for
18 obesity must be based, and we have been gratified
19 because the emphasis that this committee and the FDA
20 have placed on the need to educate consumers and
21 health care professionals about this essential
22 foundation of dietary and lifestyle changes, and would
23 urge the committee to remain mindful of this as they
24 carry out their deliberations.
25 Thank you very much, for Dr. Moore.

1 ACTING CHAIR SHERWIN: Thank you. Our next
2 speaker is Dr. Charles Lucas, from William Beaumont
3 Hospital, Birmingham, Michigan.
4 DR. LUCAS: Thank you for the opportunity to
5 speak on behalf of myself and my patients. I am a
6 Xenical™ investigator and my way has been paid here
7 today, but in spite of that, I'd like to speak
8 personally about my own interest in treating obesity
9 and for my patients as well.
10 I'd like to show two slides, one of them
11 pretty much echoing what has been said by others
12 before. This is a patient -- just to show you how
13 long I've been treating obesity, the numbers on the X-
14 axis go back to 1979 -- so this woman has kept off
15 about 50 pounds over the course of 18 years.
16 She was on insulin when she started. She
17 had a nice drop in weight, and she's been able to
18 maintain that weight loss. If you look at her
19 hemoglobin A1c's you'll notice how well-controlled
20 they really are, and she's no longer on insulin now;
21 she's being taken care of with oral medications. I
22 don't think this woman would be alive today if she
23 hadn't lost this weight and hadn't done quite as well
24 as she has.
25 But everybody in this room also knows that

1 this is not the usual response that you get when you
2 treat people with obesity. In the some 10,000
3 patients that I've treated over the last 18 years,
4 we've done several surveys and the most recent one
5 showed, using this same approach -- diet, behavior
6 therapy, and exercise -- that only about one-third of
7 patients were able to keep off an average of about 20
8 pounds. The others had gained all of their weight
9 back again.
10 Then in 1992, the next slide, Dr. Michael
11 Weintraub gave us a great deal of hope, because using
12 the same technique, the same behavior modification,
13 diet, and exercise, you can see what happened. The
14 group that didn't get drug, the placebo group,
15 responded in over a 6-month period in the yellow, but
16 in the drug group you can see a much better response
17 that was sustained for at least a couple of years.
18 And I think this has given us all a great
19 deal of hope that we can do much better in the future
20 in the treatment of obesity. So we look forward to
21 development of many, many more drugs than we have
22 today; just as we have in the treatment of hyperten-
23 sion, we may have 10 or 12 drugs we can use. In the
24 treatment of diabetes now there are many, many more.
25 We're in the infancy stage in the develop-

1 ment of drugs for the treatment of obesity, and we
2 look forward to many, many more in the future for our
3 patients and for the doctors that treat these pa-
4 tients. Thank you.
5 ACTING CHAIR SHERWIN: Thank you. Our next
6 speaker is Jerry Earll -- Dr. Jerry Earll from
7 Georgetown University Medical Center.
8 DR. EARLL: Yes, I'm Jerry Earll, professor
9 of Medicine at Georgetown University. I was a
10 Xenical™ investigator. I was the head of the Eating
11 Disorders Unit at Georgetown. I am also an Endocri-
12 nologist and Internist. My patients, at least half of
13 them, are overweight and have hyperlipidemia, hyper-
14 tension, and diabetes.
15 The interesting thing about that is, these
16 patient wind up on five medications to correct the
17 metabolic errors of obesity. It's now possible to put
18 them on seven or eight because two or three new
19 medicines are available to slow the metabolism of
20 glucose, to slow its absorption. We have to think
21 about that because this is completely reversible --
22 the metabolic errors, all of them -- just by getting
23 the weight off, which is so nicely shown in this
24 slide.
25 One of the problems is that people feel

1 defeated because they have to go so far. That's the
2 main reason I -- in weight loss. That's the main
3 reason I wanted to talk today. Small losses in weight
4 reverse a huge portion of these metabolic defects, so
5 that you get nice corrections in hypertension. It
6 doesn't have to be 50 or 100 pounds.
7 Five percent or ten percent reduction in
8 body weight is a major improvement in your health. I
9 think there are studies readily available to show
10 that. Ten percent reduction in body weight and you
11 have lost 30 percent of the visceral fat, or the waist
12 fat. We understand that that is the dangerous fat in
13 the body.
14 We tell our patients that is literally like,
15 that your bowel is floating in a sea of fat when it's
16 there. It's no wonder that it feeds on that all night
17 and keeps your triglycerides up. Remember that you
18 could do a peritoneal dialysis from that huge surface
19 membrane in there when your kidneys weren't function-
20 ing.
21 So it's an exciting thing to think that
22 there may be something available that would help
23 reduce weight, that would help keep it off for long
24 periods of time. Our patients are -- they tolerate
25 the medicine very well in the study, and they're

1 asking for it.

2 Thank you very much.

3 ACTING CHAIR SHERWIN: Thank you. Our next

4 speaker is Dr. Patricia Solbach from the Menninger

5 Center for Clinical Research.

6 DR. SOLBACH: Thank you. I paid my own way

7 here. I have been Director of Clinical Research at

8 the Menninger Clinic since 1981 and have been doing

9 clinical trials, and this was my very first opportuni-

10 ty to be able to come to an FDA hearing. I paid my

11 own expenses.

12 The Menninger Clinic was paid for undertak-

13 ing this study. We carried out protocol NM14161

14 looking at the effectiveness and the safety of

15 orlistat for the treatment of obesity in a primary

16 care setting. And we did this work from 1993 to 1995

17 and I just want to share a few comments about it.

18 The Menninger Clinic is known for its

19 endeavors, its work, in the field of psychiatry, and

20 this obesity work was a first for us. We got involved

21 because of our doctors in Primary Care. We had three

22 physicians that were seeing patients from the Topeka,

23 Shawnee County area.

24 And as those patients would come in we

25 noticed -- you know, we were aging. Doctors were

1 getting older, patients were getting older, and we
2 became more and more aware of the number of patients
3 coming that we were treating for hypertension, who
4 were borderline diabetic, who were having orthopedic
5 difficulties.
6 And we were able to say, you know, these
7 patients are getting heavier. We have got to do
8 something more about treating, helping these patients
9 lose weight. Now, we did have in place there a
10 wonderful program for dietary counseling. Had a great
11 Nurse who had had juvenile onset diabetes; really knew
12 her diet counseling and was a real go-getter about
13 getting people to try to lose weight. But it didn't
14 seem to be working.
15 We pushed exercise, as I said; we pushed
16 diet. But it looked like we needed something more.
17 Now, our Primary Care doctors will be the first to
18 tell you they are not obesity specialists, but every
19 day they were seeing people coming in who were having
20 complications due to obesity.
21 So we looked around -- and I'm the clinical
22 arm of that department -- and we got together, we
23 looked around to see if there was anything ongoing for
24 the treatment, in new investigational drugs, and
25 contacted Hoffmann-LaRouche and got involved.

1 Well, we were actually not prepared for what
2 happened. We're a very, very small community; on a
3 good day about 150,000 people would claim Topeka,
4 Kansas as their home. And one of the reporters on the
5 local paper heard that the Menninger Clinic was doing
6 a study, had a new drug they were looking at, at no
7 expenses in getting involved, and it was for weight
8 loss.
9 Now, we also -- that brief mention also said
10 that Menninger was looking for patients with schizo-
11 phrenia and depression and anxiety. Well, I got a
12 phone call from the Menninger operator Saturday
13 morning when that came out, about 8 a.m., and said,
14 hey, you've got a couple of calls here, do you want to
15 take them or shall I tell them to call back in Monday?
16 Well, I thought nothing of it and said, call
17 me on Monday. But I should have paid more attention
18 there. What she said alerted me that I might have
19 something going on Monday. She said, oh by the way,
20 I want to get into that clinical trial myself. Now,
21 in the 20 years we've been doing clinical trials at
22 Menninger, no Menninger operator has ever volunteered
23 to come in.
24 Monday morning we came to work and the
25 Menninger Clinic processed 1200 phone calls, 48 hours

1 after that brief mention in the paper. Now I thought,
2 you know, probably, most of these are going to be size
3 10s wanting to come down to a size 6. Wasn't so. The
4 vast majority of these people qualified for that
5 study. We spent 15 minutes processing each and every
6 phone call. Everybody took calls that day.
7 Those people met the BMI criteria for that
8 particular study of anywhere from 30 to 43. They were
9 telling very genuine stories about how they had had
10 repeated, failed attempts at weight loss and they
11 really wanted to do something about it.
12 So we, for the first time ever, the Mennin-
13 ger Institution, which is 75 years old, had people
14 clamoring to get into it, and you don't often see that
15 in psychiatric settings. So we started processing
16 this.
17 Now, we had contracted originally with
18 Hoffmann-LaRouche for a month study. It ended up to
19 be a 2-year study, extremely challenging. We thought
20 we'd been there, done that, knew how to do clinical
21 trials -- we had done 70 -- but nothing prepared us
22 for the complexity of this trial.
23 We informed patients up front it was going
24 to be 24 visits to our Center and they had to be there
25 anywhere from one to six hours; had to notify employ-

1 ers, can they take a lot of time off work?

2 If we weren't asking them for detailed food

3 diaries to do for three solid days -- at least ten

4 times -- we were asking them to collect stool speci-

5 mens for 72 hours. I think we asked that at least for

6 four times. They were always in our laboratory; we

7 were poking and probing them. In other words, it was

8 a very complicated study and a lot of people gave

9 time.

10 Let me just close by saying, we have a great

11 need out there in Primary Care, to get something, to

12 get choices, and that was our intent -- to get

13 involved and to see that we could do something. Thank

14 you.

15 ACTING CHAIR SHERWIN: Thank you. Our last

16 speaker is Dr. Michael Hamilton from Duke University

17 Diet and Fitness Center. He's representing the North

18 American Association for the Study of Obesity.

19 DR. HAMILTON: Good morning. My name is

20 Michael Hamilton; I'm Director of the Duke University

21 Diet and Fitness Center. I was a Xenical™ investiga-

22 tor. Part of my expenses are being paid by Hoffmann-

23 LaRouche; part of my airfare I will submit either to

24 Duke or NAASO.

25 I'm reading a statement on behalf of

1 President of NAASO, Dr. Barbara Rolls, and President-
2 Elect Dr. James Hill, which reads as follows.
3 The North American Association for the Study
4 of Obesity, NAASO, would like to express concern that
5 obesity needs to be recognized as a serious medical
6 problem with many associated health risks and compli-
7 cations. It is a lifelong problem requiring long-term
8 treatment, exercise, and behavior modification
9 programs.
10 Approximately 35 percent of men and women in
11 the United States are considered obese, and we need to
12 work harder to develop the tools and solutions to help
13 these individuals. There has been a lack of success-
14 ful, long-term treatment and recidivism continues to
15 be a critical issue.
16 NAASO welcomes the addition of new obesity
17 treatments and commends the pharmaceutical companies
18 who are trying to do something about this problem.
19 Dr. Barbara Rolls, President of NAASO would welcome
20 today's approval of Xenical™ as providing another
21 treatment option for obesity when combined with diet
22 and exercise.
23 The mission of NAASO is to develop and
24 extend knowledge in the field of obesity, and to
25 facilitate personal contact between investigators in

1 broad fields related to this area of interest. Thank
2 you very much.
3 ACTING CHAIR SHERWIN: Thank you. I don't
4 know if that's Dr. Bone or not, but what we would like
5 to do now is begin the presentation of Hoffmann-
6 LaRouche. I asked the company to do their best to
7 keep on schedule because I think the critical part of
8 the meeting for us will be the questions, and we'd
9 like to finish the whole presentation -- including the
10 FDA -- by the morning, so that we can focus.
11 In exchange for that, we will not have
12 questions during the presentation except I'd ask the
13 committee, if there are specific points of clarifica-
14 tion because specific points in the presentation are
15 unclear to them, I think it's important that we raise
16 those issues at this time rather than waiting to the
17 afternoon.
18 I also ask the forgiveness of the company,
19 if at some point along the way in this presentation,
20 Dr. Bone is going to be hooked up -- and I'm not
21 exactly sure, and we'll do our best not to interfere
22 with the presentation -- but it might happen if that
23 happens. So I ask your indulgence.
24 So guess we can begin. The final thing is,
25 I'd like to thank the speakers for keeping their

1 remarks to five minutes. It really allows to move
2 along.
3 DR. ILLINGWORTH: Dr. Bone just called.
4 We're going to call him back.
5 ACTING CHAIR SHERWIN: I would like to wait
6 one second, even though this is a technologic miracle,
7 I think. We'll hopefully get him hooked up quickly
8 and that way we won't interfere with your presenta-
9 tion. In the next century I think we'll have him up
10 on a screen somewhere, but right now --
11 MS. REEDY: Actually, we could have today if
12 we had been in another building.
13 ACTING CHAIR SHERWIN: Okay. Welcome Henry.
14 CHAIRMAN BONE: Yes, welcome. I mean,
15 hello. Thanks.
16 ACTING CHAIR SHERWIN: Okay, now we want you
17 to keep quiet from now on.
18 CHAIRMAN BONE: I'm having a little diffi-
19 culty hearing, actually.
20 ACTING CHAIR SHERWIN: So now we'll begin
21 with the presentation.
22 DR. HAUPTMAN: My name is Jonathan Hauptman
23 and I work in the Clinical Research Department at
24 Hoffmann-LaRouche. In spite of the fact that over the
25 past decade there has been increased awareness of the

1 health benefits associated with weight loss, low-fat
2 diets, increased exercise and overall improvements in
3 healthy lifestyle patterns, there's paradoxically been
4 a dramatic increase in the percentage of Americans who
5 are obese and overweight.
6 The most recent National Health Surveys have
7 shown that this has increased from 25 percent to over
8 34 percent of the adult population. It's well known
9 that excess body weight is associated with increased
10 morbidity and mortality. Much of this is due to the
11 fact that obesity is responsible for producing or
12 worsening, important risk factors and comorbid
13 conditions, including hyperlipidemia, hypertension,
14 non-insulin-dependent diabetes, and glucose intoler-
15 ance.
16 Even a moderate degree of obesity has been
17 associated with as much as tenfold increase for the
18 risk of developing non-insulin-dependent diabetes.
19 And as little as being 20 percent above ideal body
20 weight has been associated with an 8-fold greater
21 incidence of hypertension.
22 Obesity by itself, has been shown to be an
23 independent risk factor for cardiovascular disease
24 which is the leading cause of death in the United
25 States. Abnormal lipid levels are also associated

1 with cardiovascular disease and are very common in the
2 obese, with up to 30 percent reported to have signifi-
3 cantly abnormal LDL cholesterols, HDL cholesterols, or
4 an unfavorable LDL to HDL ratio.
5 As we've learned over the past few years,
6 the association between obesity and cardiovascular
7 disease is not just a concern for men. The incidence
8 of stroke in women younger than 50, increases from 8
9 to 35:1000 as body weight increases from 10 percent to
10 greater than 30 percent above ideal body weight.
11 A woman with a BMI greater than 29 has a 3-
12 fold increased risk for a non-fatal, myocardial
13 infarction, or fatal coronary artery disease. It is
14 clear that there are probably many causes for this
15 increasing rate of obesity, but it's equally clear
16 that a disease as extensive and pervasive as obesity,
17 needs new and additional forms of treatments.
18 Over the past few years, the Endocrine and
19 Metabolism Division of the FDA has had several
20 meetings evaluating guidance criteria for the develop-
21 ment of drugs for the treatment of obesity. The idea
22 that treatment should be aimed at patients achieving
23 their ideal body weight has been replaced by the idea
24 that patients should be trying to achieve a healthier
25 body weight.

1 This healthier body weight can be obtained
2 by loss of even 5 percent from a patient's initial
3 body weight, and the longer the weight is kept off,
4 the greater the overall benefit to the patient,
5 because obesity is, after all, a chronic, relapsing
6 disease requiring chronic treatment.
7 To help achieve those goals, drugs should
8 not be considered a replacement for diet, counseling,
9 or exercise, but rather an addition to those treat-
10 ments, looking for an incremental benefit above that
11 which can be obtained from the standard of care for
12 weight loss as we know it today.
13 No matter what you may hear on TV or read in
14 supermarket checkout line newspapers, there really is
15 only one way to lose weight. You must produce an
16 energy deficit by having a lower energy input relative
17 to energy expenditure. Current pharmacologic treat-
18 ment consists only of central nervous system acting
19 anorectic drugs that achieve their lower energy input
20 by decreasing appetite, producing a general decrease
21 in the total food intake.
22 Recently, there's been a great deal of new
23 research looking at genetic causes for obesity, and
24 there is the potential somewhere in the future, for
25 genetic therapy. Nevertheless, there still is an

1 immediate need for other novel approaches of pharmaco-
2 logic therapy that can add valuable new treatment
3 options for doctors and their patients.
4 The drug that we're going to discuss today
5 is unique for several reasons. Unlike all the other
6 drugs available for the treatment of obesity, orlistat
7 is not an anorectic drug; it does not act in the
8 central nervous system. It does not require systemic
9 absorption for its effect; it acts locally within the
10 lumen of the gastrointestinal tract where it inhibits
11 the absorption of fat. And in fact, its pharmacoki-
12 netics profile shows that less than one percent of an
13 administered dose of orlistat is systemically avail-
14 able.
15 Most of the drug is passed in the body
16 unchanged, with the feces, and at the clinical use
17 dosage there is no evidence of accumulation over two
18 full years of monitoring. Now, since obesity is due
19 to an excess intake of calories, which many people
20 believe comes from fat, it would seem to make sense to
21 selectively inhibit fat rather than those calories
22 coming from protein or carbohydrate.
23 Fat from triglycerides cannot be absorbed
24 without first being hydrolyzed by the gastrointestinal
25 lipases, primary pancreatic lipase, into free fatty

1 acids. On this slide you can see the basic physiology
2 of fat digestion and absorption.
3 Ingested fat in the form of triglycerides,
4 enters the duodenum where pancreatic lipase splits it,
5 hydrolizes it into free fatty acids and monoglycer-
6 ides, which in association with bile acids forms
7 micelles, which are then transported to the lining of
8 the mucosal cell of the intestine where the free fatty
9 acids and monoglycerides are, transferred into the
10 mucosal cell, re-esterified, and then enter through
11 the lymphatic system into the rest of the body.
12 Orlistat is an inhibitor of gastrointestinal
13 lipases and works locally within the intestinal lumen
14 to prevent the absorption of fat by inhibiting the
15 activity of these key enzymes.
16 As you can see on this slide, orlistat binds
17 the pancreatic lipase, rendering much of it inactive.
18 Some of the ingested fat is not broken down and
19 therefore is left unabsorbed to leave the body through
20 the intestinal tract. The arrow in red shows that
21 activity.
22 The calories in that fat are no longer
23 available as an energy source, and additional weight
24 is lost by producing a constant, caloric deficit above
25 and beyond that which can be achieved by dietary

1 change alone.

2 Since obesity is a chronic disease, the
3 emphasis of our program is long-term treatment. The
4 majority of our Phase III studies were two years in
5 duration. This enabled us not only to evaluate weight
6 control for two years, but also to prospectively
7 evaluate the effective treatment in obesity-related
8 risk factors. Up until now, this has not been done by
9 on any systematic basis for other weight loss drugs.

10 We conducted seven, Phase III clinical
11 studies in over 4,000 patients and what we've seen is
12 that these studies consistently have shown that
13 orlistat, as part of the overall weight management
14 program, helps to produce long-term, clinically-
15 meaningful weight loss. Our studies also demonstrated
16 favorable effects on risk factors associated with
17 obesity.

18 I'd now like to show you how we evaluated
19 orlistat's effects. In order to do that, we conducted
20 a series of pharmacodynamic studies looking at
21 increased fecal fat as an endpoint, since weight loss
22 by itself can't be done in the short term.

23 And this is a typical type of study. In
24 this study we had obese volunteers who entered a
25 clinical pharmacology unit during time periods -4 to

1 day -1. They were stabilized on an 1800 calorie diet
2 with about 60 grams of fat -- 30 percent of the
3 calories.
4 And you can see, this is their mean fecal
5 fat which we collected on a continuous basis, and the
6 range in the fecal fat during the lead-in period is
7 around 2 to 4 grams per day, which is normal. At day-
8 1, patients were given orlistat, 120 milligrams, three
9 times a day, with meals.
10 And within a very short period of time, two
11 or three days, we reached a maximum of effect, in
12 which about 20 grams per day, or about 30 percent of
13 the ingested fat is excreted, and it stayed as a
14 steady-state during the rest of the treatment until
15 the end of day-10, which is the last day of dosing.
16 Within several days of stopping that, the
17 amount of fat in the feces came right back down to
18 where it started. So we can see that there's a rapid
19 onset of effect and a rapid cessation once the drug is
20 stopped. When we looked at a large series of studies
21 with orlistat doses with different amounts of fat in
22 the diet, we were able to put together a dose response
23 model. And the next slide will show you the pharmaco-
24 dynamic dose modeling.
25 On the horizontal axis we have several

1 different doses of orlistat that we used in our
2 studies, and on the vertical axis we had fecal fat
3 excretion as the percent of an ingested amount of fat
4 that's been excreted into the feces.
5 Going from 30 milligrams, which produced
6 about the minimum effect, three times a day, up until
7 120 where it reached a peak. And then from 120, if
8 you double the dose to 240 milligrams three times a
9 day, or almost quadruple it to 400 milligrams three
10 times a day, there's very little additional effect,
11 and that the maximum percent of ingested fat excreted,
12 looking at this model, was 38 percent of that's what's
13 ingested.
14 At the 120 milligram dose we obtained an
15 effect of about 85 percent of the maximal effect.
16 Still, one-third percent of the fat was inhibited,
17 two-thirds of the fat was still absorbed. Based on
18 all the data that we conducted with several dose range
19 finding study -- we conducted several dose range
20 finding studies based on this data -- the longest and
21 the largest was a study done with doses of 30, 60,
22 120, and 240 milligrams three times a day for six
23 months, looking at weight loss as the endpoint.
24 Based on the weight loss differences between
25 the active drug and the placebo, the 240 milligram

1 dose did the maximal effect and for purposes of
2 comparison, on the next slide I'll present the results
3 of the other doses in comparison to the maximum weight
4 loss.
5 There we see the 240 milligram in gray, and
6 that was 100 percent which we called the maximum
7 amount. The 120 milligram dose produced about 91
8 percent of the maximum amount of weight loss; whereas
9 the 30 milligram and the 60 milligram produced
10 significantly less.
11 The side effects on 240, however, were the
12 greatest, whereas the 60 and 120 milligram dose in
13 terms of side effects, were very, very similar.
14 Therefore, based on the balance between efficacy and
15 tolerability, we felt confident that the 120 milligram
16 TID dose was the optimal dose and we planned our Phase
17 III program around those doses.
18 Now I'd like to discuss for the rest of the
19 program, our Phase III clinical trials. As I said
20 before, we did seven, large, double-blind, randomized,
21 multi-center, placebo-controlled trials in over 4,000
22 patients. Four of those studies were two years in
23 duration, and three of the studies were one year. One
24 of those 3-year studies was a study done specifically
25 in obese patients with non-insulin-dependent diabetes

1 requiring hypoglycemic medication.

2 The clinical program that we just discussed
3 evolved according to discussions with the FDA at the
4 end of our Phase II meeting in 1992. Although the FDA
5 guidance criteria became public in 1995, we feel that
6 the design of our program meets these criteria. The
7 program was designed not only to describe the effects
8 on weight loss, but also to characterize the effects
9 on other obesity-related risk factors.

10 The program contains a large number of
11 patients also studied for up to two years of duration.
12 The importance of having 2-year studies was to gain
13 sufficient understanding of the safety on a chronic
14 administration basis, as well as to demonstrate
15 continued pharmacologic effect over two full years of
16 treatment.

17 The 2-year studies were developed to look at
18 different issues in the first year compared to the
19 second year of the studies. Our goal in the first
20 year of the 2-year studies and our 1-year studies was
21 to produce weight loss and to maintain that loss. All
22 patients received the high standard of care that we
23 could provide them, and the program was designed for
24 weight loss to occur even without a drug.

25 All patients were placed on a mildly

1 hypocaloric diet, and the diet that was used was
2 generally based on published formulas to evaluate
3 their basometabolic rate, we corrected that for an
4 activity level, and then from that we subtracted
5 approximately 600 calories. And for most patients
6 that was about a 20 percent decrease in their caloric
7 intake. We wanted to put together a diet that could
8 be maintained long-term, but still produce at least
9 initially, about a quarter to a half-a-kilogram per
10 week.
11 We also had dietary counseling. In many of
12 the studies we used dieticians, and in all the studies
13 we filled out diet records on a continuing basis and
14 used them in several of the studies as feedback for
15 the patients. In other studies they weren't given the
16 feedback; we just used them for our internal purposes
17 for evaluating the results.
18 We also had behavior modification as a major
19 part of our program. This was done by psychologists
20 or other behavior modification specialists. In
21 addition, we had frequent clinic visits; initially
22 every other week and then every month, for the first
23 full year.
24 Therefore, the placebo-treated group really
25 was an active comparator. The studies were designed

1 to test and quantify though, the additional effect of
2 orlistat on an already effective weight loss program.
3 The second year differed from the first year
4 of the program in that the goal was to help prevent
5 weight regaining after you've already had a weight
6 loss. As hard as it is to lose weight, the natural
7 tendency is to regain it. The literature says on
8 average, within one year of losing weight, 60 percent
9 of that weight is regained and most people find it's
10 far greater than that.
11 So the purpose of the second year was to try
12 to evaluate if orlistat could in fact, decrease the
13 weight regain that naturally occurs. In order to do
14 that, the studies had to be deigned in a way to ensure
15 that some weight regaining would occur in order to
16 test out the drug effect. Now, what we tried to do
17 was mimic what very often happens in extended care
18 situations.
19 The diet was changed at the end of the first
20 year to meet the patient's new body weight. We used
21 the same formulas to estimate the energy expenditure,
22 but at that point we didn't give a caloric deficit.
23 And based on some newer information that's been
24 recently published in the literature, this might have
25 been an over-estimate of the caloric needs for a

1 reduced obese individual. Nevertheless, the results
2 you will see, are very consistent.
3 Also, counseling now was changed. It wasn't
4 counseling to lose weight; it was counseling to
5 diminish the weight regained -- more of a maintenance-
6 type of counseling. If patients actually began to
7 regain weight during the second year, they were not
8 allowed to go back on a hypocaloric diet. Rather,
9 they were encouraged to stay at whatever their new,
10 higher body weight was.
11 We also had longer intervals between clinic
12 visits, up to two months -- every other month -- which
13 is also more likely to happen in the outpatient
14 setting.
15 I'll present data now from the primary
16 efficacy parameter first, and then I'll present data
17 from our obesity-related risk factors later. Although
18 all our studies were very, very consistent in their
19 effect, I've chosen two representative studies to show
20 you the data. Both of those studies are two years in
21 duration and they evaluate major aspects of the weight
22 control program.
23 This study is a typical study -- it's study
24 BM14119C -- and this was conducted by our colleagues
25 in Europe. After patients were screened to eliminate

1 those with unstable, chronic, or acute medical
2 conditions, patients entered into a placebo lead-in
3 period between week -4 and zero.
4 The purpose of that placebo lead-in period,
5 while being on a hypocaloric diet, was to identify
6 those patients more capable of complying to diet and
7 other procedures. The amount of weight loss that
8 occurs in a 4-week lead-in period has been shown in
9 the literature to be a good predictor of subsequent
10 ability to lose weight. So this is needed in order to
11 balance the groups.
12 If for some reason, you had all good losers
13 in the drug group and all poor losers in the placebo
14 group, you would see a very exaggerated effect of the
15 drug -- or the other way around. By doing this we
16 ensured that both treatment groups had equal numbers
17 of potential good losers and potential bad losers.
18 We used a loss of two kilograms in that 1-
19 month lead-in period to stratify the patients. No
20 patient was eliminated if they gained weight during
21 that period. Even if a patient gained weight during
22 the placebo lead-in period, they were still randomized
23 into the study.
24 After the placebo lead-in period, while
25 being on a hypocaloric diet, half the patients in this

1 study were put on placebo, half were put on 120
2 milligrams of orlistat three times a day. At the
3 second year when we changed the diet, patients were
4 then given what we call a eucalaoric diet, or a diet
5 that was supposed to meet their energy needs after
6 they've lost weight.
7 Half of those patients in each group were
8 then re-randomized to placebo or orlistat. And we'll
9 discuss the second part later. But first I'll show
10 you the demography of the patients entering the study.
11 This was a large study; over 680 patients
12 entered. The majority of the patients, as is fre-
13 quently seen in weight loss studies, were women. The
14 age on average, was 44. This study being done in
15 Europe, the majority of the patients were white and
16 they had a body mass index as a mean of 36. The body
17 mass index range was from 28 to over 43.
18 Now we'll take a look at the withdrawal
19 rate. The withdrawal rate in this study was relative-
20 ly low compared to what you see in the literature.
21 The literature shows on average, 40 to 45 percent of
22 the people during one year of treatment will withdraw
23 from a clinical study. This was slightly better. It
24 was about 24 percent of the placebo patients withdraw-
25 ing for any reason, and close to 18 percent of the

1 orlistat patients withdrawing for any reason. We'll
2 discuss adverse events later in the safety section.
3 Now I'm going to show you the results, which
4 are the mean changes over time, of the weight loss and
5 maintenance of lost weight for both the placebo
6 patients and the orlistat patients. This is from our
7 intent-to-treat population, meaning that patients had
8 to enter and have just one follow-up visit and they
9 were included.
10 During week -4 to zero, during the placebo
11 lead-in period, there was close to a 3 percent
12 decrease in all patient's body weight. Then at time
13 zero when patients were randomized to orlistat or
14 placebo, there was an immediate difference in the
15 effect. The people on placebo had a decrease that
16 lasted until about week 24 to 28, and then plateaued,
17 so by the end of the study their mean decrease was
18 about 6 percent of their starting weight.
19 Those patients on orlistat had a greater
20 immediate effect and a continued effect. They
21 continued losing weight until week 36 in which they
22 plateaued and maintained that weight. So by the end
23 of the study they had lost slightly more than 10
24 percent of their initial body weight. We believe that
25 this is a very vigorous test of the effect of orlistat

1 since the placebo group lost a considerable amount of
2 weight.
3 Now, statistical significance was tested in
4 this study using least square mean differences between
5 the orlistat group and the placebo group from random-
6 ization until the end of treatment using the last
7 observation carried forward technique. Yes?
8 MALE VOICE: What was the actual average
9 pound weight loss?
10 DR. HAUPTMAN: The average weight loss was
11 about 6 kilos versus 10 kilos, because the mean
12 starting body weight was 100 kilos, on average. And
13 this was statistically significant with p of less than
14 .001. Now, in your briefing documents you'll find
15 similar graphs and standard error bars and other
16 supporting data, including 95 percent confidence
17 intervals, if you'd like to take a look at that.
18 I'll next show you the completers popula-
19 tion. It looks very similar -- in fact, it's virtual-
20 ly the same -- 6.2 percent versus 10.2 percent. And
21 in the completers population the placebo group was
22 approximately 73 percent of all patients and the
23 orlistat group about 78 percent of all patients.
24 The next measure of efficacy I'm going to
25 show you is a responders analysis which looks at the

1 percent of patients losing at least 5 percent of their
2 baseline body weight, or 10 percent of their baseline
3 body weight. Now, this does not include the amount of
4 weight that was lost during the 4-week lead-in period;
5 it's any weight after that.
6 Again, 55 percent of orlistat patients lost
7 at least 5 percent of their body weight, compared to
8 only 27 percent of the placebo patients. And 25
9 percent of the orlistat patients lost at least 10
10 percent; that's three times more than the placebo
11 patients.
12 Now, this is based upon change from baseline
13 and the statistical data was performed using the last
14 observation carried forward again, and the difference
15 was highly significant. I'll show you now the
16 completers population which shows a slightly greater
17 amount of weight loss.
18 It was 66 percent of the patients on
19 orlistat lost at least 5 percent of their initial body
20 weight, versus only 33 percent of those on placebo.
21 And again, about 30 percent lost more than 10 percent,
22 versus about 10 percent of the placebo patients.
23 Now we'll talk about the second year of the
24 study. I blacked out the bottom because each of these
25 two separate legs of the study are almost like looking

1 at different studies. Because in the first group we
2 looked only at those people on placebo in year-1 who
3 then got re-randomized to orlistat or placebo in year-
4 2.
5 Remember, this is the time they had their
6 diet changed, their counseling changed, and the whole
7 paradigm of the program shifted trying to prevent the
8 regain of whatever they lost. And we'll look at the
9 total effect over one year.
10 In the white, from week -4 to week 52, are
11 those patients who lost weight on placebo only, and
12 then from week 52 out to week 104, is the amount of
13 regain. And as you can see, the placebo people began
14 to regain weight very quickly, whereas those patients
15 on orlistat actually continued and had additional
16 weight loss.
17 And if we look at that, these differences
18 were highly different statistically. If we look at
19 the mean percent regain of lost weight, the patients
20 on placebo regained 43 percent of what they had lost
21 that first year, while the patients on orlistat
22 actually lost an additional 15 percent more.
23 Now, another way to look at regain, other
24 than this, is to look at it as a quartile analysis,
25 and this has been done in the literature, so I'm just

1 going to reproduce some of that type of information.
2 That means you look at the percentage of
3 patients who regained less than 25 percent of what
4 they lost -- which is considered a very, very good
5 response -- and you look at those patients that
6 regained more than 75 percent -- which is essentially
7 a failure -- and then take a look at the quartiles in
8 between that show you very interesting data as well.
9 Now, the analysis that we did included
10 patients who lost at least 5 percent of their initial
11 weight, which is the minimum thought necessary for
12 medical benefit. At the left of the slide where it
13 says, less than or equal to 25 percent, 72 percent of
14 the orlistat patients regained less than 25 percent of
15 what they had lost that first year. And that compares
16 to 49 percent of those patients on placebo.
17 At the other end of the spectrum, those
18 patients regaining virtually everything they had lost,
19 it was 13.6 percent for the placebo group and only 6
20 percent for the orlistat group. And in fact, those
21 people regaining 50 to 75 percent -- which is also not
22 a very good response -- it was approximately 22
23 percent of the patients on placebo but virtually no
24 patients on orlistat, because their entire shift was
25 to the left, here.

1 And in fact, of those patients on orlistat
2 who regained less than 25 percent of what they
3 regained, half of them regained absolutely no weight
4 at all.
5 Now we'll look at the second leg of the
6 study which are those patients who lost more weight to
7 start with because they were on drug, and they were a
8 homogenous group of patients, and then they got re-
9 randomized to either placebo or orlistat again.
10 Here you see that on average, the weight
11 loss in the first year was about 10 percent and then
12 at the time that we switched the drug -- re-randomized
13 drug and placebo, or switched the study paradigm --
14 the placebo patients had an immediate regain of their
15 lost weight, whereas those patients on orlistat had a
16 much slower rise, and actually began to plateau a bit
17 near the end.
18 Again, looking at this -- and those differ-
19 ences were, again, highly statistically significant --
20 we look at mean percent regain of lost weight. The
21 patients on placebo regained 52 percent on average, of
22 what they had lost, and that compares to only 26
23 percent of the people on orlistat. So as you can see,
24 this shows much better than what the literatures shows
25 of 60 percent for the orlistat group. But the placebo

1 group comes very close to what we see in the litera-
2 ture, without the additional benefit of pharmacologic
3 therapy.
4 Once again now, we'll look at the quartile
5 analysis to see if we can understand where these
6 differences occur. And again, on the left side of the
7 slide, those patients -- over 56 percent of patients
8 regained less than 25 percent on orlistat, compared to
9 23 percent of the placebo patients. And again, half
10 of those patients in that group on orlistat regained
11 no weight at all. And these were overall significant
12 as well -- p was less than .001.
13 And what's actually quite interesting on
14 this slide is that each of the placebo group breaks
15 out quite nicely into these four quartiles -- the same
16 percentage of patients -- whereas there's an obvious
17 increase of those patients on orlistat who regained
18 very little of what they had lost.
19 I now want to show you a study that was done
20 in the United States. This is study NM14185. It was
21 done a little bit differently than the previous study,
22 but had very similar study design concepts to it.
23 After the 4-week placebo lead-in period when patients
24 were stratified, 25 percent of the patients were
25 placed on placebo and 75 percent were given orlistat,

1 along with the hypocaloric diet.

2 At the end of the first year, those patients

3 on placebo continued on placebo and those patients on

4 orlistat went on to either placebo or 120 milligrams

5 three times a day, or 60 milligrams -- an intermediate

6 dose, to see if we had any differences there.

7 This was also a very large study. There

8 were over 880 patients in this study -- exactly 880

9 patients. The demographic distribution of males and

10 females was again, very similar to our previous

11 studies. And this study, because it was done in the

12 United States, is a larger representation of minori-

13 ties, but the weight and the body mass index average

14 was about the same as the previous study.

15 The withdrawal rate in this study was a bit

16 higher than previous studies that I previously today

17 showed you -- about 38 percent for placebo and 31

18 percent for the 120 group -- but still less than what

19 you would expect from what the literature shows.

20 Now I'm going to show you the mean loss

21 again, over time, like you've seen before, and you see

22 a very, very similar curve. During the placebo lead-

23 in period the mean loss was about two-and-a-half to

24 two-and-a-quarter pounds, and then as soon as you

25 started orlistat treatment there was a separation in

1 the effect.

2 Those patients on placebo had less weight
3 and then plateaued and maintained that weight, so by
4 the end of the study they had lost about 5.8 percent
5 of their initial body weight. And those patients on
6 orlistat had a greater decrease that continued for a
7 longer period of time, and their decrease at the end
8 of the study was about 9 percent; slightly less than
9 the study that was done in Europe, but still highly
10 different statistically based on last observation
11 carried forward and least square mean differences.

12 When we look at the responders analysis we
13 see once again, a very similar pattern. Forty-three
14 percent of orlistat patients lost at least 5 percent
15 of their baseline body weight compared to only 22
16 percent of those patients on placebo. And 18 percent
17 of orlistat patients lost at least 10 percent of their
18 body weight compared to only 10 percent of those
19 patients on placebo.

20 Look at the completers, and for the complet-
21 ers the numbers are: 55 percent of the orlistat
22 people versus 33 percent of those patients on placebo.
23 So it's 55 versus 33 and for those patients losing
24 more than 10 percent, it was 25 percent of the
25 orlistat patients versus 15 percent.

1 Now I'd like to show you that second year;
2 what happens when you then re-randomize the patients
3 in the second year to the three different doses. The
4 white is the placebo, the blue is 60 milligrams three
5 times a day, and the yellow continues to be orlistat,
6 120 milligrams three times a day.
7 And you see the same exact pattern. Those
8 people who were randomized to placebo had a relatively
9 rapid increase in their body weight, approaching close
10 to what their baseline body weight was, anyhow. Those
11 patients on 120 milligrams really kind of increased a
12 little bit then plateaued, and those people at 60 were
13 somewhere in between.
14 You can see that better in terms of mean
15 percent regain of lost weight. The placebo patients
16 regained, on average, over 63 percent of the weight
17 they had lost, whereas the people on orlistat 120
18 regained only 35 percent of what they had lost. the
19 60 milligram group did worse than the 120, regaining
20 about half of what the patients lost.
21 We did another study very similar to this
22 looking again, at regain at different doses, including
23 the 60 and the 120 milligram dose, and in that study
24 only 120 milligrams three times a day was statistical-
25 ly significant. Sixty milligrams as well as 30

1 milligrams, had no benefit in regain during the second
2 year.
3 This is a quartile analysis again, of the
4 185 study looking at the placebo and the 120 group,
5 and we see once again, the highly significant,
6 statistically meaningful difference, very, very
7 similar to what we've seen before. And again, in this
8 study, of those patients regaining less than a quarter
9 of what they lost on orlistat, half regained no weight
10 at all, so they were very successful.
11 So both of the studies that we've shown you
12 so far looking at body weight changes, have shown a
13 very, very similar effect. But now I'd like to show
14 you some data on two full years of treatment, because
15 these studies that I've shown -- the 185 and the 119C
16 -- were not designed to look initially at two full
17 years in the same treatment, but other studies did.
18 This is study BM14149 in which we looked at
19 patients who were on the same dose of medicine --
20 orlistat or placebo -- for two full years. Again, the
21 first year was the hypocaloric diet and the second
22 year was the eucaloric, or regain portion of the
23 study.
24 And what we see here is a very, very
25 consistent effect. During the first year, the type of

1 weight loss that you see is very similar to all our
2 other studies. After 52 weeks of randomized treatment
3 the additional benefits of orlistat are the greatest.
4 And during the second year, despite the fact
5 that there is some regain of lost weight due to the
6 change in our study design and study procedures, the
7 differences between placebo and orlistat remain the
8 same out through the end of the two full years,
9 showing that the pharmacologic effect producing the
10 additional benefit of orlistat, is being maintained.
11 Now, just for comparison purposes, I'll just
12 show you briefly again, the 119C study and the 185
13 study, where we show you those legs that we connected
14 placebo to placebo, and 120 to 120, to show you the
15 similarity of the effect.
16 This is the 119C study and this is the 185
17 study. So all these studies have shown, over two full
18 years, the pharmacologic effect of orlistat has
19 maintained -- the weight maintaining or weight
20 reducing effect of orlistat is maintained in that
21 first year. We were able to prevent regaining during
22 that second year. The studies were not designed to be
23 hypocaloric throughout the two full years of treatment
24 because it was a study designed looking to see if we
25 can prevent what is the normal occurrence of weight

1 regain.

2 So just to summarize what we've seen in
3 terms of the primary endpoint of weight loss, orlistat
4 produces clinically meaningful, sustained weight loss.
5 There's a greater mean weight loss over time. The
6 placebo lost an appreciable amount of weight but the
7 orlistat patients lost considerably more -- an
8 additional 50 to 75 percent more -- and they were able
9 to keep it off.

10 Twice as many patients on orlistat lost at
11 least 5 percent of their baseline body weight, and two
12 to three times as many patients lost at least 10
13 percent of their baseline body weight. We were able
14 to show that orlistat diminishes weight regain. On
15 average, patients on orlistat regained only half as
16 much as those patients on placebo, and the weight
17 regain effect was shown during that second year as
18 well.

19 And we were able to show that orlistat was
20 effective long-term. And on average, at the end of
21 two full years, patients on orlistat lost, from their
22 very initial and kept off, more than seven-and-a-half
23 percent of their initial body weight, which is
24 compared to only half that in the placebo group.

25 Now we're going to turn our attention to

1 obesity-related risk factors, which we heard this
2 morning, are a very important part of overall obesity
3 treatment. We looked at the following factors -- we
4 looked at others as well, but these are the ones that
5 I thought we could present in a reasonable amount of
6 time.
7 Now, looking at obesity-related risk
8 factors, we wanted to see not just the overall effect
9 on all these risk factors, but we wanted to look at
10 those patients that actually had abnormal values at
11 baseline. Therefore, to be able to analyze this
12 important group of patients, we did a meta-analysis
13 since all our studies were designed in a very similar
14 manner and that we have an integrated database that
15 will allow us to do that.
16 Nevertheless, the results from individual
17 studies for these other parameters, are absolutely
18 consistent. This is LDL cholesterol mean percent
19 change. Let me show you how we're going to take a
20 look at that. The results of these are going to be
21 shown, like we've seen here, over time to look for
22 just the mean change over baseline and the extent and
23 the duration of the effect.
24 First, the important thing is to notice that
25 the number of patients in the placebo group was over

1 1100 patients in the integrated data base, and over
2 1500 patients on orlistat. What this slide shows is,
3 during that 4-week placebo lead-in period, which is
4 just diet alone, there is a pretty reasonable amount
5 of decrease in LDL cholesterol values -- about 8
6 percent compared to the baseline value.
7 Then at the time of randomization, all
8 patients were still losing weight, as they continued
9 losing weight, those patients on placebo actually
10 began to have an increase in their LDL cholesterol and
11 then plateaued.
12 But by the end of the study, their value was
13 still lower than their initial value, but higher than
14 their baseline value; whereas, those patients on
15 orlistat had an additional decrease and then main-
16 tained that during the rest of the time. And the
17 differences, the least square mean differences,
18 between the placebo group and the 120 group, were
19 highly significant.
20 Now we'll take a look at those patients who
21 have an LDL cholesterol at baseline of greater than
22 130 -- or 3.6 millimoles per liter -- and that was
23 after four weeks in of appropriate hypocaloric, low
24 calorie, low fat diet.
25 What this slide shows us is that the amount

1 of LDL lowering during the lead-in period in these
2 patients was much less -- in the range of only 3 to 4
3 percent. And then after randomization, those patients
4 on placebo were really flat and maintained that lipid
5 lower level for the entire length of the program.
6 Those patients who were on orlistat had an
7 additional 8 to 10 percent decrease in their LDL
8 cholesterol value, and maintained that almost for the
9 entire time. And the differences here, based on least
10 square mean differences also, were highly significant.
11 Now we'll look at year-1 and year-2 in terms
12 of change from initial, for comparison purposes, to
13 see if the results are maintained over two full years.
14 And what we see here is that the placebo and orlistat
15 effects are very similar, that the differences between
16 treatment effects are similar, and maintained during
17 the end of the second year. And this is last observa-
18 tion carried forward, and the differences here are
19 highly significant.
20 The next thing we looked at were LDL
21 cholesterol. During the placebo lead-in period, all
22 patients were on placebo on the weight loss diet.
23 There was about 10 percent decrease for all patients
24 on the LDL cholesterol. At the time of randomization,
25 while the diet was continuing, there was an increase

1 in both the placebo group and the 120 group from their
2 baseline value.
3 By the end of the study, both groups were
4 higher than their initial value, but there was a
5 difference, about two-and-a-half percent, between the
6 placebo and the orlistat group, and that was however,
7 statistically significant. If you look at those
8 patients --
9 ACTING CHAIR SHERWIN: You are referring to
10 HDL cholesterol?
11 DR. HAUPTMAN: Yes, the HDL cholesterol, I'm
12 sorry. That the difference is significant, but both
13 of those are still higher, and from the time that they
14 were actually put on orlistat or placebo, they
15 actually increased from their baseline value.
16 The drop that occurred during the placebo
17 lead-in period is probably due to the low-fat,
18 hypocaloric diet, and it's also probably due to the
19 fact that the majority of the patients were women, and
20 it has been shown that in the initial part of dieting,
21 women actually have a decrease in the HDLs greater
22 than men do. But then as weight loss continues, the
23 HDL values increase over time.
24 Now we'll look at the subgroup of patients.
25 These are patients who have an HDL value of less than

1 .9 millimoles per liter, or less than 35 milligrams
2 per deciliter at baseline. And again you see a
3 relatively large drop between week -4 and zero, when
4 everybody's on placebo and diet.
5 And then you see a rather brisk increase,
6 and so by the end of 52 weeks, both the placebo group
7 and the 120 milligram group are essentially the same.
8 The differences are not significant and they're all
9 higher than their initial value.
10 And this shows you that by the end of year-
11 2, also the differences are not there; that both
12 orlistat and placebo have increases from their
13 baseline value, but the differences between treatment
14 effects aren't there. But to put all this in perspec-
15 tive we looked at the LDL to HDL ratio.
16 And here, the LDL to HDL ratio shows a very
17 similar pattern to what we've seen before; that at the
18 time of randomization there's a decrease in both the
19 placebo group and the orlistat group -- about a 50
20 percent greater effect with orlistat than placebo, 50
21 to 100 percent -- and these differences are highly
22 significant.
23 If you look at those people that start off
24 with an LDL/HDL ratio of greater than 3.5 -- which is
25 a risk -- you see an even greater effect. For reasons

1 that we don't have an explanation, there was a small
2 increase, probably due to the fact that there was a
3 decrease in HDL during the 4-week lead-in period. And
4 then from their high point, which is baseline, until
5 the end of treatment for one year, the people on
6 orlistat had a significantly greater decrease compared
7 to placebo.
8 And now we can look at two full years of
9 this sub-population which started off with an elevated
10 LDL/HDL ratio. And here you see essentially the exact
11 same figure; that the effect of orlistat, in terms of
12 the differences between treatment with orlistat or
13 treatment with placebo, were essentially the same --
14 unchanged.
15 Next we'll look at diastolic blood pressure.
16 Again, I think one of the most important things that
17 we've seen in our studies is, you can't underestimate
18 how much even a small change in diet can have an
19 effect, even in a 4-week period, because here, just
20 the fact that patients were changed to a hypocaloric,
21 low-fat diet, there was a 3 millimeter decrease in
22 mercury compared to their baseline value.
23 At the time of randomization to orlistat or
24 placebo, the people on placebo had a very small
25 increase in their diastolic blood pressure, whereas

1 those patients on orlistat had a further decrease.
2 The differences are small, but they were statistically
3 significant. The difference between treatments is
4 about one-and-a-half millimeters of mercury.
5 Okay, now what we'll do is show you the
6 diastolic blood pressure greater than 90, again
7 looking at -- well, this is actual data here, millime-
8 ters of mercury -- but you can see here, during the
9 lead-in period at the time of time zero, the blood
10 pressure here, for example, is 94. And then between
11 time week-zero and week-52, the placebo groups drops
12 from 94 down to 83, and the people on orlistat drop
13 from 94 down to about 85.
14 And that's the absolute effect of the drug.
15 But the differences here did not quite meet signifi-
16 cance. The p-value is .06. Now we'll show you the
17 comparison to the first year and the second year as
18 well. Again, in terms of millimeters of mercury, mean
19 change between treatment groups, there is always an
20 effect, an additional benefit -- both groups had a
21 decrease, but there was always that additional benefit
22 in the people on orlistat.
23 The next thing that we'll look at in terms
24 of secondary efficacy parameters and risk factors, are
25 fasting insulin levels. And in this instance we don't

1 have initial values for the U.S. so everything, in
2 order to show both the U.S. and non-U.S. combined and
3 integrated, will go from just time-zero, but the
4 results are very similar.
5 You see a separation between effects with a
6 difference in placebo and orlistat, and again, the
7 differences here are highly significant. Although
8 they're small they're still significant and always in
9 the favor of additional benefit of orlistat.
10 When you look at those people who have a
11 baseline fasting insulin greater than 90 -- or greater
12 than 15 if you use conventional units -- for example,
13 these people start at the time-zero with a mean value
14 -- for both orlistat and placebo -- of a value of 150
15 picamoles per liter, and then by the end of treatment
16 those people on placebo are at a level of 146 pica-
17 moles per liter; whereas those people on orlistat
18 dropped from 150 down to 125 -- a difference of about
19 15 picamoles.
20 And if you look at least square mean
21 differences, it's 20 picamoles, and the differences
22 were highly significant. And that 20 picamoles
23 translates to about three-and-a-half units of insulin.
24 And then we look here and we see by the end of two
25 years, there's even a greater difference over time.

1 In our studies we also did glucose tolerance
2 testing in a very large percentage. On placebo we had
3 400 patients in which we obtained glucose tolerance
4 testing; in our orlistat 120 group we had 800 pa-
5 tients. And we'll next look at the mean change in
6 glucose, insulin, and C-peptide over time.
7 For glucose at the baseline, for the people
8 on placebo, their values were -- this is AUC 9.5 and
9 the 120 group was 10.23, so they're very similar.
10 There was a small increase after year-1 for glucose in
11 the placebo group, and a decrease of about 15 percent
12 for those people on orlistat, and these differences
13 were in fact, significant.
14 The same thing holds for insulin and C-
15 peptide. For insulin there was a small decrease in
16 the people on placebo, and a much larger decrease of
17 those people on orlistat, and the same thing happens
18 for C-peptide. And for both insulin and C-peptide,
19 the differences are significant.
20 We can also show you this data looking at
21 those people who are diabetic at baseline, based on
22 OGTTs, and those people who had impaired glucose
23 tolerance, and look at their actual mean curves to see
24 if we can get any information from that.
25 So here on this oral glucose tolerance test

1 which we think adds some very valuable data to our
2 database, the people on placebo -- the solid line is
3 day-1 and dashed line is day-365 -- at the end of that
4 time period there's no difference in terms of the
5 effective treatment on them; whereas those people who
6 are on orlistat, you can see what happens between day-
7 1 and day-365, and the decreased AUC for those people
8 who are diabetic is highly significant.
9 And to give you just an example of what the
10 2-hour fasting glucose level was, for the people on
11 placebo at day-1, their glucose at two hours was about
12 250 and it stayed at 250. For the people on orlistat,
13 their 2-hour value was about 222 -- so it started a
14 little bit lower -- and at the end of one year of
15 treatment their mean 2-hour glucose value in an oral
16 glucose tolerance test was 175. So there was a
17 significant decrease there.
18 Now we'll look at those people who had
19 impaired glucose tolerance in this population. There
20 was a very small effect of treatment in the placebo
21 people, and a much greater effect similar to what you
22 saw in the diabetic population. And these differences
23 also were very, very significant.
24 And again, just to give you an example of
25 what we saw at the 2-hour data point, in the people on

1 placebo their 2-hour glucose was 157 before treatment
2 and 146 after treatment, so they stayed the same. The
3 people on orlistat started out with a 2-hour value of
4 159, and at the end of one year of treatment was 120.
5 Now, we also looked at oral glucose toler-
6 ance using the shift in people's categories looking to
7 see where they started off and how they ended up. And
8 let me just show you what that data looks like.
9 Here we have people who started off at
10 baseline as diabetic, impaired, or normal, and how
11 they ended up in treatment. So for example, if you
12 look under diabetic, you have the percentage of
13 patients on placebo who started out as diabetic and
14 then who ended up normal or who ended up impaired at
15 the end of one year. Compared to the people on
16 orlistat who start off diabetic and end up normal or
17 end up impaired.
18 So 15 percent of the placebo patients who
19 had a diabetic OGTT at baseline ended up as normal,
20 versus 25 percent of those patients on orlistat; of
21 those patients who were diabetic and ended up im-
22 paired, 15 percent of the placebo patients and 43.8
23 percent of those on orlistat.
24 The next category, impaired, is very
25 important because patients there can either normalize

1 or go on to have diabetes. So for placebo patients or
2 for those placebo patients who had impaired glucose
3 tolerance tests, 10 percent of them at the end of one
4 year were found to be diabetic, compared to 2.6
5 percent of those on orlistat.
6 For those placebo patients who were impaired
7 and ended up normal, it was 45 percent -- which is a
8 good number -- but it was 72 percent of the people on
9 orlistat. And if you look at people who start off
10 normal and ended up diabetic, it was 1.3 percent of
11 placebo patients who were normal became diabetic at
12 the end.
13 Yes?
14 MR. MOLITCH: Do you have the n's for each
15 of those three groups on the left?
16 DR. HAUPTMAN: Yes, we do. We can show them
17 at the question and answer section. We have the
18 actual numbers of patients for each of the groups that
19 we can show you and how they shifted.
20 Now, let's just summarize some of the
21 benefits that we've seen for these risk factors.
22 We've seen so far that orlistat improves with the
23 profiles, it also decreases elevated blood pressure,
24 it decreases fasting insulin levels, and it normalizes
25 some people with abnormal glucose tolerance tests.

1 But now I'd like to show you one study that
2 was done in an obese population of non-insulin-
3 dependent patients on oral hypoglycemic medication to
4 see if an effective treatment was there.
5 It's a very simple study design. It's one
6 year but the study design is very similar to the other
7 ones. The patients had a 5-week lead-in period where
8 they had to be stabilized on a dose of oral hypoglyce-
9 mic medication, and then they were followed throughout
10 the study for many parameters. I'll show you weight
11 loss first.
12 This is the weight loss difference, and this
13 is the n for the total number of patients. Overall,
14 the mean weight loss in this population was about 4.3
15 for the placebo group, and 6.2 for the orlistat group
16 -- less than our non-oral hypoglycemic maintained
17 patients, but still significantly different between
18 the two.
19 Look at fasting glucose, the entire fasting
20 glucose mean change over time for those patients. We
21 see a decrease from week -5 to zero, and then during
22 the rest of treatment, while they continue to lose
23 their weight, there was a slight upward trend in the
24 placebo group and the orlistat group, but the differ-
25 ences between treatments were highly significant.

1 We also picked out those patients whose
2 fasting glucoses were greater than 7.7 at baseline,
3 and we followed them to see if they acted any differ-
4 ently. What the data shows is that there's actually
5 a greater decrease and it stays down longer. Near the
6 very end of the study there was a small increase, but
7 the differences between treatment in terms of fasting
8 glucose to least square mean difference was highly
9 significant between treatments.
10 Now we'll look at hemoglobin A1c as the next
11 parameter that we measure. For all patients, there
12 was an increase of about .28 percent of hemoglobin A1c
13 over treatment, whereas those patients in orlistat had
14 a decrease of .18 percent, for an absolute difference
15 of about .46 percent, which again, was highly signifi-
16 cant.
17 And to just give you what the actual numbers
18 were, it started off with the placebo group at 7.48
19 and went up actually, to 7.56, and for the people on
20 orlistat it started at 7.55 and went down to 7.22.
21 Now we also looked at people who started off
22 with hemoglobin A1c's greater than eight -- more, you
23 know, quality controlled at the beginning. Both
24 orlistat and placebo groups have decreases in this
25 instance. Instead of one going up and one going down,

1 they both go down. The people on placebo decreased
2 from 8.65 to 8.6, and the people on orlistat decreased
3 from 8.76 to 8.26, for an absolute difference of about
4 a half a unit. And again, this was statistically
5 significant.
6 We also looked at what happened to their
7 medication treatment. Did they need less medication,
8 could they be discontinued from medication, or did
9 they get to the point where medication -- oral medica-
10 tion -- was no longer of value to them?
11 We looked at those patients where their
12 medication was drawn, those who had their oral
13 hypoglycemic medication dose decreased, or increased,
14 or the patient withdraw because they reached the
15 maximum dose of oral hypoglycemic medication and still
16 had poor glycemic control. So within a half-percent
17 of the placebo patients were able to have their
18 medications drawn, versus 11.7 percent of those on
19 orlistat.
20 In terms of dose decreasing, the numbers are
21 there. In terms of patients with increased -- the
22 dose increased -- twice as many people on placebo
23 needed a dose increase versus those on orlistat. And
24 patients withdrawing because they were hyperglycemic
25 and they no longer could be maintained on oral

1 hypoglycemic medication, it was 8.8 percent versus 2.5
2 percent, and the overall significance was significant
3 to this study.
4 We looked at lipid values for this total
5 population because of the known problems of obese
6 diabetic patients with hypolipidemia. And this is
7 just a summary of the least square mean percent
8 differences from placebo. There's a total decrease of
9 cholesterol by 9 percent, the LDLs decreased by 12.8
10 percent, and the triglycerides decreased by about 10
11 percent. And all these were significant.
12 So now I'd like to just summarize, basical-
13 ly, what we think we've seen in obesity-related risk
14 factors. We think that orlistat improved lipid
15 profiles -- treatment with orlistat improved lipid
16 profiles. The LDL value and the LDL/HDL ratio
17 improved to a greater extent in the orlistat group
18 than the placebo group, and the effects were very
19 apparent, especially in those people who started out
20 with elevated values at baseline.
21 There's a decrease in elevated blood
22 pressure, especially in patients with elevated levels.
23 And in fact, for those patients on orlistat who had
24 blood pressure greater than 90 millimeters of mercury
25 at baseline, at the end of treatment they had an 8

1 millimeter decrease in their diastolic blood pressure.

2 We looked at oral glucose tolerance status

3 and improved glycemic control and we felt that there

4 was an overall improvement in patients who had

5 impaired glucose tolerance or who were overtly

6 diabetic, with a decreased need for oral hypoglycemic

7 medication.

8 Now, some of these effects were probably due

9 to the greater weight loss associated with those

10 patients taking orlistat than placebo. But other of

11 those effects we think are probably due to an addi-

12 tional effect, especially in lipids, that orlistat, in

13 terms of its mechanism of action, might have in the

14 treatment.

15 So to conclude our efficacy portion, we

16 think that orlistat produces clinically meaningful,

17 sustained weight loss; that it diminishes weight

18 regain; that it diminishes -- improves risk factors;

19 and that orlistat after all, is effective for very

20 long-term treatment.

21 Now, we've demonstrated the benefits of

22 orlistat on these types of parameters are due to its

23 inhibition of fat absorption in the gastrointestinal

24 tract. But also, its safety and tolerability are also

25 a reflection of its pharmacologic action. A total of

1 7,000 patients and volunteers have participated in our
2 global program with over 5,000 patients receiving
3 orlistat.
4 Since our Phase III program is very large,
5 we'll begin by presenting data of safety and tolera-
6 bility from our integrated database. This is the
7 extent of exposure that we'll be talking about.
8 Approximately 2500 patients had at least six months of
9 treatment with orlistat, and over 2200 patients had at
10 least 12 months of treatment, with the majority of the
11 patients on the top dose of 120 milligrams three times
12 a day.
13 After one year in treatment there appears to
14 be a decrease in the amount of patients on drug;
15 that's because the study designs changed and only four
16 of the studies were two years in duration. Neverthe-
17 less, by the end of the study there were a total of
18 800 patients who had two full years of orlistat
19 treatment, and over 500 of those patients at the dose
20 of 120.
21 When these studies were developed there were
22 very few long-term studies available for comparison
23 purposes, and the ones that were, reported as we said
24 before, a dropout rate of about 50 percent during one
25 year. No 2-year, double-blind, placebo-controlled,

1 multi-center trials to the best of our knowledge, were
2 either conducted or reported in the literature, so we
3 really didn't have a gauge as what to expect for the
4 dropout rate during the year-2 portion of the study.
5 This is what we found, though. For the
6 overall integrated database, for those patients on
7 placebo, the dropout rate was a modest 35 percent,
8 versus about 30 percent of those patients on orlistat.
9 For year-2 -- and this is information that was not
10 available from anyone, so we didn't know what to
11 expect -- it was also quite modest: 18 percent of
12 both the placebo patients and the orlistat patients
13 discontinued in year-2 for any reason.
14 And we'll discuss now, some of the other
15 causes for terminations. In terms of adverse events,
16 the major difference between treatment groups are the
17 gastrointestinal adverse events -- which we'll discuss
18 in a few minutes -- but first I'd like to look at
19 serious adverse events. These adverse events were
20 found to occur equally in the placebo group and at an
21 incidence of approximately 6 percent in both year-1
22 and in year-2 of treatment.
23 Most of these were sporadic and isolated
24 occurrences. The events were also found to occur
25 equally between the orlistat and the placebo group,

1 and equally within body systems, with the exception of
2 one finding that I'd like to discuss now.
3 Due to the large size and long-term nature
4 of our studies, we expected to identify a number of
5 patients with different types of neoplasm during the
6 course of the study. And we expected them to be
7 equally distributed among the placebo and the orlistat
8 groups.
9 When we broke the double-blind code, we were
10 surprised to find an unequal distribution of female
11 patients with a breast neoplasm. Based on epidemio-
12 logic data there was an underrepresentation in the
13 placebo group and an overrepresentation in the
14 orlistat 120 group.
15 This slide shows the expected incidence rate
16 -- from the general population, not the obese popula-
17 tion -- based on patient exposure by dose. It
18 includes the ratio of the observed to expected cases
19 and their associated confidence intervals. Several
20 factors argue against there being a link between the
21 occurrence of these events and drug administration.
22 Based on the fact that orlistat has very
23 minimal systemic bioavailability, this was a surpris-
24 ing finding. As we discussed before, less than one
25 percent of an administered dose of orlistat is found

1 to be systemically bioavailable.

2 The finding was also surprising based on the
3 fact that low-fat diets and decreased body weight in
4 women are associated with decreased breast tumor risk.
5 Based on the pre-clinical studies there is no evidence
6 to expect this finding.

7 The genotoxicity and mutagenicity study
8 showed no effect. Also carcinogenicity studies in
9 animals showed no increased findings compared to
10 placebo. In these studies, animals received doses up
11 to 400 times higher than the human dose, which
12 resulted in systemic exposure of up to 800 times
13 higher.

14 The results of the carcinogenicity studies
15 in mice showed no difference for breast tumor develop-
16 ment across the range of doses, and there are two
17 placebo groups which are both zero. And for compari-
18 son purposes, the milligram per kilogram dose for man
19 is about five milligrams per kilogram per day. So
20 these are all considerably higher than that.

21 In rats, there was in fact, a significant
22 decrease in fibroadenoma development with increase in
23 dose, and no difference with respect to other breast
24 tumors. You can see on that slide.

25 So in order to better evaluate all of our

1 findings, we convened a panel of independent experts
2 to evaluate the data we had. The panel included
3 breast cancer specialists, epidemiologists, patholo-
4 gists, and mammographers. In their review of the
5 data, they noted that several of the cases were found
6 too soon after the start of drug administration to
7 plausibly attribute it to drug.
8 This slide shows that of the 11 cases, five
9 were identified between the start of the study and the
10 6-month visit. These five are half of all the cases
11 that occurred in the orlistat group, and many of the
12 cases had relatively large tumor or multiple node
13 involvement, reinforcing the impression that they were
14 pre-existing at the time of study start.
15 Of the remaining six cases, one on placebo
16 and five on orlistat, five were picked up on routine
17 mammography, and several had also been found to have
18 large-size tumors.
19 Best estimates are, it takes five to eight
20 years for a breast neoplasm to develop, and in the
21 case of radiation, which is a known causative agent,
22 it can take 15 years. It's also important to note
23 that the neoplasms were found to be of several
24 different pathologic types.
25 The possibility that there was an indirect

1 effect of the drug was also considered. During the
2 studies we measured fat soluble vitamins in beta
3 carotene. These patients had values that were
4 consistently within the normal reference range. One
5 patient had their last value in the study for vitamin
6 D low, but all their other values were normal.
7 So this left us with two, reasonable
8 possibilities. First, we're dealing with a very small
9 number of events and the findings of several addition-
10 al cases on orlistat or fewer cases than expected on
11 placebo, could really be a chance finding, especially
12 since the study was not set out to test this hypothe-
13 sis.
14 Alternatively, the identification of these
15 findings could be due to a detection bias. Most of
16 the events were picked up on routine mammography and
17 it has been shown that weight loss is capable of
18 changing breast architecture sufficiently to enable
19 detection of breast changes more easily. In this
20 study, the average loss at the time of diagnosis was
21 7 kilos in the orlistat group compared to the one
22 patient on placebo who lost only two-and-a-half kilos.
23 Unfortunately, the total number of patients
24 who had mammography during the course of the study, is
25 not readily available, because the study physicians

1 were generally not the patient's primary care provid-
2 ers. Our assessments of these findings are consistent
3 with those of the independent expert panel that we set
4 up -- and let's review their findings.
5 Mutagenicity and pre-clinical studies are
6 not indicative of any increased risk. A number of
7 cases in the orlistat group were diagnosed too soon
8 after randomization, to be considered an effective
9 treatment. A direct effect of orlistat is unlikely
10 due to the fact that systemic absorption is negligi-
11 ble, and if there is no obvious mechanism for a
12 secondary effective of orlistat, which leave us with,
13 chance and/or bias detection are possible explanations
14 for these findings.
15 Based on these data that we've discussed
16 with you this morning, we don't believe the findings
17 are drug-related. Nevertheless, we are going to
18 continue to monitor our safety on an ongoing basis.
19 I'd now like to talk about more commonly
20 occurring adverse events. We defined the most
21 commonly occurring adverse events reasonably associat-
22 ed with orlistat as those occurring at a rate of at
23 least five percent in the orlistat group, and being at
24 least twice as frequent as in the placebo group.
25 When we looked at our entire database, the

1 only adverse events meeting these criteria were
2 gastrointestinal in nature and were associated with
3 the pharmacodynamic action of the compound. To best
4 characterize the nature of the gastrointestinal
5 adverse events, the terms diarrhea and steatorrhea
6 were not used since they don't accurately reflect
7 these events.
8 Typically, clinicians see diarrhea as
9 frequent watery stools associated with potential
10 dehydration or loss of electrolytes, and steatorrhea
11 as a broad malabsorption syndrome. However, patients
12 on orlistat do not have dehydration or loss of
13 electrolytes, and they don't have a broad malabsorp-
14 tion syndrome, especially since we've been able to
15 show that other actions of the pancreas are not
16 affected.
17 To better characterize these findings we put
18 together a dictionary of standard terms for changes in
19 defecation patterns, and provided them to investiga-
20 tors to have consistency across sites. Investigators
21 used these definitions when documenting reports of
22 events from patients during the study. And these are
23 the adverse events that met that criteria.
24 The most striking thing here is, if you
25 first look at the percentage of patients who had an

1 instance of one of these seven adverse events, and
2 then you take a look at the withdrawals due to these
3 adverse events, there is a very large difference.
4 Although the range is from approximately 27 to about
5 8 percent of patients, the withdrawals during one year
6 of study was less than 2 percent across the board
7 there, for year-1, with less than .5 or .6 for most of
8 them.
9 When you look at your two, for all the
10 adverse events, the incidence is extremely low. Going
11 down for example, from 26 to about 4, and the with-
12 drawals due to these adverse events are also remark-
13 ably low. This very low withdrawal rate showed that
14 these events seem to be very well tolerated, and the
15 reason they were well tolerated is due to the fact
16 that the majority were mild in intensity -- you have
17 mild, moderate, and severe percent of all patients --
18 and most of them were limited to just one general
19 episode.
20 And many of these occurred early in the
21 treatment, with half occurring within the first month,
22 and a full one-third of these episodes occurring in
23 the first week of treatment.
24 Now to further evaluate adverse events we
25 used a broader definition. We looked at adverse

1 events that occurred either on orlistat or placebo,
2 with a frequency of at least 5 percent, and there was
3 no requirement for there being a minimum difference
4 between treatment groups. When we used this criteria,
5 we identified other gastrointestinal findings.
6 The slide shows that although there is, on
7 orlistat, a relatively large number of gastrointesti-
8 nal findings such as abdominal pain or flatulence, the
9 placebo people also had a very large percentage of
10 these. In year-2 we see the same finding, and there's
11 in fact, no favor of orlistat or placebo in general
12 for these other GI adverse events.
13 I want to just remark about liquid stools
14 and infectious diarrhea, which are the two that most
15 people might commonly actually consider as diarrhea,
16 and although there is a slight greater amount in the
17 orlistat people, the people who were on placebo had a
18 very, very high amount also, and the difference was
19 quite small between them.
20 Now we had looked at other non-GI adverse
21 events meeting this criteria. And in general, over
22 one year and two years of treatment in a very large
23 percentage of patients, we can see that the differenc-
24 es between orlistat and placebo were very small,
25 although the total number of these adverse events were

1 very large for things such as headache, upper respira-
2 tory tract infection, flu or flu-like syndromes, but
3 the differences between treatment were really quite
4 modest, as they were also seen in year-2.
5 Now, in order to help clarify the overall
6 tolerability of orlistat in comparison to its benefits
7 as perceived by the patient, we performed a quality of
8 life assessment throughout the course of the study.
9 A quality of life instrument was developed and
10 validated by independent experts for our project, and
11 was developed specifically to evaluate obese patients
12 on a weight loss diet, because no instruments evaluat-
13 ing the effects of weight loss were available.
14 Three major domains were evaluated. They
15 were: overweight stress, which measures a person's
16 health status due to his or her obese state; depres-
17 sion; and lastly, satisfaction with treatment.
18 For overweight stress and depression, an
19 improvement is associated with a decrease, while with
20 satisfaction with treatment it's the opposite. So for
21 overweight distress there's a significant improvement
22 on those people on orlistat compared to placebo, and
23 these differences of at least 10 percent in the scale
24 are considered clinically meaningful by the people in
25 the quality of life area.

1 Also, we looked at those people who were
2 depressed at baseline, who had a score greater than or
3 equal to 16; they also had a significant improvement
4 on orlistat compared to placebo. And in satisfaction
5 of treatment relative to placebo, patients on orlistat
6 were more satisfied with the overall program.
7 Now, we also included other safety assess-
8 ment such as cardiograms. And here you can see, there
9 is very little difference between the orlistat and the
10 placebo group for ECG findings between year-1 and
11 year-2, in either between the orlistat group and the
12 placebo group.
13 We looked at vital signs. This is the pulse
14 rate, a baseline value. There was a very small
15 increase in the placebo group and a small decrease in
16 the orlistat group, and the overall difference
17 however, was statistically significant in favor of a
18 decrease on orlistat.
19 We looked at gallstone development since
20 this is an area of concern with people losing weight.
21 We did ultrasound evaluations in the vast majorities
22 of our studies. We did them at baseline, at the end
23 of year-1, and at the end of year-2. The data here
24 shows that there's virtually no difference in gall-
25 stone development between orlistat and placebo. It was

1 higher during the first year of treatment and the
2 second year of treatment in both, but the differences
3 were not there.
4 We looked at patients who had adverse events
5 that could be related to gallstones. Here we have --
6 should be symptomatic cholelithiasis, cholecystitis,
7 or cholecystectomy. And in fact once again, there is
8 no difference in any of these gallstone-related
9 adverse events between treatments.
10 We finally looked at renal stone development
11 because of the hypothetical possibility that orlistat
12 may produce increased renal stones. We did ultrasound
13 again, in a very large percent of the patients.
14 During year-1 there was a .2 percent incidence of
15 stone development in people on placebo, and .8 percent
16 on orlistat. The differences however, were not
17 statistically significant, but they were different.
18 In year-2 there were no differences in
19 treatment, and this is based on patients who did not
20 have stones at baseline, and had stones at the end of
21 the treatment of year-2. They could have other
22 abnormalities in their ultrasound, such as 50 percent
23 of the patients with other baseline abnormalities had
24 cysts but they didn't have stone.
25 When we look at renal adverse events, those

1 that could possibly be related to renal stone develop-
2 ment, we see actually a slightly different pattern.
3 This is renal colic, pain associated with renal
4 calculus as evaluated by the investigator, and renal
5 pain in general.
6 What the data here show are that the placebo
7 group actually had a higher incidence -- again, small
8 but higher -- and that there's no major difference
9 between orlistat treatment and placebo treatment.
10 At this point of the presentation I'd like
11 to have Dr. Roberto Guerciolini from our Clinical
12 Pharmacology Department, present some new data on
13 recently completed mineral balance studies which we
14 think are important for you to hear.
15 DR. GUERCIOLINI: Good morning. I'm Dr.
16 Guerciolini from Hoffmann-LaRouche Clinical Pharmacol-
17 ogy. We learned from the previous presentation that
18 orlistat inhibits the absorption of about 30 percent
19 of dietary fat. The potential consequence of this
20 event, the presence of increased fat in the intestine
21 on local physiological process, gastrointestinal
22 physiological processes, as well as systemic physio-
23 logical processes, have been the substance for a
24 variety of investigations conducted either in a normal
25 volunteer as well an obese subject, to fully charac-

1 terize the extent of such a possibility.

2 Even through across studies we have been
3 collecting and measuring urinary and serum electro-
4 lytes, as well as urinary and fecal excretion on some
5 minerals, particularly calcium, a specially designed
6 study was conducted and recently completed investigat-
7 ing the effect of therapeutic doses of orlistat on the
8 balance of six representative minerals.

9 The objective of the study was to evaluate
10 whether therapeutic doses of orlistat has any effect
11 on the balance of three representative trace elements
12 -- zinc, copper, and iron -- as well as three repre-
13 sentative microminerals -- calcium, magnesium, and
14 phosphorus.

15 The study was conducted according with the
16 double-blind, randomized, placebo-controlled design in
17 a single center, a metabolic ward, where obese
18 subjects were enrolled upon meeting the entry criteria
19 and they were in-house, hospitalized, for the entire
20 duration of the study -- 22 days. From day-1 on, the
21 subjects were enrolled in a diet, a hypocaloric diet,
22 and a treatment -- placebo or orlistat -- and they
23 used a capsule containing radiopaque marker, which are
24 instrumental for fecal recovery of the minerals.

25 The first two weeks actually were our so-

1 called equilibration period, an extremely important
2 period, in order to obtain several objectives. First,
3 the cleaning of minerals from the gastrointestinal
4 tract deriving from the free diet period preceding the
5 hospitalization.
6 Secondly, the reaching of a new steady-state
7 in terms of calorie intake -- represented by the diet,
8 mineral intake, supported by the presence into the
9 diet, as well as pharmacological effect of orlistat.
10 As we know, orlistat's pharmacological effect is
11 achieved within two or three days of administration
12 and then sustained over time afterward.
13 The actual balance period was the last seven
14 days of the in-house period where samples of meals,
15 toilet collection of feces and urine were used to
16 evaluate the balance concentration using atonic
17 absorption as a methodology.
18 Two groups of 14 subjects were enrolled --
19 a total of 28 obese subjects with a BMI larger than 30
20 were enrolled. Half of them were allocated to the
21 placebo group, half of them were allocated to the
22 traditional recommended dose of orlistat, 120 milli-
23 grams three times a day, administered with the three
24 main meals.
25 The diet was represented by a mildly

1 hypocaloric diet, which upon measurement of its
2 constituents, resulted to be providing 1500 kilocal-
3 ories per day. Resulting also to provide the recom-
4 mended dietary allowance or sometimes exceeding the
5 six minerals in question.
6 Capsule containing radiopaque marker also
7 administered for each single meal in order to allow
8 the recovery calculation of the mineral from the
9 feces. The first assessment of the study was the
10 gastrointestinal absorption of the six minerals
11 represented on this slide by the so-called, net
12 fractional absorption -- the percentage of the
13 administered meals which are actually being absorbed
14 the gastrointestinal tract.
15 The result of the report are the mean for
16 each group for each of the minerals, for the placebo
17 group as well as for the orlistat treatment group.
18 The results are in line as has been reported in the
19 literature; they are pretty similar between the two
20 groups.
21 The small, negative percentage per item is
22 not surprising on a population of adults, individuals
23 with very solid storage of iron and poorly efficacious
24 systems of the gastrointestinal tract for these
25 minerals.

1 The second assessment was the urine excre-
2 tion of the minerals. The importance of this slide,
3 again, as a mean for each group and for each individu-
4 al mineral are the three trace elements as micrograms
5 per day excretion, as well as the three milligrams per
6 day excretion.
7 The results are very, very similar between
8 the two treatment groups, and are very much in line
9 with reported reference range in the literature.
10 Finally, the resulting balance, the mineral balance,
11 which is the difference between the dietary intake
12 versus the sum of the excretion of fecal and urinary
13 excretion, were reported and depicted here in this
14 comprehensive table.
15 Let's focus first on the effect of diet
16 alone. Diet alone resulted in a slightly negative
17 balance for the majority of the minerals, with the
18 exception of copper which is very slightly at a
19 positive balance. With the exception of phosphorus
20 which is relatively larger in terms of absolute
21 amount, this number is very small. They are gravitat-
22 ing across the neutrality value, spanning from a
23 minimum of 1.7 percent, referring to the dietary
24 intake, to a maximum of 7 percent negative.
25 The additional orlistat to the treatment and

1 the confirmed presence of one third of dietary fat
2 into the feces, confirming the pharmacological effect
3 of orlistat, did not result in any quantitative
4 changes of the balance. If any qualitative changes,
5 the zinc balance was actually positive in the orlistat
6 group, and the larger negative balance for phosphorus
7 was confirmed.
8 Again, this number is very close to the zero
9 level. They are not exceeding 7 percent negative
10 balance for any of these elements. Importantly, and
11 the ultimate purpose of the study, was to compare the
12 difference between the treatment groups, and the 95
13 percent confidence interval around the difference
14 between the treatment groups clearly indicated the
15 absence of any statistically significant difference
16 between the treatment groups.
17 It also demonstrated that the addition of
18 orlistat in the pharmacological effect of orlistat,
19 the inhibition of absorption of 30 percent of dietary
20 fat, did not result in any significant difference,
21 neither on the gastrointestinal capability of the
22 gastrointestinal tract to absorb the minerals repre-
23 sented by the net fractional absorption, nor on the
24 urine excretion figures, and on the resulting overall
25 mineral balance.

1 From the results of this study it's then
2 possible to conclude that the net fractional absorp-
3 tion, as well as the overall balance of the selected
4 minerals, during an hypocaloric diet in obese sub-
5 jects, is not affected by the administration of
6 therapeutic doses of orlistat.
7 I would like to introduce now Dr. Bill
8 Cannovatchel, from the Clinical Research Department of
9 Hoffmann-LaRouche, which will report on the fat
10 soluble vitamin monitoring program.
11 DR. CANNOVATCHEL: Good morning. I'm Dr.
12 Bill Cannovatchel from the International Clinical
13 Research Group at Hoffmann-LaRouche.
14 Because orlistat selectively inhibits the
15 absorption of fat in the gastrointestinal tract, we
16 prospectively examine plasma levels of the fat-soluble
17 vitamins in all of our Phase III studies. Even though
18 none of our patients were on very low calorie diets
19 which can dramatically diminish the vitamin intake,
20 they were on mildly hypocaloric diets that can reduce
21 the nutrient intake.
22 Nonetheless, to fully characterize the
23 effect of orlistat, we discontinued any vitamin
24 supplements prior to study entry even though patients
25 would normally receive a vitamin supplement at the

1 beginning of a weight loss program. Despite the fact
2 that two-thirds of the fat is still absorbed during
3 orlistat treatment, we actively measured plasma
4 vitamin levels throughout the duration of each of our
5 studies.
6 The fat-soluble vitamins examined included
7 vitamin A, vitamin D, vitamin E, vitamin K, and beta
8 carotene, a carotenoid. At the time our studies were
9 designed, beta carotene had a number of possible roles
10 described in the literature, although today the only
11 confirmed role is as a pro-vitamin A.
12 Through measurement of these vitamins, in
13 over 3,000 patients we had the opportunity to collect
14 a great deal of information about the vitamin status
15 in obese patients. This is the largest such database
16 assembled. We assessed these vitamins in a very
17 rigorous manner. Although patients would normally be
18 recommended to start a vitamin supplement, as per our
19 protocol, patients discontinued vitamin supplemen-
20 tation eight weeks prior to entry.
21 Plasma levels were drawn and sent for
22 analysis at entry into the study and throughout their
23 study participation. These samples were sent to one
24 of two clinical labs: one in the U.S. and one in
25 Europe. Because of slight difference in their

1 reference ranges, this morning I will be reporting the
2 results of the U.S. studies, in particular our 2-year
3 studies, although the results from Europe are compara-
4 ble.
5 These central labs reported the results to
6 the investigator in a blinded manner, each report with
7 a code indicating whether the patient plasma levels
8 were within the reference range or below the reference
9 range. If there were two consecutive low values
10 reported, the patients were to be started on a vitamin
11 supplement.
12 Supplementation was provided in a standard-
13 ized manner as each protocol called for. The vitamin
14 supplement given was that of an over-the-counter-type
15 multivitamin available in many pharmacies and grocery
16 stores, and the type that would normally be recom-
17 mended as part of a weight loss program.
18 As recorded in the literature and confirmed
19 on analysis of our food intake records completed
20 during the diet lead-in period, the lower the caloric
21 diet intake the lower the vitamin intake. An analysis
22 of our food intake records, we found that those on the
23 1200 calorie-a-day diet had significantly lower intake
24 of these nutrients compared to those on an 1800 or
25 greater calorie-a-day diet.

1 Although intake of vitamin A and vitamin E
2 met the recommended dietary allowance, in particular
3 in the 1200 calorie-a-day group, vitamin D was
4 significantly below the RDA -- less than half of the
5 RDA. And this is an example of why, typically as
6 patients go on a weight loss program, they are
7 recommended to take the vitamin, to ensure adequacy of
8 intake.
9 What follows are the results of each
10 vitamin. The data set is for those patients who
11 participated in our 2-year studies. This will enable
12 us to see what long-term effect orlistat treatment may
13 have on those levels.
14 Upon measurement of vitamin A, measured as
15 retinol, the reference range indicated in gray, our
16 patient population for both patient groups were
17 comparable during the diet lead-in period. Both
18 groups decreased slightly. After randomization, both
19 treatment groups were also similar, with a slight
20 increase over the 2-year period, and many times their
21 values superimposable upon one another.
22 As these are mean levels we wanted to also
23 identify how many patients had two consecutive low
24 value use during this time period. Very few of either
25 treatment group had such low levels: one-and-a-half

1 percent of the placebo group compared to two-and-a-
2 half percent of the orlistat group.
3 And the percentage of patients with normal
4 levels at the completion of their study participation,
5 was comparable -- almost all. This suggests that the
6 addition of orlistat to a weight loss program causes
7 no long-term decrease in vitamin a levels.
8 Turning now to vitamin D, it is made
9 available from one of two major sources. The major
10 source is through dermal production on exposure to
11 sunlight. Although this production is modified
12 depending on skin pigmentation, and that those with
13 greater melanin content will have a lower production
14 of vitamin D in the skin.
15 The other source of vitamin D is from the
16 diet. Vitamin D is then hydrolyzed to 25 hydroxy
17 vitamin D which is the best indicator of clinical
18 vitamin D status, and this is the parameter measured
19 to assess vitamin D in our studies. The 25 hydroxy D
20 is then hydrolyzed again to 25 dihydroxy vitamin D,
21 the active form of the vitamin.
22 Vitamin D has a role in the maintenance of
23 calcium homeostasis, and should there be a decrease in
24 vitamin D, there is a decrease in calcium absorption
25 from the gastrointestinal tract. This results in a

1 decrease in serum calcium which then results in an
2 increase in the parathyroid hormone level. Parathy-
3 roid hormone is a sensitive indicator of vitamin D
4 status since the maintenance of serum calcium levels
5 is tightly controlled.
6 We knew from the literature that obese
7 patients have been reported to have significantly low
8 levels of 25 hydroxy vitamin D. Many of these reports
9 were of small sample numbers. Typical of these
10 reports, among the first, was by Bell, et. al., where
11 in measuring the levels of 25 hydroxy D in the obese
12 and comparing it to the non-obese, found levels were
13 less than half that in the obese as compared to the
14 non-obese: 20 nanomoles per liter in the obese
15 compared to 50 nanomoles per liter in the non-obese.
16 As for those familiar with the nanogram per milliliter
17 range, this would be eight compared to 20.
18 An assessment of over 3300 samples drawn on
19 the day patients entered our diet lead-in period, and
20 determining the 2.5 to 97.5 percentile, we determined
21 a reference range for the obese patient population.
22 This reference range was significantly lower consis-
23 tent with the data reported in the literature.
24 Our reference range determined on the obese
25 patient population was 20 to 102 nanomole per liter,

1 less than half that of the general population labora-
2 tory reference range of 40 to 200 nanomoles per liter.
3 The findings on assessment of the 25 hydroxy
4 D levels in our studies -- again, the reference range
5 20 to 100 nanomoles per liter indicated in gray --
6 found that at entry, our patient populations were
7 significantly different. The placebo group had
8 slightly but significantly higher level of 25 hydroxy
9 D as compared to the orlistat group at entry. And
10 this was continued at randomization as well.
11 Following randomization, these levels
12 essentially paralleled each other over the 2-year
13 treatment period, although there was a slight separa-
14 tion in the last couple of months of the study period.
15 On least square mean analysis we found that the levels
16 at the end of the 2-year period were approximately 8
17 percent lower in the orlistat-treated group as
18 compared to the placebo group.
19 The incidence of two consecutive low values
20 was greater in both treatment groups: 13 percent of
21 placebo patients compared to 18 percent of orlistat
22 patients. There was no significant different on chi
23 squared analysis of these results although there was
24 a similar incidence of normal values at the end of
25 their study participation. Over 90 percent of

1 patients had normal levels.

2 On further analysis of those patients who
3 had two consecutive low levels and received a vitamin
4 supplement, we found that the mean levels of these
5 patients was between 40 and 45 nanomoles per liter in
6 either treatment group. That the lowest point in
7 their levels of the two consecutive low values, they
8 decreased to 12 nanomoles per liter.

9 Subsequent to vitamin supplementation,
10 levels in both patient groups increased significantly,
11 returning to their prior, normal range. And that
12 there was a slightly greater increase in the orlistat
13 group, even though they have continued on their
14 orlistat treatment during the study, so that the
15 levels return to the normal range.

16 In order to assess whether any small
17 decrease in 25 hydroxy D levels would have an effect
18 on the calcium parathyroid axis, in one of our 2-year
19 studies we included those parameters -- calcium and
20 parathyroid hormone -- in the study.

21 That study, a 2-year study conducted in the
22 U.S., study 14161, had results similar to the overall
23 2-year study database set in that patients paralleled
24 over the 2-year treatment period for most of the time,
25 although again there was a slight separation towards

1 the last months of the treatment period where there
2 was about a 6 percent lower 25 hydroxy D level in the
3 orlistat group as compared to placebo.
4 Mean calcium levels, serum calcium levels
5 though, were unchanged at any time during this 2-year
6 treatment period in either treatment group. No
7 differences over time or between groups. Similarly,
8 the ionized calcium was also unchanged over this 2-
9 year treatment period in either group, consistent with
10 the tight control of serum calcium levels.
11 This slight decrease in 25 hydroxy D had no
12 effect on the parathyroid hormone levels. Those
13 levels also unchanged over the 2-year study period; no
14 difference between treatment groups or over time.
15 Suggests showing that there's no physiologic conse-
16 quence to the small decrease in vitamin D.
17 In order to identify a higher risk group, we
18 identified those patients who started with a lower 25
19 hydroxy D level at randomization -- 40 nanomoles per
20 liter or less. And eventually had two consecutive low
21 values to assess their levels. These levels, only
22 excluding those levels drawn at the time a patient may
23 have been on a multi-vitamin, show that they're very
24 comparable at placebo lead-in period, and then
25 essentially there's no difference over the 2-year

1 study period.

2 And that further, there is no change in

3 their parathyroid hormone levels either, over time or

4 between treatment groups. Again, no physiologic

5 consequence noted during this treatment period.

6 To summarize the effects on vitamin 25

7 hydroxy D levels as assessed during orlistat treat-

8 ment, in all subjects we found that there was an 8

9 percent mean decrease in the orlistat group in the 25

10 hydroxy vitamin D levels, and that this decrease was

11 associated with no change in either the serum calcium

12 levels or the parathyroid hormone levels.

13 In patients at higher risk, either those who

14 had two consecutive low values at some point during

15 the study, or those who started the study with lower

16 levels of 40 nanomoles or less, we found that there

17 was no other decrease in 25 hydroxy D as compared to

18 the placebo group, and that with supplementation, we

19 normalize the 25 hydroxy D levels equally in both

20 treatment groups, orlistat and placebo.

21 Moving on to vitamin E, which we measured as

22 alpha-tocopherol, its reference range again, indicated

23 in gray, both treatment groups were comparable during

24 the placebo lead-in period, a slight decrease in both

25 groups. After randomization, the placebo group

1 essentially plateaued over the 2-year period.

2 In comparison, the orlistat group had a

3 slight decrease at week 4, and then plateaued,

4 trending up slightly for the remainder of the 2-year

5 period. The incidence of two low values was one

6 percent in the placebo group compared to 4 percent in

7 the orlistat group, and at the end of study partici-

8 pation, nearly all patients in both treatment groups

9 had normal levels of vitamin E.

10 The major portions of both vitamin E and

11 cholesterol are carried on low density lipoprotein.

12 Any significant change in LDL can result in a signifi-

13 cant change in total vitamin E levels. Because of

14 this, a standard manner in which to report vitamin E

15 is as a ratio of vitamin E over LDL. We have seen

16 that orlistat-treated patients have a significant

17 decrease in their LDL levels.

18 On review of the 4 percent of patients, the

19 12 patients who had two consecutive low values, the

20 majority of these patients had a mean decrease of 20

21 percent in their LDL levels, commensurate with their

22 decrease in vitamin E.

23 On further analysis of the total 2-year

24 population, as vitamin E to LDL level ratio, we found

25 that there was no significant difference between

1 treatment groups. There was a slight increase over
2 the 2-year period, with the orlistat group tending to
3 have higher levels than the placebo group. This
4 suggests that the addition of orlistat to a weight
5 loss program causes no long-term decrease in vitamin
6 E levels.
7 Vitamin K was assessed indirectly by
8 measurement of the prothrombin time. Vitamin K exists
9 in the body as a small pool, that in deficiency states
10 is rapidly depleted. So should there be any depletion
11 of that we would expect an increase in the prothrombin
12 time.
13 We found though, that over a 2-year period
14 there was no change in the prothrombin time in either
15 treatment group over the 2-year period. In a separate
16 study we also examined the direct effect of orlistat
17 on several measures of vitamin K, all of which were
18 negative. This suggests that the addition of orlistat
19 to a weight loss program causes no long-term decrease
20 in vitamin K levels.
21 An assessment of beta carotene, our data is
22 consistent with that reported in the literature, and
23 that an inverse relationship exists between the degree
24 of obesity and level of beta carotene in the plasma.
25 The more obese a person is, the lower their beta

1 carotene levels.

2 Our patients fell at entry into the lower

3 quartile of the reference range consistent with that

4 finding. Both groups were comparable in that they

5 both increased during the diet lead-in period, perhaps

6 because of additional fruits and vegetables in their

7 diets.

8 After randomization, patients in the placebo

9 group essentially plateaued over the 2-year treatment

10 period. In comparison, the orlistat group had a

11 decrease noted at week-4 and then plateaued for the

12 duration of the 2-year study period, establishing a

13 new steady-state.

14 The incidence of two consecutive low values

15 were 2.5 percent in the placebo group, compared to

16 slightly more, 8 percent, in the orlistat group. The

17 percentage of patient with normal values at the end of

18 their study participation were comparable -- 98

19 percent per group. This suggests that the addition of

20 orlistat to a weight loss program causes no long-term

21 decrease in beta carotene levels.

22 Overall, the effect of orlistat on the fat-

23 soluble vitamins during orlistat treatment, in a time

24 when vitamin supplementation would normally be started

25 but we discontinued prior to entry, during the 2-year

1 study period vitamin levels remained well within the
2 reference range.
3 Vitamins A, E, and K were unchanged. There
4 were modest decreases in vitamin D and beta carotene
5 as compared to placebo. A multi-vitamin supplement
6 reversed these decreased values. The standard of care
7 includes the same type of multi-vitamin supplement as
8 used in our studies.
9 Our studies have shown that a multi-vitamin
10 supplement is sufficient to return patient's plasma
11 levels to their normal range. To optimize the
12 absorption of the multi-vitamin, a patient could take
13 their vitamin three hours after their dose, such as
14 bedtime, the time in which orlistat would not affect
15 the absorption of the vitamin.
16 Dr. Hauptman will now return to the lectern.
17 DR. HAUPTMAN: We've seen a great deal of
18 data this morning in a very short period of time, so
19 I'd like to just be able to take a couple of minutes
20 to put it into some perspective. When we're looking
21 at the overall tolerability, we found that the drug
22 was generally well tolerated. Adverse events were
23 well characterized and predictable, based on the
24 mechanism of action, and involved primarily the
25 gastrointestinal system.

1 Due to the fact that most of these events
2 were mild in intensity, occurred early-on in the
3 program, and resolved spontaneously, only a small
4 percentage of patients discontinued due to them. By
5 the second year of treatment the percent of gastroin-
6 testinal adverse events related to orlistat treatment,
7 decreased dramatically.
8 The possibility of other findings related to
9 the inhibition of fat absorption were anticipated
10 prior to starting our clinical program. Extensive and
11 detailed evaluations were done to determine what, if
12 any, effects occurred. We identified some effects on
13 fat-soluble vitamins which we followed long-term.
14 These effects were generally small and
15 remained stable over time, and were reversible.
16 Nevertheless, based on what we have learned about
17 vitamin status in the obese in general, it would be
18 prudent, clinical practice to recommend that obese
19 patients on a weight loss program should receive a
20 multi-vitamin supplement, and in fact, that is
21 generally what is done.
22 Other adverse findings in the program were
23 generally seen at a similar rate in the placebo and
24 the orlistat groups and if anything, were only
25 minimally different between treatments.

1 Regarding orlistat's efficacy, orlistat
2 produces clinically meaningful, sustained weight loss.
3 There was a greater mean weight los over time. The
4 placebo patients lost a large amount of weight but the
5 orlistat patients lost considerably more -- an
6 additional 50 to 70 percent more -- and they were able
7 to keep it off.
8 Twice as many patients in the orlistat group
9 lost at least 5 percent of their baseline body weight,
10 and two to three times as many patients lost as much
11 as 10 percent of their initial body weight. We have
12 shown that orlistat diminishes weight regain after
13 initial weight loss. On average, patients on orlistat
14 regained only half as much of their weight as did
15 placebo patients, and a larger percentage of orlistat
16 patients regained no weight at all at the end of two
17 full years of treatment.
18 We were able to show that we have effective,
19 long-term treatment. On average, patients were able
20 to lose and keep off, over seven-and-a-half percent of
21 their initial body weight as compared to only half
22 that amount after two full years of treatment.
23 As for obesity-related risk factors,
24 cardiovascular disease risk profiles are improved by
25 the overall effects of orlistat. The lipid research

1 clinic data show that for every one percent decrease
2 in cholesterol, there's a 2 percent decrease in
3 cardiovascular disease risk.
4 To review our data, orlistat lowered LDL
5 cholesterol by an additional 8 to 10 percent compared
6 to the placebo group, and that the LDL/HDL ratio
7 decreased by 50 percent more than the placebo group.
8 Hypertension is intimately associated with cardiovas-
9 cular disease risk. The benefits of weight loss and
10 lowering blood pressure are very clear.
11 The Fifth Joint National Committee on
12 Detection, Evaluation, and Treatment of High Blood
13 Pressure recommends that weight reduction is an
14 important goal for hypertensive individuals. They
15 also recommend weight reduction for primary prevention
16 of hypertension. In fact, studies have shown that for
17 every kilogram of body weight loss, there is a one
18 millimeter decrease in mercury in diastolic blood
19 pressure.
20 In our studies, patients with pre-existing
21 diastolic hypertension at baseline who were treated
22 with orlistat, had overall decrease of about 8
23 millimeters of mercury. We have also seen the overall
24 effect on carbohydrate metabolism. There are signifi-
25 cant improvements in glucose, insulin, and C-peptide

1 responses to an oral glucose challenge in patients
2 with orals that compared to those on placebo.
3 Modest amounts of sustained weight loss have
4 been shown to improve insulin sensitivity. Our data
5 show that 72 percent of obese people with impaired
6 glucose tolerance normalized in orlistat, compared to
7 46 percent of those on placebo. Ten percent of
8 placebo patients with impaired glucose tolerance went
9 on to develop non-insulin-dependent diabetes as
10 diagnosed by an oral glucose tolerance test, compared
11 to only two-and-a-half percent of the orlistat
12 patient.
13 For those diabetic patients receiving oral
14 hypoglycemic agents, a significantly greater number of
15 orlistat-treated patients, decreased or discontinued
16 diabetic medication compared to those on placebo, and
17 there was a significant decrease in hemoglobin A1c
18 levels as well.
19 Some authors have shown that for every one
20 kilogram of weight loss in a patient with non-insulin-
21 dependent diabetes, there's a three to four month
22 increase in overall survival. Our patients lost 50
23 percent more weight than did the placebo patients.
24 What does all this mean on average to an
25 obese person? With the use of orlistat this person

1 will lose more weight and keep more of that weight
2 off, long-term. This person will have a lower risk
3 for cardiovascular disease as showed by improved blood
4 pressure and lipid level status, as well as having
5 less chance for developing non-insulin-dependent
6 diabetes or impaired glucose tolerance.
7 Obese patients can also be expected to have
8 general improvements in quality of life as measured by
9 overweight distress and depression scales. As for the
10 physician, orlistat provides an option for pharmaco-
11 logic treatment that is not an anorectic, that is not
12 central nervous system acting, has minimal systemic
13 bioavailability, and has been evaluated in a large,
14 at-risk population in well-controlled studies for two
15 years.
16 So based on all the data that we've looked
17 at this morning, considering the overall efficacy and
18 tolerability of orlistat, we can conclude that
19 orlistat, administered as part of an overall weight
20 control program, is effective and generally well
21 tolerated in producing and maintaining, a clinically
22 meaningful weight loss with concomitant improvement in
23 obesity-related risk factors.
24 Thank you.
25 ACTING CHAIR SHERWIN: Thank you. I would

1 like to entertain any questions from the committee at
2 this point, regarding the data that was presented,
3 specifically focusing on points that were unclear in
4 the presentation. Dr. Molitch.
5 MR. MOLITCH: Actually, I have several
6 questions in several different areas. The first deals
7 with the breast neoplasm, breast cancer issue. I
8 would think that the data that you obtain in all these
9 studies is not something that should have appeared
10 yesterday, but you had studies that were ongoing and
11 completing over several years, and trends must have
12 become apparent over time in this regard.
13 And I'm really quite disappointed that we
14 don't have a better estimate of the denominators of
15 the mammograms that were done in these various groups
16 to get what a true fraction -- a real number here. I
17 don't understand why we don't have a better handle on
18 that number.
19 DR. HAUPTMAN: The studies actually were
20 completed in a very, very short period of time. The
21 general enrollment from all the studies was between
22 six months and a year, and the studies all started
23 late-'92 and all finished in 1995, approximately. So
24 they were all done within a short period of time, so
25 they weren't really done over a long period of time.

1 We did try to look through our database
2 looking for anything that would be a mammography-
3 related event, and that data was just generally
4 collected because of the nature of what we were
5 looking at. This was a surprising finding and there
6 was no reason to believe in the beginning of the study
7 that this would be something that we should actually
8 look for.
9 MR. MOLITCH: It does -- is a concerning in
10 our finding that a lot of effort would be expended in
11 going back to those patients and trying to ascertain
12 that data, and retrospectively, I'm still not happy.
13 DR. HAUPTMAN: We're still evaluating how to
14 continue to follow-up these patients, and there are
15 many different ways of doing that. One of the things
16 that we've been doing is trying to again, go back and
17 look through the data that we have. But because most
18 of these patients were referral patients, the center
19 is not being treated by their primary doctors --
20 they've lost contact with them.
21 ACTING CHAIR SHERWIN: The question though,
22 I think we still wanted to hear was, the denominator.
23 I don't have a sense -- most of the people in the
24 studies were women.
25 CHAIRMAN BONE: Hello. Is anyone there?

1 ACTING CHAIR SHERWIN: We're all here,
2 Henry. Do you have a question? I'm sorry that --
3 CHAIRMAN BONE: Call me back again, please.
4 ACTING CHAIR SHERWIN: We're here.
5 CHAIRMAN BONE: Can you hear me now?
6 ACTING CHAIR SHERWIN: Yes.
7 CHAIRMAN BONE: I'm sorry. I have trouble
8 hearing you, then. I have a question if I'm not
9 interrupting someone.
10 ACTING CHAIR SHERWIN: Well you were, but
11 that's okay.
12 CHAIRMAN BONE: I apologize then.
13 ACTING CHAIR SHERWIN: Go ahead, Henry.
14 CHAIRMAN BONE: I'm trying to find out
15 whether there was a relationship between the decline
16 in fat-soluble vitamin levels and the amount of weight
17 lost? In other words, did the people who lost more
18 weight have a greater decline or not?
19 DR. HAUPTMAN: I'd need to ask my colleague,
20 Dr. Cannovatchel. Do we have data regarding that?
21 Yes.
22 CHAIRMAN BONE: Okay.
23 DR. CANNOVATCHEL: I'm Dr. Bill Cannovat-
24 chel, and yes, we did assess the sub-population of
25 patients who had greater than 5 percent weight loss

1 and compared the changes in their fat-soluble vita-
2 mins. If I could have the slide that would enable me
3 to share some of that data with you. Other --
4 ACTING CHAIR SHERWIN: I would describe
5 carefully the slide since -- although Dr. Bone has all
6 the slides that were presented, I don't think he'll be
7 able to see this data.
8 DR. CANNOVATCHEL: Okay. I will try to be
9 descriptive --
10 ACTING CHAIR SHERWIN: Unless he has x-ray
11 vision or something.
12 DR. CANNOVATCHEL: What we found in regards
13 to 25 hydroxy D levels in patients who lost 5 percent
14 or more of their body weight over a 2-year period, is
15 that their mean levels were about 55 to 60, depending
16 on which group entry, mean levels of about 54, and
17 that over the 2-year study period, paralleled each
18 other with a slightly lower level in the orlistat
19 group.
20 Although, if I could have the statisticals
21 -- thank you. Next, please. The incidence of two
22 consecutive low values in this group were 10 percent
23 in the placebo group compared to twenty-one-and-a-half
24 percent in the orlistat group. Although at the end of
25 the study participation their levels were comparable

1 to the overall population with 90 percent of patients
2 having normal levels.
3 Next regarding statistics. Could I have the
4 next slide, please? On the square mean analysis of
5 these results, on the lower we see those who lost more
6 than 5 percent of their baseline body weight, these
7 patients had a mean baseline level of between 55 in
8 placebo and 57 in orlistat. The least square mean
9 difference was almost 7 nanomoles per liter, although
10 it did not reach statistical significance.
11 ACTING CHAIR SHERWIN: Could you summarize
12 --
13 CHAIRMAN BONE: I'm sorry, the speakerphone
14 is just cutting out too much. Maybe somebody could
15 get on the line and answer the question during the
16 break? I'm missing a lot of the answer; I'm sorry.
17 ACTING CHAIR SHERWIN: Right. The key
18 question is, the people that lost more weight, do they
19 have a greater fall in vitamins, such as vitamin D
20 levels? Can you give us a succinct yes or no?
21 DR. CANNOVATCHEL: They actually tended to
22 have -- there was less difference between their levels
23 as compared to the overall population.
24 ACTING CHAIR SHERWIN: So the people who
25 lost more weight had less of a fall in vitamins?

1 DR. CANNOVATCHEL: Less of a difference
2 between treatment groups.
3 ACTING CHAIR SHERWIN: Are there other
4 questions?
5 MR. MOLITCH: I've got several others. I've
6 got several other questions.
7 ACTING CHAIR SHERWIN: Oh, I'm sorry. I
8 don't want -- Dr. Molitch.
9 DR. CARA: Could you answer the question,
10 please? What you answered was not the original
11 question.
12 DR. CANNOVATCHEL: If I may ask to hear the
13 question again, please, so I'll be clear --
14 DR. CARA: Was there a greater fall in
15 vitamin D levels in the patients that lost more
16 weight?
17 DR. CANNOVATCHEL: The decrease was approxi-
18 mately a decrease of 6 nanomoles, so it's about a 10
19 percent decrease from their baseline levels, which is
20 comparable to an overall -- in the overall study
21 population of an 8 percent decrease.
22 ACTING CHAIR SHERWIN: It's a little
23 confusing, but I think what you're saying is that they
24 didn't have a greater -- no, the way I interpreted it,
25 that those people who lost more weight didn't have a

1 greater fall in soluble vitamins. Is that what you're
2 saying?
3 DR. CANNOVATCHEL: Yes. There was not a
4 greater difference --
5 DR. CARA: Compared to what?
6 DR. CANNOVATCHEL: Compared to the changes
7 in the placebo group.
8 DR. CARA: I'm not asking about placebo
9 group; I'm asking about the group as a whole.
10 Regardless of what the placebo group did, what did the
11 treatment group do in terms of vitamin D levels, the
12 group that lost less weight -- less than 5 percent
13 versus more than 5 percent?
14 DR. CANNOVATCHEL: Can we have that last
15 slide please, where we showed the differences and the
16 changes.
17 DR. CARA: You're basing a lot of your
18 responses and a lot of the data that you've presented
19 comparing treatment to placebo. I think what I would
20 like is just treatment alone, regardless of what
21 happened to placebo. I want to see the actual data,
22 please.
23 DR. CANNOVATCHEL: Okay. If I could have
24 the, please, slide on? The patients who lost less
25 than 5 percent of their initial body weight, the

1 orlistat group had a least square mean change -- the
2 orlistat group -- of 11 nanomoles per liter. In
3 comparison, those who lost more than 5 percent of
4 their body weight, had a decrease of 5 nanomoles per
5 liter -- less of a decrease compared to those that
6 lost less weight.
7 There are similar data available in the
8 other vitamins, if that would be helpful. Is this
9 helpful?
10 DR. CARA: That's helpful, yes. Do you have
11 the actual data?
12 DR. CANNOVATCHEL: In terms of -- the graph
13 was the actual data. If I could have them show that
14 for us.
15 ACTING CHAIR SHERWIN: Well, I think you can
16 see that, you know, the absolute mean baseline and
17 then the change, so you can figure out the differenc-
18 es. But I think it's right, that weight loss didn't
19 seem to relate to the change or the fall, at least in
20 this one vitamin level.
21 So Henry, I hope we answered your question.
22 CHAIRMAN BONE: I'm sorry, I'm going to have
23 to have someone repeat that during the break, because
24 as I said, the phone has been cutting out.
25 ACTING CHAIR SHERWIN: Okay, we'll talk to

1 you over the phone later.

2 CHAIRMAN BONE: Thank you.

3 ACTING CHAIR SHERWIN: Dr. Molitch has a few

4 more questions.

5 MR. MOLITCH: With respect to the diabetes

6 studies, although actually we could stay with the --

7 well, let's go to the diabetes studies. I have two

8 questions. The number of people in those three

9 categories who then went on to change category, you

10 had a group with diabetes with impaired glucose

11 tolerance, and a group of normal. You then gave

12 percentages that changed. What were the n's of the

13 original groups?

14 DR. HAUPTMAN: We have that data on backup

15 overheads that we'll get for you.

16 ACTING CHAIR SHERWIN: Were there statisti-

17 cal differences between some of these numbers?

18 DR. HAUPTMAN: There were. There are

19 statistical differences for the people who were in the

20 impaired group, the p-value is .006, and for the

21 people who were diabetic, it was just .06. It didn't

22 come close -- it came very close. For the people who

23 were normal, it was just a trend.

24 Could I have the first slide please? Okay,

25 this is, based on the new WHO criteria, and what this

1 number shows that it has the number of people who were
2 normal and this then shows -- I'm not sure that this
3 is exactly -- let's take a look -- referring to the
4 diabetic population.
5 So there were 13 people on placebo, but
6 baselines were diabetic, and there were 32 people on
7 120 owing to the different size in population. Of
8 those people -- do we actually have the slide with the
9 actual numbers in there as well? That might be more
10 helpful, because this is -- this might give you some
11 idea -- is this okay? Yes.
12 So what we see here is that the total number
13 of people that are diabetic -- and these are people
14 that didn't know they were diabetic -- it was just
15 diagnosed -- is relatively small but it's enough to
16 show the trend. And the people who are impaired, it
17 was a much larger number, and this gives you a better
18 feeling for the exact number.
19 For the people who were normal -- which was
20 the vast majority -- the 1.3 percent that became
21 diabetic is a small number but would have a much
22 larger group of patients. Okay, let's see the next
23 slide. I think that may go into more detail; it might
24 help you.
25 Okay. These are people who are diabetic --

1 this is year-1 and year-2; there are a few people in
2 year-2 --but the same trend is there at year-2. Would
3 you like me to go back to the previous slide, or does
4 this give enough information?
5 MR. MOLITCH: My second question with regard
6 to diabetes, you had people who had a change in dose
7 of their sulfonylurea, or they stopped the drug. Were
8 specific criteria used in both treatment groups for
9 when those changes would occur, or were those solely
10 at the discretion of the investigators on a kind of a
11 clinical -- this is kind of what we do type of thing
12 -- or did you have specific -- either glycohemoglobin
13 or blood glucose criteria for those changes in dose,
14 or withdrawal?
15 DR. HAUPTMAN: We were very compulsive about
16 that to ensure that there was consistency, being in a
17 multi-center study, so there were absolute definitive
18 criteria. For example, if the patient had a fasting
19 glucose of less than 65 on one visit, or a fasting
20 glucose being 65 and 90 on two consecutive visits
21 would be a reason for changing the dose. Or if they
22 had hypoglycemic symptoms at home on two consecutive
23 visits.
24 MR. MOLITCH: You also showed urinary
25 oxalate data in our books of one of the patients who

1 developed kidney stones. Do we have urinary oxalate
2 on the larger group as well? I didn't see that data.
3 I wonder if there are any changes in urinary oxalate?
4 DR. HAUPTMAN: Yes. We have that data
5 available. We'll pull it up on a slide for you. This
6 is the summary statistics for 24-hour urines. This is
7 the two studies that we looked at urinary oxalates --
8 161 and 185 -- which were both U.S. studies. We have
9 the year-1 data and this is a large number of pa-
10 tients, placebo and orlistat.
11 The difference between the two treatments in
12 the 95 percent confidence evolves on the far righthand
13 to show that there are no statistical difference
14 between the two treatments in terms of least square
15 mean difference.
16 MR. MOLITCH: There's no baseline data,
17 though?
18 DR. HAUPTMAN: Yes, the baseline data --
19 MR. MOLITCH: Oh, I'm sorry.
20 DR. HAUPTMAN: For example, under placebo
21 there's n, then BL is baseline, and then the change at
22 the end of one year, next to it.
23 MR. MOLITCH: Okay, all right. And my last
24 question relates to the fact that you keep stressing
25 that there's a very small amount of systemic absorp-

1 tion and so we wouldn't expect much systemic problems
2 related to the systemic absorption. This comes then,
3 down to the issues of teratogenicity and pregnancy.
4 Are we concerned about a woman who might
5 become pregnant while taking the medication, or do we
6 have enough data on teratogenicity studies in animals
7 or anybody else that that's not a concern? We don't
8 have to worry about this?
9 DR. HAUPTMAN: Well, we never want a patient
10 to become pregnant while under medication, just in
11 general. But we did do the appropriate reproductive
12 toxicity studies which we have data on, and during the
13 trial we did have a number of patients who become
14 pregnant and the vast majority of the outcomes
15 initially -- all the outcomes were for normal pregnan-
16 cies -- let's see the -- is it the pregnancy slide?
17 We'll show you first, during the study they
18 were not supposed to become pregnant; they were
19 supposed to practice conception. There were 21
20 patients in the placebo group and there were 24
21 patients in the orlistat group. That's the total of
22 live births; spontaneous abortions seemed to be much
23 higher in the placebo group, for whatever reason. And
24 then the others means that we don't know what they
25 are, and the number of induced abortions.

1 But we can show you some information from
2 our pre-clinical data about the reproductive toxicity
3 studies, if you'd like to see some of that.
4 MR. MOLITCH: And no glaring problems with
5 the live births themselves as far as malformations or
6 anything? There was nothing obvious?
7 DR. HAUPTMAN: There was no apparent,
8 reproductive toxicity problems in the studies.
9 ACTING CHAIR SHERWIN: I think there was one
10 baby, wasn't there, that had some problem?
11 DR. HAUPTMAN: There was one patient that
12 had bowed legs at birth -- which was a normal variant.
13 We looked at the vitamin D level of the mother. It
14 was just above the upper level of one value, but they
15 thought that that was a normal variant; all the others
16 were normal births, to the best of our understanding.
17 ACTING CHAIR SHERWIN: And the animal data?
18 DR. HAUPTMAN: We can show the animal data.
19 ACTING CHAIR SHERWIN: You don't have to be
20 -- we can trust you. I mean, if you could tell us.
21 We're trustful people here.
22 DR. KAMM: I don't have the data with me,
23 but --
24 ACTING CHAIR SHERWIN: Okay, well we're
25 going to trust you.

1 DR. KAMM: We conducted the standard
2 reproductive toxicology studies, and so just to
3 explain those. We did a study in the rat on fertility
4 and reproductive performance, and the doses there were
5 up to 800 milligrams per kilogram per day. We did
6 teratology studies in the rat and in the rabbit, also
7 up to 800 milligrams per kilogram per day.
8 And finally, we did a peri-postnatal, so-
9 called Phase III study in the rat up to doses of 800
10 milligrams per kilogram per day. And we saw no
11 adverse effects in any of those studies.
12 ACTING CHAIR SHERWIN: The n's on these rat
13 studies, roughly?
14 DR. KAMM: I'm sorry?
15 ACTING CHAIR SHERWIN: The n's -- just to
16 get a feeling --
17 DR. KAMM: Oh, the standard for these kinds
18 of studies, I believe they were -- the teratology
19 studies at each dose requires 20 pregnant females.
20 ACTING CHAIR SHERWIN: Okay. Dr. Illing-
21 worth? Dr. Critchlow, and then we'll get to Dr.
22 Hirsch -- don't worry.
23 DR. CRITCHLOW: Yes, this is for Dr.
24 Guerciolini. The mineral balance study, sample size
25 of 14. Was that a sample size of convenience or was

1 that designed to -- or, if not, was that designed to
2 detect what difference? You indicated there was no
3 difference in the drug and placebo with those sample
4 sizes, but again, that's fairly small.
5 DR. GUERCIOLINI: Dr. Guerciolini from
6 Clinical Pharmacology. The typical sample size for a
7 mineral balance study is an intensive, well-controlled
8 setting. It usually is small -- six to eight subjects
9 are usually used under this very controlled condition.
10 We actually opted for a larger number of
11 sample, 14 bridge group, in order to meet the statis-
12 tical hypothesis of testing, having a 95 percent
13 confidence interval and an 80 percent power to detect
14 a difference about 10 percent off a body of 5 percent.
15 ACTING CHAIR SHERWIN: Dr. Illingworth.
16 DR. ILLINGWORTH: Because weight loss
17 generally increases biliary lithogenicity, one
18 important question I think is, with a drug that is
19 affecting the absorption potentially of cholesterol
20 and bile acids, what does it do to bile composition?
21 Do you have any data on bile composition from gall-
22 bladder bile?
23 DR. HAUPTMAN: Yes, we do. We did an
24 extensive evaluation. We looked at several aspects,
25 including cholesterol saturation index which showed no

1 change. But Dr. Guerciolini can show you more details
2 of the study if you'd like to see specifically the
3 different components and what happened to them.
4 DR. ILLINGWORTH: Well, if there's no effect
5 then the saturation remains the same?
6 DR. HAUPTMAN: Right. And nor were there
7 microcrystals found, as well.
8 ACTING CHAIR SHERWIN: Dr. Hirsch.
9 DR. HIRSCH: Two or three questions. I may
10 have misunderstood one, so this had to do with the
11 quality of life changes. I thought that there was one
12 parameter of that in year-2 in which there seemed to
13 be an adverse effect on those taking -- it may have
14 gone too quickly for me. Was that --
15 DR. HAUPTMAN: The data -- we can go back
16 and show you that slide.
17 DR. HIRSCH: That's all right. Just tell me
18 -- were they always the same or better for drug
19 treated groups in all parameters?
20 DR. HAUPTMAN: They're always -- the trend
21 was always for improvement with the drug treatment.
22 During the second year there were some differences
23 between the treatments, but the data that I showed was
24 1-year data. It was always better for the drug
25 treated patients.

1 DR. HIRSCH: Okay, several brief things.
2 These were largely -- the ratio of female to male is
3 what, three or four to one?
4 DR. HAUPTMAN: Yes.
5 DR. HIRSCH: Were any of the women on
6 estrogen replacements?
7 DR. HAUPTMAN: Yes, a great deal if I
8 remember. We actually have that data. Most of the
9 post-menopausal women --
10 DR. HIRSCH: How about the ten cases or
11 whatever of the neoplasm -- any difference in whether
12 they were or were not on estrogen replacement?
13 DR. HAUPTMAN: I believe the vast majority
14 were on. Do we have -- I think we have the slide with
15 that, but I think the vast majority were on estrogen
16 replacement. Only three were? We have a slide that
17 actually goes through that.
18 DR. HIRSCH: Okay, but you found no signifi-
19 cant -- I mean, the numbers are so small that I guess
20 you can't tell anything about that.
21 DR. HAUPTMAN: No.
22 DR. HIRSCH: You did no studies of catechol-
23 estrogen secretion. Is there any change in the kind
24 of secretory rates of estrogens as a function of
25 weight loss or drug or --

1 DR. HAUPTMAN: Because this was a surprising
2 finding, we didn't look specifically for that, and
3 based on the mechanism of how the drug worked, we
4 didn't expect to find the problem. Although weight
5 loss itself may change estrogen levels, the grossest
6 way of evaluating it is in the reprotox studies in
7 which there was a disturbance in the metabolism of
8 estrogen, the pregnancy rate may not have held, the
9 more spontaneous abortions. That was a very crude
10 measure. We didn't see anything. But due to the fact
11 that this was something that was totally unexpected --
12 DR. HIRSCH: So there are no detailed
13 studies of estrogen?
14 DR. HAUPTMAN: No.
15 DR. HIRSCH: That might be -- were the drug
16 to be used in the future that might be a good thing to
17 look at perhaps. The concern with malignancy however,
18 is in another division, completely, and that's in the
19 gastrointestinal tract where presumably the drug acts.
20 And I read through very carefully a lot of data on
21 that, which is very reassuring, about no changes in
22 rates of differentiation of colonic cells, various
23 markers for molecular events and colonic epithelium.
24 I did not see, however, something that I
25 would have thought you probably did and you haven't

1 mentioned here, and that is, feeding animals known
2 mutagens for colonic malignancy -- nitroso, diazo
3 compounds, etc. -- with and without alestra, because
4 the natural state would be that we're always eating,
5 or may be eating carcinogens, and one would like to
6 know whether coating the colon with lipid makes a
7 difference in how these things act.
8 Do you have any studies of that? Must be.
9 DR. HAUPTMAN: No, I don't believe there
10 were any studies that were specifically done looking
11 at that.
12 DR. HIRSCH: Beg your pardon?
13 DR. HAUPTMAN: There were no studies done
14 specifically looking at a mutagen of some kind.
15 DR. HIRSCH: Last question is the issue of
16 pancreatic function. Amylases done are normal
17 throughout the studies --
18 DR. HAUPTMAN: Yes. We could have Dr. -- we
19 did a --
20 DR. HIRSCH: I think just an answer.
21 DR. HAUPTMAN: Well, he can -- we looked at
22 amylase, we looked at trypsin -- we saw no decrease
23 following a meal. We measured actual levels following
24 those --
25 DR. HIRSCH: Of trypsin as well? And no

1 changes in groups. Thank you

2 ACTING CHAIR SHERWIN: Dr. Colley.

3 DR. COLLEY: I have three questions. Were

4 you able to identify responders within the first month

5 of treatment?

6 DR. HAUPTMAN: It's very difficult to

7 determine who's going to respond to any treatment in

8 general, and we found something very important when we

9 analyzed all our data and that is, that the effect of

10 orlistat will actually take people who would not

11 respond to treatment and responded. I'll show you

12 some of that information.

13 Remember, we looked at people who were

14 stratified during the placebo lead-in period, and

15 identified people who were good losers or bad losers,

16 and those are the people who are likely -- the good

17 losers who are likely, subsequently, to continue to

18 lose weight at a reasonable rate. And the people who

19 are the poor in that first four weeks of placebo by

20 itself, who don't lose weight, we would predict won't

21 lose weight later on. That's been shown in the

22 literature.

23 Could we have the first slide, please? We

24 called stratum one the poor losers, and these people

25 actually lost very little weight during that lead-in

1 period -- about .6 kilos -- compared to the good loser
2 group, the stratum two group, who lost almost 4 kilos
3 during that four weeks.
4 But then if you look at the mean change,
5 those people on placebo in the stratum one, you would
6 have predicted won't do well later on, still didn't do
7 well -- by the end of one full year, they only lost 2
8 percent of their body weight. The people on orlistat
9 lost over 5 percent.
10 Let's go to the next slide, please. I'm
11 going to show you the difference. These are people
12 who, based on one month of lead-in in which they
13 didn't lose weight, when you put them on orlistat or
14 placebo, the placebo people still don't lose weight,
15 and the orlistat people actually lose a significant
16 amount of weight, so by the end of the study their
17 mean was about 5 percent decrease.
18 Let's go to the next slide which would be
19 the stratum two -- this is stratum two. These are the
20 people during the first month of placebo who you would
21 predict would do well. And in fact, they do much
22 better. The people on orlistat do significantly
23 better.
24 So just to recapsulize, that if you were to
25 predict based on just weight loss alone, that somebody

1 who only lost a half-a-kilo during a lead-in period
2 shouldn't go on drug, you'd be missing a lot of
3 people. Once they're on drug, I would think it's
4 reasonable because weight loss doesn't occur over a
5 short period of time -- it requires a minimum of three
6 months and four months.
7 That a patient who starts off with orlistat
8 should start with a diet and orlistat, and after three
9 or four months, if they haven't lost a reasonable
10 amount of weight -- 5 percent, 6 percent of their body
11 weight -- then they might want to continue, look at
12 some other therapies. But I don't think it's very
13 possible to predict who is going to respond, although
14 those people that we predict who wouldn't respond,
15 that poor loser group, does seem to do quite a bit
16 better.
17 DR. COLLEY: How about in the first month of
18 therapy on treatment though? Is there any difference
19 in overall weight loss with weight loss in the first
20 month? Was that predictive at all?
21 DR. HAUPTMAN: We looked at that also, and
22 those people who are on the first month -- I don't
23 think we have a slide for that -- but those people on
24 the first month who lost very little weight, I think
25 we used the criteria of less than, I think about a

1 kilo or so in the first month, didn't lose weight
2 later on as well.
3 So the fact is, again, it's very difficult
4 to predict who would lose weight and who wouldn't lose
5 weight, and basically most patients should be given a
6 trial, given the opportunity to use the drug, and the
7 diet, and whatever else they need to help lose weight,
8 and after a time that they and the doctor decide is
9 reasonable, then say, well the drug is working, the
10 program isn't working.
11 DR. COLLEY: The second question refers to
12 the improvement in gastrointestinal, or lower GI
13 adverse effects. To what extent is that due to a
14 self-imposed reduction in dietary fat?
15 DR. HAUPTMAN: We looked at those people who
16 were able to lose weight well, losing more than 5
17 percent of their body weight on orlistat versus those
18 who lost less than 5 percent. And we looked at their
19 recall diaries, which are very difficult -- they're
20 useful for comparison between treatment groups, but
21 not useful for estimated total amount.
22 And we didn't see a difference, so I am not
23 sure that GI side effects impose some sort of restric-
24 tion on the patient. And globally, the patients show
25 that, but we don't see a difference in recorded fat

1 intake in the patients who had side effects who didn't
2 have side effects, who lost a lot weight, who didn't
3 lose a lot of weight.
4 Although it might be something that would
5 make sense, but we didn't have any data to show that.
6 DR. COLLEY: Third question refers to the
7 reduction in HDL. There was a reduction early-on in
8 a lead-in period and later on some recovery of that.
9 In patients who started out with and HDL above 35,
10 were there any who ended up on treatment with an HDL
11 below 35? What you showed us is percent reduction but
12 no absolute data on patients who might develop low
13 HDLs, given that it's an independent risk.
14 DR. HAUPTMAN: I do have some data -- why
15 don't we go back -- I'm not sure this will answer
16 exactly the information what -- we may not have, but
17 I think it comes close. Can we go back to the primary
18 B, slide 6, please? This is the HDL with people who
19 have a baseline of less than 35, and we'll see what
20 that shows.
21 But it's important to realize that the
22 decrease in HDL occurred prior to treatment. It was
23 during the placebo lead-in, purely by the change of
24 the diet, the lower fat, the lower cholesterol -- and
25 like I said, data has shown that women in particular,

1 as they begin to lose weight, have greater decreases
2 in HDLs than men.
3 Okay, great. At the week -4 datapoint, it's
4 the mean LDL at week -4 for the placebo group and
5 orlistat group is 35 and 36, respectively. After four
6 weeks of treatment with just placebo alone and diet,
7 it dropped down to a mean of 31 in both groups, and
8 then by the end of treatment it was up to 37.
9 So we haven't looked at people who started
10 out high and ended low, but it probably would be in
11 our database. But the trends were that losing well --
12 it's well known that losing weight will increase the
13 LDLs, but not as much as you would expect assuming
14 that looking for -- as far as your initial -- from
15 your initial to the end of treatment, is a small
16 increase -- maybe 3, 4, 5 percent.
17 So weight loss by itself is not that great,
18 especially for people with lower levels to start with.
19 ACTING CHAIR SHERWIN: Dr. Cara.
20 DR. CARA: Why were most of the women, or a
21 large number of women, on estrogen? What percent
22 actually were and why?
23 DR. HAUPTMAN: Estrogen replacement therapy
24 for post-menopausal women?
25 DR. CARA: Yes. Oh, I see. And what -- do

1 you have any sense of what percent?

2 DR. HAUPTMAN: Ninety percent of the post-

3 menopausal women in the study -- and these people were

4 on it prior to entering the study, for the most part.

5 DR. CARA: How would that have skewed the

6 information that you presented regarding vitamin D and

7 calcium?

8 DR. CANNOVATCHEL: Dr. Cannovatchel. We

9 identified those women who were post-menopausal at the

10 time of randomization, receiving estrogen replacement

11 therapy. Of that population that then continued the

12 estrogen throughout the study participation, which was

13 -- when we looked at their vitamin D levels, realizing

14 that estrogen replacement will increase vitamin D

15 binding protein.

16 So in order to make these groups more

17 comparable, over a 1-year period to have the largest

18 amount possible of post-menopausal women on estrogen,

19 over the 1-year period we see that essentially there's

20 no difference between either treatment group.

21 DR. CARA: How about the women that were not

22 on estrogen therapy?

23 DR. CANNOVATCHEL: the numbers were very

24 small -- three and five -- and I --

25 DR. CARA: Do you have similar data, though?

1 DR. CANNOVATCHEL. It was difficult to
2 compare. We'd have to go and get the data. It was
3 similar -- not different enough that.
4 DR. CARA: Did you look at sex hormone
5 levels in the men?
6 DR. CANNOVATCHEL: Sex hormone levels in men
7 were not done.
8 DR. CARA: In the men in the study, they
9 were not done?
10 DR. CANNOVATCHEL: Sex hormone levels in men
11 were not studied.
12 DR. CARA: Thank you.
13 ACTING CHAIR SHERWIN: Cathy.
14 DR. CRITCHLOW: Just a quick follow-up to
15 one of Dr. Colley's questions. Were food diaries or
16 some other measure of compliance with the diets, used
17 or assessed, and was there any difference in compli-
18 ance in diet between drug and placebo?
19 DR. HAUPTMAN: We did do food diaries and we
20 looked at it, not for purposes of compliance, but just
21 to understand what was happening during the study, and
22 there were no essential differences between the
23 orlistat group and the placebo group over two full
24 years. They remained very similar -- wherever they
25 started from they remained similar over time. And

1 again, these are difficult things to look at, but
2 there were no major differences.
3 DR. CRITCHLOW: And with the breast cancer,
4 was the detection of those neoplasms incidental, in
5 the sense -- I mean, there was no breast exam or
6 mammograph, that was routinely used, either at
7 baseline or during follow-up?
8 DR. HAUPTMAN: Mammography was not routinely
9 used. Physical exam was used, but I can't attest as
10 to whether or not the patients exactly got breast
11 exams at that time. But the vast majority of these
12 were incidental findings on mammography.
13 ACTING CHAIR SHERWIN: I guess one of the
14 questions that had been asked earlier was, the
15 denominator for how many people actually had breast
16 exams or mammography. We know that a certain percent-
17 age of the patients are reduced because they were men,
18 and then of the women of that studied, we don't really
19 know how many women were actually examined.
20 Is there any way to get that information,
21 because it could be 9 out of 100 or it could be 9 out
22 of 1000. I don't have a good sense of the numbers and
23 whether there are statistical differences.
24 DR. HAUPTMAN: Yes, this is of concern to us
25 as well, and we've been thinking of ways of getting it

1 other than the possibility of tracking down each
2 patient and trying to -- you know, there are 4,000
3 patients, half of them in the United States, half in
4 Europe. The mammographies that are done in Europe are
5 done under a different schedule, suggested schedule --
6 they're done much less frequently versus the ones in
7 the United States.
8 So we're, given this thought, we felt that
9 this was just such a difficult task and we're not sure
10 what the yield rate would be. It's something that we
11 just don't have.
12 ACTING CHAIR SHERWIN: I think there must be
13 a simple question is that you could send out to the
14 people to just ask if they've had a breast exam or
15 mammography during the course of the study. I don't
16 think that would be a very difficult thing to accom-
17 plish.
18 Because I think it is important, because
19 we're not given statistics. Am I right on that or am
20 I wrong? I wasn't sure if we actually had statistical
21 data on the incidence, you know, the relative risk.
22 Is there statistical difference? Even though obvious-
23 ly, the numbers are small.
24 DR. HAUPTMAN: I'm going to ask one of our
25 consultants from our expert panel, to provide some

1 information on this. I think we may also get the
2 slide of the relative risks -- of the risks, as well.
3 But I'd like to introduce Dr. Robert
4 Greenberg; he's a professor of Medicine from Dartmouth
5 Medical School. Dr. Greenberg is Director of the
6 Norris Cotton Cancer Center and the Board of Scientif-
7 ic Counselors, Division of Cancer Prevention and
8 Control, The National Cancer Institute, who may be
9 able to shed some light on how we looked at our data
10 and what we used to support our database.
11 DR. GREENBERG: I'll try to answer the two
12 questions that were raised as best I can. I think the
13 first question had to do with screening behavior and
14 surveillance of these women, and I think the answer
15 that -- we asked the same question and I don't think
16 there is an answer. It was not recorded.
17 I think it would be difficult to get the
18 information in a believable way. Women actually
19 aren't that good at reporting their recollections of
20 breast screening procedures in the remote past, and it
21 would require probably going to medical records, and
22 we were told that that might not be feasible.
23 To get an estimate of the actual numbers, I
24 think if you look at the expected numbers that were on
25 the slide, that gives you a pretty good estimate of

1 the actual denominators of women at risk.

2 And I don't have the exact data from which
3 those numbers were calculated, but it was based on the
4 age distribution of the women, their length of time
5 under observation. And the last part was the area,
6 either in Europe or U.S. Those numbers observed
7 probably should be diminished by one in the placebo
8 group and by one in the orlistat group, because two
9 cases were carcinoma in situ, which would not ordi-
10 narily go into the calculation of expected cases.

11 In women in this age range, as a rough
12 estimate, there would be one to two breast cancer
13 cases per 1000 women per year, so that gives you an
14 idea of the actual number of women under observation.

15 For tests of statistical significance, if
16 you had specified this hypothesis a priori, this
17 almost certainly would achieve statistical signifi-
18 cance. Since the hypothesis was not specific a
19 priori, it became very difficult to put any kind of
20 meaningful interpretation on this. As was suggested,
21 this was a wholly unexpected finding and in part, the
22 analysis of the data were directed by the observations
23 themselves.

24 So for example, this slide does not have
25 data for women who received 30 milligrams of orlistat,

1 and that too, would add to the expected cases. I hope
2 that helps.
3 ACTING CHAIR SHERWIN: The last question on
4 that issue is, what's the effect of altering fat in
5 the diet, on breast cancer?
6 DR. GREENBERG: Well in -- I think we know
7 the answer to that much better in animals than we do
8 in humans, and in fact as I'm sure many of you are
9 aware, there's a very large clinical trial that's
10 addressing exactly that issue.
11 Among people who strongly adhere to the diet
12 breast cancer hypothesis, the notion is that if you
13 reduce dietary fat you'll reduce breast cancer risk.
14 But the epidemiological data are not totally consis-
15 tent on that, but the prevailing opinion would be that
16 reduction of dietary fat or reduction of reduction of
17 dietary fat absorption would if anything, reduce risk
18 rather than increase it.
19 ACTING CHAIR SHERWIN: Right, right. That
20 was my understanding, too. I just have a couple more
21 questions. I know it's late and I'll keep it brief
22 because I know we all want a break. One thing that
23 struck me was that as you look at the weight reduction
24 over time in the individuals, even in the first year
25 it does begin to plateau out. And also over time, the

1 symptoms diminish.

2 And so my question is, does the effect of
3 the drug on fat absorption persist over time? Is this
4 effect related -- could it be that over time the drug
5 becomes less effective? Have you look at fat excre-
6 tion, not just in the first couple of weeks but after
7 one year?

8 DR. HAUPTMAN: We looked at fat excretion at
9 the beginning of the study, at six months, one year,
10 and two years. For the patients on the 120 milligram
11 dose of orlistat, the average fecal fat excretion was
12 about 22 grams of fat per day, and that stayed
13 constant over the entire two full years of the
14 program.

15 The reason for there being a plateau is
16 probably due to the fact that as patients lose weight
17 their total energy expenditure decreases and they'd be
18 coming to a new balanced, steady state. And the
19 plateau that we've seen with the drugs that are
20 available and some of the standard diets available
21 today, produce around a 10 percent decrease before you
22 get a plateau.

23 ACTING CHAIR SHERWIN: Okay, I can accept
24 that. Did you look at post-prandial triglyceride
25 levels? I think there was some data in the handout on

1 that, although I didn't have a sense of how carefully
2 that was looked at in individuals with insulin-
3 resistance or hyperlipidemia. You'd theoretically
4 think that it might increase post-prandial triglycer-
5 ide.
6 DR. HAUPTMAN: We looked at post-prandial
7 triglyceride levels following a load of oral fat,
8 usually around 100 grams. We didn't do it in all
9 patients. We did it in special clinical pharmacology
10 studies and we did some other detailed analysis and
11 sometimes studies by using retinol palmitate versus
12 triglyceride, which may be a better marker.
13 I think we have some data that we can just
14 show you the triglyceride levels. They are either the
15 same or decreased compared to the placebo group, but
16 we didn't look at it specifically for the hyperinsuli-
17 nemia.
18 ACTING CHAIR SHERWIN: Okay. Did you finish
19 your 1.25 dihydroxy vitamin D as well?
20 DR. HAUPTMAN: I don't think we did -- no,
21 we didn't do 1.25; we just did 25 and PTH.
22 ACTING CHAIR SHERWIN: Okay. And one other
23 question in terms of, the patients were on a specific
24 diet that was relatively low in fat. If people had
25 increased their fat intake, does that affect their

1 symptoms?

2 DR. HAUPTMAN: It does. The drug will
3 inhibit 30 percent, on average, of however much fat
4 you take in. If you take in a diet of 90 grams of fat
5 per day, you'll lose on average, 30 grams of fat --
6 which is about the limit of tolerability based on
7 studies looking at people with chronic pancreatic
8 insufficiency.

9 We did early studies on, in our clinical
10 pharmacology program, with the same dose of drug and
11 different amount of fat. We found that the lower the
12 amount of fat, the better the tolerability. When you
13 get to very high levels of fat, the worse the tolera-
14 bility.

15 ACTING CHAIR SHERWIN: Dr. Cara.

16 DR. CARA: It appears that you're requesting
17 the FDA to approve Xenical™ for a very broad indica-
18 tion: long-term therapy of obesity. Have you thought
19 about what sorts of patients you're going to exclude,
20 what contraindications there might be? The issues
21 that I'm considering specifically is the potential use
22 and abuse of the medication by teenagers -- teenage
23 girls especially.

24 Have you thought about what sort of warning
25 labels, methods you might use to kind of decrease that

1 likelihood?

2 DR. HAUPTMAN: We have. The drug is to be,
3 obviously, used and prescribed by a physician in
4 consultation with the patient. As for any individual
5 patient -- first I'll answer about the length of
6 therapy -- that question first.

7 Obesity being a chronic, long-term disease,
8 it requires chronic, long-term treatment. Our drug
9 was studied for two full years to give the physician
10 the ability to treat a patient long-term and to know
11 what they can expect in terms of side effects,
12 tolerability, and efficacy.

13 For any individual and patient, the decision
14 on how long will you take pharmacologic treatment, how
15 long will you use behavioral modification -- this is
16 on an individual basis. Nevertheless our studies were
17 able to show that you could use it long-term.

18 As for preventing the wrong people from
19 getting the drug, we perfectly agree with you that
20 people who are not obese, people who have bulimia or
21 anorexia or young teenage girls who want to lose a few
22 pounds, are the inappropriate group of patients to use
23 it. But we at this point, can only rely on the
24 doctors and the people giving the drug, to prevent it
25 from getting in the wrong hands.

1 That being said, we believe that the
2 tolerability of the drug is at a very low level, and
3 that the risks of somebody inappropriate using the
4 drug, are quite low. And not the risks of somebody
5 inappropriately using it but somebody inappropriately
6 using it having an increased risk because of using the
7 drug.
8 We believe that's quite low based on the low
9 systemic absorption, and it does have this built-in
10 mechanism to prevent you from using it too inappropri-
11 ately because patients who have, in our clinical
12 studies, tried to take milkshakes or binge, thinking
13 the drug would help that, have found out very quickly
14 that the side effects prevent them from doing that
15 again. Most people try it once and don't try it
16 again.
17 Nevertheless, it's still, you know, really
18 very much in the hands of the practicing physician to
19 give it appropriately.
20 ACTING CHAIR SHERWIN: I think we'll get
21 into the issues about who should be using the drug a
22 little later, and we'll expand on this. But I think
23 it's time for a break. We've been here way beyond our
24 limits here. And I would like to call a break for
25 only about five minutes -- or ten minutes, I'll give

1 you ten. I'll give you a compromise.

2 (Whereupon, the foregoing matter went off

3 the record at 11:33 a.m. and went back on

4 the record at 11:51 a.m.)

5 ACTING CHAIR SHERWIN: I think we can begin.

6 I think we have two choices: either we begin or we

7 all move to Paris and convene the meeting there.

8 Okay, we'll now begin with the FDA presentation and

9 that will be conducted by Eric Coleman.

10 DR. COLEMAN: I'd like to begin my presenta-

11 tion focusing on some issues related to efficacy; in

12 particular look at the weight loss results over one

13 year of treatment, and talk a little bit about the

14 weight loss results from two years of treatment. And

15 finish up efficacy taking a look at the effect of

16 orlistat on some of the major obesity-related comor-

17 bidities: those being lipids and blood pressure.

18 The second part of my discussion will focus

19 on some safety issues. Fat soluble vitamins we've

20 heard about. I'd also like to spend some time

21 discussing issues related to kidney stones and some

22 issues related to bone metabolism.

23 There were seven Phase III studies conducted

24 with orlistat. The studies I've shown here in blue

25 all contained a 1-year treatment arm. The four top

1 studies in blue contained 2-year treatment arms.

2 Now, these studies were very similar in

3 design. They contained similar patient populations,

4 and moreover, the results across the studies were

5 comparable. And therefore I've chosen to pool these

6 data and show you the results from the pooled analy-

7 ses. So when I show you one year of pooled data it is

8 from these five studies, and any reference to two-year

9 pooled data refers to these four blurry studies.

10 One last thing. Because the proposed dose

11 for marketing is 120 milligrams, I will restrict my

12 comparisons to placebo versus 120, and I will not

13 mention 60 or 30 milligrams.

14 This is to give you a sense of the number of

15 patients who were studied over the course of a year in

16 the five pooled studies. There were over 1500

17 orlistat patients randomized, and over 1000 placebo

18 patients randomized. These numbers here are not

19 accurate. For numbers who completed, this was about

20 1,072 patients in the orlistat group, and just over

21 700 patients completed in the placebo group.

22 That translates into a completion rate of

23 about 68 percent for orlistat and 62 percent for

24 placebo. Those are rather impressive completion

25 rates.

1 The placebo and orlistat groups were well
2 matched at baseline. That majority of the patients
3 were female and caucasian; the mean age was 44 years;
4 and the mean BMI was 35.
5 Now we'll get into the weight loss data.
6 This slide shows a mean percent change in body weight
7 over the course of a year, and it does include that 4-
8 week placebo lead-in case, during which time patients
9 in the pooled analysis lost about two-and-a-half
10 percent of their initial body weight.
11 You can see that there was a fairly rapid
12 loss of weight for the first 12 weeks in both groups,
13 and then there was a plateauing -- somewhat of a
14 plateauing down here in orlistat towards the end of
15 the 52 weeks of double-blind treatment.
16 At the end of the study the orlistat group
17 had lost about 9 percent of initial body weight, and
18 about six-and-a-half percent of baseline body weight.
19 The placebo group had lost somewhere between 5 and 6
20 percent of initial body weight, and two-and-a-half to
21 3 percent of baseline body weight. The difference
22 between the two groups here in mean percent weight
23 loss was about 3 to 4 percent.
24 Now, another way to look at weight loss
25 efficacy is by the so-called categorical analysis.

1 This slide shows the percent of patients who lost at
2 least 5 percent of baseline body weight following one
3 year of treatment. And as you can see, there was
4 significantly more patients in the orlistat group who
5 achieved this 5 percent weight loss goal compared to
6 placebo. Roughly 57 percent versus 32 percent, and
7 the difference was statistically significant.
8 In a similar manner, if you look at the
9 percent of patients who lost at least 10 percent of
10 baseline weight, again you see a significant differ-
11 ence between drug and placebo. Roughly 27 percent of
12 orlistat patients achieved this 10 percent goal versus
13 12 percent of placebo. Again, the difference being
14 statistically significant.
15 At this point I'd like to show you the 2-
16 year weight-loss data. This show the mean percent
17 change in body weight for continuous treatment over
18 two years. Placebo received placebo for two continu-
19 ous years and orlistat was 120 milligrams for two
20 continuous years. Again, this is pooled data from
21 four Phase III studies.
22 During the 4-week placebo lead-in period
23 patients lost about 3 percent of initial body weight.
24 Thereafter, you again see this rapid weight loss
25 during the first 12 weeks and then a plateauing, and

1 then a gradual increase towards the end of the study.

2 As we heard earlier, at the beginning of the

3 second year of treatment, things changed. The diet

4 was changed by-and-large, from a hypocaloric to a

5 eucaloric diet; there was less intense behavior

6 modification; and in general, the patients did not

7 receive the same amount of attention they did during

8 the first year. This may in some ways, reflect what

9 will happen out in the marketplace, rather than the

10 strict conditions followed during the first year of

11 the trial.

12 Again, by the completion of the study, the

13 orlistat group had lost about 3 to 4 percent more

14 weight loss on a mean basis compared to placebo --

15 similar to the one-year results.

16 Categorically, again, there were signifi-

17 cantly more patients in the orlistat group who lost at

18 least 5 percent of baseline weight after two years of

19 treatment compared to the placebo subjects. The same

20 pattern was seen when you look at the percent of

21 patients who lost at least 10 percent of baseline

22 weight following two years of treatment. Again,

23 orlistat was significantly greater than placebo.

24 To quickly summarize the efficacy results,

25 the guidance document that the Division has published,

1 states two efficacy criteria. The first criteria
2 states that the mean drug-associated weight loss be 5
3 percent greater than the mean placebo-associated
4 weight loss, and that difference should be statisti-
5 cally significant.
6 Well, we see here that using that first
7 criterion, orlistat fell a little bit short of the 5
8 percent. However, when we look at the categorical
9 analysis which says that the proportion of patients
10 who maintain a 5 percent weight loss should be
11 significantly greater in drug versus placebo, certain-
12 ly orlistat met this second criterion. And again,
13 significantly more orlistat-treated subjects lost at
14 least 5 and 10 percent of baseline weight.
15 Onto some issues of comorbidities, the major
16 comorbidities with obesity being hyperlipidemia,
17 hypertension, and glucose intolerance. I want to show
18 you some data on the lipids and blood pressure and
19 then briefly mention some of the glucose and insulin
20 data.
21 This slide shows the mean percent change in
22 lipids from baseline to year-1. Again, this is
23 baseline, not initial value. This is at the point
24 where patients were randomized to drug or placebo.
25 Placebo is shown in orange; aqua represents orlistat;

1 percent change along the Y-axis.

2 You can see that with total cholesterol and

3 LDL cholesterol there were small increases from

4 baseline in placebo group, whereas there were small

5 reductions in total cholesterol and LDL from baseline

6 in the orlistat group; such that the differences

7 between the two groups were statistically significant.

8 The clinical significance of those individu-

9 al changes is minor to modest. With regard to HDL,

10 you can -- the mean HDL levels increased in both

11 groups, and actually increased to a greater extent in

12 the placebo group; whereas triglyceride levels did not

13 do much of anything in either of the two groups.

14 Now, this is analogous to looking at the

15 weight loss by group means, and we also can look at

16 weight loss by categorical analysis. This next slide

17 is somewhat of a categorical analysis for the lipid

18 data. This shows the mean percent change in lipids by

19 degree of weight loss -- again, baseline to year-1.

20 And the categories of weight loss are: less

21 than 5 percent of weight loss -- which include weight

22 gain; we have greater than or equal to 5 percent but

23 less than 10 percent weight loss; and greater than or

24 equal to 10 percent weight loss.

25 If we look at total cholesterol first and

1 focus on the placebo patients, you see that as you
2 lose more weight, there was not much change in total
3 cholesterol in the placebo subjects. It did go down
4 a little bit when they got up to 10 percent weight
5 loss, however, it was still above the baseline.
6 In contrast, if you look at the orlistat
7 numbers you do see a graded reduction in total
8 cholesterol as you increase the weight loss. A
9 similar pattern was seen with LDL. Again, graded
10 reductions with increasing weight loss on orlistat.
11 And the differences between these two treatment groups
12 were statistically significant for total cholesterol
13 and LDL.
14 If you recall, the HDL, the mean levels,
15 increased in both groups and they increased to a
16 greater extent on placebo, and that is reflected in
17 this analysis as well. You see that as weight loss
18 increases, you see graded increases in the HDL levels
19 in both groups, and to a greater extent in placebo
20 versus orlistat. Again, these were statistically
21 significant.
22 Triglycerides didn't change much at all on
23 the mean analysis, but you did see a nice reduction in
24 triglyceride levels in both groups when you had
25 increasing amounts of weight loss. This is what you

1 would expect.

2 Onto blood pressure. This is a slide
3 showing the mean change in blood pressure from
4 baseline year-1. Again this reflects pooled data.
5 I'd like to point out the Y-axis here; it's a rather
6 tight axis. This goes from zero to 0.6 millimeters of
7 mercury, and zero to -1.2 millimeters of mercury.

8 You can see that in placebo there were small
9 increases from baseline in both systolic and diastolic
10 blood pressure; whereas there were small reductions
11 from baseline in systolic and diastolic blood pressure
12 in the orlistat group. Again, the relative difference
13 here is significant, both statistically and some would
14 argue that this is a clinically meaningful change,
15 even though it's on the order of one-and-a-half to 2
16 millimeters of mercury.

17 I briefly want to just comment on fasting
18 blood sugar and fasting insulin as far as the mean
19 changes. They were more or less similar to this
20 pattern. There was a relative improvement in fasting
21 blood sugar of about one milligram per deciliter in
22 favor of orlistat, and there was a relative improve-
23 ment in fasting insulin of about 10 picamoles per
24 liter for fasting insulin.

25 To summarize, there were small-to-modest

1 improvements in the individual comorbidities, but when
2 viewed in total, they represent a more substantial
3 improvement in the overall risk factor profile. All
4 of the comorbidities did change in the appropriate
5 direction.
6 I'd like to shift now to some safety issues
7 starting with the fat-soluble vitamins and then
8 mention kidney stones and bone metabolism. We've
9 heard a lot this morning about the fat-soluble
10 vitamins; I won't spend a great deal of time on them.
11 I just want to refresh your memory that vitamin status
12 was assessed by measuring plasma levels for some of
13 the vitamins. And those were vitamins A, D, E, and
14 beta carotene. And vitamin K status was assessed by
15 measured prothrombin time.
16 At this point I'm going to shift and go to
17 the overhead to show you a summary slide. This slide
18 represents data from four Phase III studies: two U.S.
19 and two non-U.S. studies. I think it's a nice
20 summary. It shows the percent of patients with at
21 least two consecutive low vitamin values. And low is
22 defined as below the lower limit of normal for the
23 laboratory.
24 You can see that with vitamin D, E, and beta
25 carotene there were significantly more patients on

1 orlistat versus placebo that had two consecutive low
2 values. In the case of vitamin D it was 12 percent
3 versus 6, and for vitamin E it was roughly 6 percent
4 versus one-and-a-half percent, and similar for beta
5 carotene.
6 As we heard earlier, vitamin A levels -- the
7 plasma levels -- did not change significantly through-
8 out the studies, and there were no differences between
9 the two groups.
10 I think it's fair to say that orlistat does
11 inhibit the absorption of vitamins D, E, and beta
12 carotene. There is some merit to saying that when you
13 express vitamin E to LDL ratio, the reductions are not
14 quite as significant, but in some studies there were
15 still some significant differences between drug and
16 placebo when you expressed it as a ratio.
17 In addition, by-and-large, when you looked
18 at the mean changes, they were not great. However,
19 throughout the protocol, more orlistat-treated
20 patients received or required a vitamin supplement,
21 and in many cases they received a multi-vitamin
22 supplement, so it included other fat-soluble vitamins.
23 So that by the end of two years of treatment you may
24 have minimized the difference between the two groups
25 simply because more subjects on drugs were supplement-

1 ed with multi-vitamins.

2 And I'd like to briefly comment on vitamin

3 K; I think this requires some thought. Prothrombin

4 time was used to assess vitamin K status and prothrom-

5 bin time by most people's account, is a fairly

6 insensitive measure of vitamin K status.

7 PT did not change significantly throughout

8 the clinical trials, that is true. But I suspect that

9 unless you had severe vitamin K deficiency you

10 wouldn't see changes in prothrombin time. There are

11 more sensitive measures of vitamin K status, one being

12 under carboxylated osteocalcin.

13 The company did mention they did do a small

14 study -- I believe it was an interaction study with

15 coumadin -- where they did look at osteocalcin and

16 under carboxylated osteocalcin. I would just add that

17 that was a fairly small study and it was short-term,

18 and that is the only data I know of in the NDA that

19 used some more sensitive measures of vitamin K status.

20 So I would be left saying that we don't have

21 a complete picture of what orlistat does to vitamin K.

22 Again, we can feel assured that it doesn't cause

23 severe vitamin K deficiency, but more subtle deficien-

24 cies may have been missed because of the methodology

25 used.

1 One other issue related to vitamin supple-
2 mentation. I think this is an interesting study; it
3 has a unique feature. In study NM14302 -- this is a
4 large study. The first six months all patients
5 received placebo and they were then randomized for a
6 double-blind treatment for a year with placebo or
7 drug. It was a large study.
8 And the unique feature about this study is
9 all patients received a multi-vitamin supplement with
10 breakfast from the very beginning of the study. And
11 this is the only study in the NDA where all patients
12 are supplemented up-front. The fact that they were
13 instructed to take it with breakfast and therefore we
14 assume they took it with orlistat, may be something to
15 think about.
16 The supplement was a Centrum and this is
17 what the Centrum contains as far as the fat-soluble
18 vitamins, and this is the actual type of vitamin. It
19 also contained the routine water-soluble vitamins.
20 This slide shows the percent of patients
21 with at least two consecutive low vitamin values for
22 this study. And we see the same pattern here for a
23 larger number of patients on drug versus placebo who
24 met this goal. However, in this case these differenc-
25 es were not statistically significant.

1 Now, that may reflect that the supplementa-
2 tion actually worked or maybe this is a reflection of
3 sample size. Again, vitamin A levels did not do much
4 of anything.
5 This slide shows the percent of patients
6 that required an additional supplement on top of the
7 supplement that they had already received from the
8 beginning of the study. And this shows that roughly
9 20 percent of orlistat patients compared to 4 percent
10 of placebo patients required an additional supplement
11 because they had two consecutive vitamin levels.
12 Again, the difference was statistically significant.
13 And what I'm left with when I look at these
14 data is, this comment. Providing a vitamin supplement
15 with breakfast may not be the optimal dosing regime.
16 It's not simply breakfast, but I think the fact that
17 the drug was given around that time is going to
18 interfere with the absorption on the fat-soluble
19 vitamins.
20 This raises some questions. What is the
21 optimal time to supplement patients, if indeed all
22 patients are going to be -- if we're going to require
23 or suggest that all patients are supplemented. What
24 time should they be supplemented?
25 The other issue is, would it be worthy of

1 consideration to do a placebo-controlled study where
2 half of the orlistat patients get a multi-vitamin and
3 the other half get a placebo vitamin? That is really
4 the only true way to look at the efficacy and safety
5 of a vitamin supplement.
6 I'll leave you with those thoughts as I move
7 on to kidney stones. We know that patients that have
8 malabsorption of fat have an increased incidence of
9 calcium oxalate stones, and this is presumably due to
10 the fact that when the dietary fat reaches the colon,
11 it increases the permeability of the mucosa to dietary
12 oxalate, and then the oxalate load reaches the kidney.
13 The sponsor was aware of this and they did
14 several things to address this concern. They measured
15 renal ultrasounds on a large number of patients. They
16 did, in one study, measure 24-hour urinary oxalate
17 after a year and two years of treatment. And of
18 course, we have the adverse event reporting related to
19 kidney stones.
20 But first, the ultrasounds. This slide
21 shows the percent of patients with kidney stones
22 visualized by ultrasound after one year of treatment.
23 And these are patients who had absolutely normal
24 baseline ultrasounds. Again, I want to emphasize, the
25 scale here goes from zero to 0.8 percent, so we're

1 talking about a very small number of patients.

2 What was seen there was, one patient out of

3 573 placebo who developed a stone after one year of

4 treatment, and that was visualized by ultrasound. It

5 was presumably asymptomatic as well. In the orlistat

6 group there were 7 out of 871 patients who had a

7 newly-visualized zone. The p-value here is .12.

8 If you look at 2-year data, this is percent

9 of patients with kidney stones. This doesn't reflect

10 year-2 in the sense of, at the end of year-1 to year-

11 2; this reflects two years of continuous treatment.

12 And again, the scale here is fairly narrow. What

13 we're seeing here -- there was one out of 380 placebo

14 patients who had a newly-visualized kidney stone, and

15 5 out of 548 placebo patients had a newly-visualized

16 kidney stone. Again, presumably asymptomatic. P-

17 value here of .15.

18 The 24-hour urinary oxalate data was

19 developed in study NM14161. Patients had urinary

20 oxalate measured at baseline and after one and two

21 years of treatment. At baseline there were 191

22 orlistat and 199 placebo patients. This slide shows

23 the changes in 24-hour oxalate after one year and two

24 years of treatment. Oxalate levels in milligrams per

25 deciliter along the Y-axis.

1 You can see after one year of treatment
2 essentially no changes in urinary oxalate levels in
3 either group. At year-2 the oxalate level increased,
4 the mean level increased by about 8 milligrams per
5 deciliter in the orlistat and it did not change at all
6 in the placebo group. This p-value was .26.
7 Another way to look at the oxalate data from
8 this study, percent of patients with marked elevations
9 of urinary oxalate, and that's defined as greater than
10 1111 micromoles per day. There were roughly 5 percent
11 of orlistat patients who achieved this cut-off in
12 contrast to 1.8 or so placebo patients. And the p-
13 value here is .05 if you use an intent-to-treat
14 analysis that is in the denominator including all
15 patients at baseline.
16 Moving on to adverse event reporting, here
17 we see no evidence that orlistat has any effect on the
18 symptomatic development of -- development of symptom-
19 atic kidney stones. The incidence of recorded stones
20 is actually lower in orlistat than placebo, renal
21 colic was actually lower in orlistat versus placebo.
22 To try to interpret this, orlistat may
23 increase the levels of urinary oxalate, but that is
24 not conclusive by any means. Orlistat may increase
25 the incidence of kidney stones visualized by ultra-

1 sound. Again, there's a suggestion for that, but
2 these were asymptomatic stones.
3 Again, it's not definitive; there is a
4 possibility that the differences were due to change,
5 although the p-values were not extremely high. And
6 there was no evidence that orlistat increased the
7 incidence of symptomatic stones.
8 I'd like to finish off with a discussion of
9 the effect of orlistat on bone metabolism. Because of
10 concern about the effects of the drug on vitamin D
11 absorption and possibly on calcium absorption, the
12 company did look at a number of different bone
13 parameters in patients treated with drug and placebo.
14 I'd like to show you some of these data.
15 In one center in this study, 119C, 16
16 orlistat and 14 placebo patients were treated for one
17 year. And they had a number of bone metabolism
18 studies conducted, among them parathyroid hormone and
19 bone mineral density by DEXA.
20 This first slide shows that the groups were
21 well matched. The mean age was 41 years; they were
22 predominantly female; all caucasians; and the mean BMI
23 was thirty-five-and-a-half. If you look at the mean
24 change in parathyroid hormone from baseline to year-1
25 we see very little change in the mean levels. And

1 these are the changes. Again, the difference in the
2 changes is not statistically significant.
3 This slide shows the mean change in bone
4 mineral density from baseline to year-1. We have
5 total BMD, LSpine BMD, and forearm BMD. Again,
6 strictly speaking, there were no statistically
7 significant differences between the two groups. The
8 greatest absolute difference was shown at the LSpine
9 where the placebo group had an increase of .07 grams
10 per centimeter squared, and the orlistat group had a
11 reduction of 1.1 grams per centimeter squared. Again,
12 the p-value was .2.
13 I'm going to return to the overhead. These
14 were some other data that were collected during this
15 study. Osteocalcin is shown here. Again, these are
16 the changes from baseline. In the placebo group it
17 went up .7, in the orlistat group .1; not statistical-
18 ly significant.
19 This shows the ratio of urinary hydroxypro-
20 line to creatinine, and in the placebo group it
21 increased by two and it increased by eight in the
22 orlistat group. P-value was .02. I showed you the
23 parathyroid hormone; it didn't show anything. And
24 this is 25 hydroxy D_2, D_3. Again, changes were
25 comparable and no significant different.

1 The hydroxyproline is the only one that
2 merits any kind of comment, and I must admit it's
3 difficult to interpret, given the rest of the data.
4 And afterwards, the company may want to respond to
5 this finding.
6 There was another study where they measured
7 bone mineral density. This was in a subset in this
8 study, BM1419. At baseline there were 17 orlistat
9 patients and 19 placebo patients who were culled out
10 to be studied with bone mineral density. This shows
11 the ages of the participants. They were primarily
12 female, the mean BMI was 34. The orlistat group lost
13 a mean of 7 kilograms and the placebo lost a mean of
14 4 kilograms.
15 And this shows the baseline total body mass,
16 total bone mineral density at baseline was 1.24 in the
17 orlistat group. After two years of treatment it was
18 down to 1.23. In the placebo group they started at
19 1.21 and went up to 1.22.
20 The company also mentioned some of the
21 parathyroid hormone data earlier which didn't show
22 anything significant. Therefore, to provide an
23 overall conclusion regarding efficacy, the categorical
24 analysis support the weight loss efficacy of orlistat.
25 The comorbidities are so important that I now call

1 them "cormorbidities".

2 And the comorbidities do improve as weight
3 loss increases -- what you'd expect and hope for.
4 Regarding some safety issues, I believe that there is
5 good evidence that orlistat does inhibit the absorp-
6 tion of some of the fat-soluble vitamins. Vitamin A
7 levels did not change in the plasma, but it's entirely
8 possible that hepatic stores were reduced to maintain
9 the plasma levels, and that's supported by some of the
10 pre-clinical data.

11 I put a question mark behind kidney stones
12 simply because the increase -- the possible increase
13 in incidence of kidney stones was detected by ultra-
14 sound. They're presumably asymptomatic. There's
15 still a change the differences -- a possibility the
16 differences were due to chance -- and there was no
17 difference in the symptomatic reporting of kidney
18 stones.

19 So the clinical relevance of those stones
20 that were visualized, if they're very small they may
21 stay very small and never amount to anything. We just
22 don't know at this point.

23 And I've put a question mark behind bone
24 simply because if there is concern about vitamin D and
25 calcium with this drug, the most definitive way to

1 answer a question about bone metabolism is to measure
2 bone mineral density in a fairly large number of
3 patients over a fairly long period of time. And this
4 question mark simply reflects the fact that we had
5 very few patients measured over one and two years with
6 bone mineral density DEXA data.
7 So I think I'll stop at that point and take
8 questions if there are any.
9 ACTING CHAIR SHERWIN: Dr. Colley. You
10 raised your hand?
11 DR. COLLEY: I did. Do you recommend any
12 routine monitoring of vitamin D levels, and if so, at
13 what kind of interval?
14 DR. COLEMAN: Well, I think the whole issue
15 of vitamin monitoring and supplementation -- there
16 were some data generated that looked at the cumulative
17 incidence of low vitamin levels, and it looks as
18 though there's a fairly steady accumulation over the
19 course of two years.
20 So that if you were going to monitor people
21 you'd have to monitor everyone, and you would have to
22 do it fairly frequently. I don't think that would be
23 practical.
24 ACTING CHAIR SHERWIN: Dr. Illingworth.
25 DR. ILLINGWORTH: By analogy, with patients

1 with a beta lipoproteinemia, of a complete block of
2 fat absorption, they get efficiency of vitamin E,
3 vitamin A, and vitamin K -- not vitamin D. They get
4 enough from sunshine. So I think the one to monitor
5 long-term would be vitamin E, from vitamin cystic
6 fibrosis as well as impaired absorption.
7 One quesetion concerning the oxalate issue.
8 Would you consider recommending that patients who are
9 given this not take several months of large amounts of
10 vitamin C because of the potential for that to
11 increase oxalate formation?
12 DR. COLEMAN: Again, I hesitate to make any
13 kind of definitive comment, simply because, although
14 there was a suggestion that the oxalate level at two
15 years went up, the p-value was .26. So we have to be
16 a little careful about making comments that this
17 definitely increases oxalate. The mechanism is
18 certainly there with the fatty acids in the colon.
19 It may be worthy of further study, but I
20 think to be on the safe side, patients probably should
21 avoid any situation that increases their oxalate load
22 such as vitamin C. Because we know vitamin C can
23 increase the risk of oxalate stone by itself.
24 CHAIRMAN BONE: Hello? A couple of comments
25 and related questions. First of all a comment, and

1 that is that the reference ranges for vitamin D
2 typically include a large proportion of individuals
3 who are regarded as having vitamin D levels that are
4 below what is optimal.
5 In other words, reference in healthy range
6 are not the same thing. So typically, if you had a
7 substantial number of individuals in the low end of
8 the reference range, you'd have quite a number who
9 were suboptimal. And while I take Dr. Illingworth's
10 point, we actually do see quite a lot of trouble with
11 vitamin D deficiency in patients with some other
12 malabsorptive disorders such as Crohn's disease or
13 celiac disease.
14 So I do think that this may have some
15 implications which would be very gradual and insidious
16 since there are fat-soluble vitamins, one would expect
17 the stores go be depleted rather slowly. It might
18 even be that more than two years would be required to
19 see the full effect, but that with chronic dosing over
20 an extended period, the effect might be, as was
21 mentioned, cumulative and considerably greater than
22 was reflected in the observation during the studies.
23 The other thing is that, while there are
24 concerns about the implication of the hydroxyproline
25 -- do I understand correctly that this was a -- was

1 this a fasting second void of hydroxyproline to
2 creatine ratio, or were these 24-hour values?
3 DR. COLEMAN: Fasting spot samples.
4 ACTING CHAIR SHERWIN: Henry, are you there?
5 CHAIRMAN BONE: Yes, I couldn't hear it.
6 DR. ILLINGWORTH: Spot samples.
7 CHAIRMAN BONE: Fasting second voided
8 specimens in the morning?
9 DR. ILLINGWORTH: Spot urine samples.
10 CHAIRMAN BONE: Spot urine samples. Well,
11 the issue with hydroxyproline with creatine ratios is,
12 is that if you have a fasting second voided sample
13 from the morning, that's fairly representative of bone
14 metabolism, although it's certainly not the measure-
15 ment of choice these days where more specific measure-
16 ments are available.
17 But if you measure under other circumstanc-
18 es, obviously absorption of dietary collagen is a very
19 important factor. I should have thought that these
20 days this would have been done using entylopeptide or
21 the carboxytylopeptide measurements, or possibly d-
22 peradinoline, which are widely considered preferable.
23 If in fact, these are the fasting second
24 voided hydroxyproline to creatine ratios, then a
25 significant rise does suggest an increase in bone

1 resorption, which could be indicative of it beginning
2 to have some difficulty absorbing calcium as a result
3 of developing vitamin D deficiency.
4 And the obvious question is, was the
5 relationship looked for between the change in hydroxy-
6 proline and the decline in 25 hydroxy vitamin D
7 levels?
8 DR. COLEMAN: Not to my knowledge.
9 ACTING CHAIR SHERWIN: Anyone from Hoffmann-
10 LaRouche want to comment?
11 DR. CANNOVATCHEL: This study conducted at
12 a single center in Europe, we know that the instruc-
13 tions were for a fasting sample. We do not know if
14 the specification of the second void was given to the
15 patients.
16 In regards to correlating the absolute
17 change on a patient-to-patient comparison in their
18 urinary hydroxyproline, by which also we are not aware
19 of any instruction -- there was no control for diet
20 during the days or day of the sampling, which could
21 introduce also, the collagen factor to these results.
22 We would have to check that data for you.
23 At least as per conversations with the investigator,
24 he did not feel that there was a relationship between
25 the changes.

1 CHAIRMAN BONE: Well, if you do a fasting
2 second voided sample, it really does not influence
3 very much by dietary collagen intake except under
4 extraordinary extremes. And is a fair measure of the
5 degree of bone resorption, done properly, and assuming
6 that the methodology is good for separating hydroxy-
7 proline from other substances with similar absorption
8 characteristics on the chromatogram.
9 I take it then, the question I asked wasn't
10 specifically addressed? About the relationship to
11 change in vitamin D levels?
12 ACTING CHAIR SHERWIN: Yes, I think that's
13 correct. That's what I'm getting. Dr. Cara.
14 DR. CARA: In relationship to this, Henry,
15 do you have any additional concerns? I don't know if
16 you heard that a great number -- most of the women in
17 the studies were actually on estrogen. Do you have
18 any concerns off what that might imply for the use of
19 the medication in younger women who may not be on
20 pharmacological estrogen therapy, in regards to their
21 vitamin D status?
22 CHAIRMAN BONE: Well, I guess that's a
23 little bit complicated. I'm sure the issue is whether
24 the vitamin D absorption is directly affected, but I
25 mean, we know that patients on estrogen actually have

1 higher serum vitamin D levels, both 25 hydroxy vitamin
2 D and 1.25 dihydroxide vitamin D, which is in part due
3 to their relatively high levels of vitamin D binding
4 protein in serum.
5 So to an extent, any decline in vitamin D
6 absorption as indicated by serum 25 hydroxy vitamin D
7 levels, would tend to be masked or buffered by the
8 higher levels of vitamin D binding protein.
9 It gets a little more complicated if you
10 want to look at free 25 hydroxy vitamin D or free 1.25
11 dihydroxide vitamin D because those are rather
12 difficult measurements. And that's why questions
13 like, markers of bone resorptions and indices of
14 parathyroid hormone secretion are pertinent.
15 DR. CARA: Another question to Dr. Coleman.
16 I think it -- on the one hand it's commendable that
17 the sponsor has done the sort of comorbidity studies
18 that have been quoted this morning, and I'm frankly
19 quite impressed by, not only him doing it, but showing
20 that a relatively small amount of weight loss actually
21 has quite an effect on the comorbidities.
22 Apparently that small effect was statisti-
23 cally significant because of the large patient numbers
24 and by the pooling of the patients in their studies.
25 Typically, the FDA requires at least two studies about

1 efficacy. Are you content with their pooling all the
2 patients rather than looking at each specific study
3 individually, or perhaps two related studies?
4 DR. COLEMAN: Yes, actually, my review did
5 include a review of all seven Phase III studies, in
6 addition to review of the pooling data. I just chose
7 to show the pooled data for this session, but I
8 reviewed all seven individual studies as well.
9 DR. CARA: And you're content with the
10 pooled data?
11 DR. COLEMAN: Yes, I think it's a valid --
12 I mean, our statisticians looked at the issue and we
13 thought it was a valid -- it's not a meta-analysis,
14 it's simply a pooling, but we didn't have any strong
15 objection to doing that.
16 ACTING CHAIR SHERWIN: Dr. Bone.
17 CHAIRMAN BONE: Could we come back for a
18 moment to this question about the fat-soluble vita-
19 mins, because it relates to the question which I asked
20 after the sponsor's presentation and had difficulty
21 hearing the answer.
22 If I understood correctly -- well first, my
23 question was: Was there a relationship between the
24 magnitude of weight loss and the decline in levels of
25 fat-soluble vitamins?

1 And if I understand correctly, the answer
2 was confined to vitamin D, and with respect to vitamin
3 D there did not appear to be a relationship between
4 the decline in 25 hydroxy vitamin D levels in serum
5 and the amount of weight lost, and we didn't have much
6 information on the relationship between other fat-
7 soluble vitamin changes and the magnitude of weight
8 loss.
9 Is that a correct understanding on my part?
10 ACTING CHAIR SHERWIN: Yes. Do you want to
11 ask anything else?
12 CHAIRMAN BONE: No, I just wanted -- this
13 seemed like an apt moment. I did have one more
14 question for Dr. Coleman, and that had to do with the
15 question of the excess of breast cancers. And part of
16 -- well, I'd just be very interested in his views on
17 this topic.
18 DR. COLEMAN: Well, when we first discovered
19 the discrepancy in the numbers, we obviously got on
20 the phone and talked to the company. I worked in
21 concert with Dr. Bruce Stadel, our Epidemiologist in
22 the Division.
23 And we both agreed just from the initial
24 data, given the fact that the pre-clinical data did
25 not suggest any potential for carcinogenicity, the

1 fact that I believe, half of the cases were detected
2 within six months of initiation in the study, I felt
3 strongly ruling against orlistat as a causative agent.
4 We looked at the vitamin levels for these
5 women and they all were within the normal range, and
6 moreover, they didn't decrease by a significant
7 amount. I believe in one of the women we did have
8 plasma levels of the drug, and they were extremely
9 low; I believe less than 5 nanograms.
10 So trying to make some biological plausibil-
11 ity linking the drug to the breast cancer, I had a
12 great deal of trouble doing that. I won't speak for
13 Dr. Stadel; he may want to mention his feelings on
14 this. Bruce, do you want to --
15 DR. STADEL: I think everything's been
16 looked into that I can think of, and I cannot see any
17 basis there for -- and fueling causality. What's left
18 with is the company expressed an element of unease
19 that you don't have a clear explanation, but every-
20 thing weighs toward the side of it either being a
21 fluke or detectionable --
22 CHAIRMAN BONE: I guess I wondering, if you
23 exclude patients where clearly the breast cancer must
24 have been present prior to study entry, was any
25 estimate made of the probability of achieving the

1 difference between groups due to chance?

2 DR. STADEL: Do you have something on that?

3 I think the company needs to address. If you censor

4 those that were diagnosed in a very short period of

5 time, do you have statistics on what happens when you

6 do that?

7 DR. HAUPTMAN: No, we just included all

8 patients as an intent-to-treat analysis; we didn't do

9 the analysis by taking out the people during the first

10 six months.

11 CHAIRMAN BONE: Well, it sounds like, what

12 was it, 6:1 or 6:0, if you censor the early patients?

13 DR. STADEL: Five to one.

14 CHAIRMAN BONE: Five to one? Right. And no

15 estimate was make about -- I mean, I take the point

16 completely about biological plausibility, but I was

17 curious to know whether anyone had actually tried to

18 quantify the likelihood of that being a random error

19 -- or a random occurrence?

20 DR. STADEL: You can compute a p-value about

21 that kind of thing and it will go down -- the p-value

22 will go down a little bit from what you have current-

23 ly, but you'll see -- it will still probably be

24 significant. And if it's .51 versus .449, you're

25 still left with -- I don't have that p-value, Henry.

1 It's appropriate to talk about it.

2 I think one's still left with the fact that

3 there is, if you do -- I think they did really, the

4 strictly correct thing, which is a straight intent-to-

5 treat analysis and you don't start sort of chopping

6 based at what you want to be true. That you do it

7 that way; everything's been investigated; you are left

8 with the observation.

9 It's a small number but it is significant

10 statistically. Everything, looking at, says we can't

11 see any way that it's causal, and I think one just has

12 to decide then, what to do.

13 ACTING CHAIR SHERWIN: Dr. Hirsch had

14 mentioned that I asked about smoking history and how

15 that might impact on all of this. Do we know anything

16 about smoking histories?

17 DR. HIRSCH: Or change in smoking behavior

18 with taking the drug?

19 DR. HAUPTMAN: For reasons due to energy

20 balance, patients were instructed not to change their

21 smoking behavior during the term of the study because

22 the weight loss or weight gain. So that was an

23 inclusion or exclusion criteria.

24 ACTING CHAIR SHERWIN: But do we know about

25 smokers and whether the women who developed cancer

1 were, or --

2 DR. HAUPTMAN: We can find out that data if

3 it's available; I don't think we have that in our

4 initial analysis. But I don't know as there's an

5 association between smoking and breast cancer. I

6 don't believe so.

7 DR. HIRSCH: No, if anything, there would be

8 a weak inverse one because of the catecholestrogen

9 secretion story.

10 CHAIRMAN BONE: Was there any genetic

11 investigation of the women with breast cancer?

12 DR. HAUPTMAN: No.

13 ACTING CHAIR SHERWIN: How does the FDA feel

14 about recommendations, given the uncertainties? You

15 know, if this drug is approved, do you advise women to

16 have a breast exam on a yearly basis? You know, what

17 would you recommend that we do, or should we ignore

18 it? I mean, we can recommend, but I'm just curious

19 what you think. Dr. Bilstad.

20 DR. BILSTAD: Well, I don't think we're in

21 a position at this point to make a recommendation on

22 that, and in fact, presenting it to the committee,

23 we're asking for your recommendations and comments on

24 this point.

25 ACTING CHAIR SHERWIN: I know that. I got

1 that sense, but I just wanted to get your feeling
2 because we're not experts in this area and it is a
3 concern. We may want you to convene a group or have
4 a discussion about what should be recommended if we go
5 forward, because this is -- you know, even though we
6 can't explain it doesn't mean it isn't true.
7 DR. BILSTAD: Well, it is a statistically
8 significant finding, and I think nobody is quite sure
9 how to interpret it at this point.
10 ACTING CHAIR SHERWIN: Right.
11 DR. BILSTAD: One of the possibilities is if
12 the drug were to be approved, to note it in the
13 labeling -- in fact, we certainly would note it in the
14 labeling -- pointing out that there was this differ-
15 ence, and not make specific recommendations in terms
16 of how to interpret it.
17 DR. SOBEL: The biological plausibility and
18 pre-clinical findings give some reassurance. What we
19 might consider is a longer-term follow-up of patients
20 who have exposure, and hopefully there would be
21 convergence of findings over time. That would be a
22 thought we should pursue with the company, of having
23 a rather complete ascertainment in a longitudinal way
24 that would perhaps mitigate this finding.
25 CHAIRMAN BONE: Could I ask one more

1 question related to this, about another correlation,
2 and it may have been covered in the sponsor's presen-
3 tation and I might just have missed it. But was there
4 any kind of indication that there was a relationship
5 between the amount of weight lost and the finding of
6 the breast cancer?
7 DR. HAUPTMAN: I can address that. The
8 average weight loss of the patients who had identified
9 tumors, was approximately seven-and-a-half kilograms,
10 and the weight loss in the one patient on the placebo
11 was a loss of two-and-a-half kilograms.
12 CHAIRMAN BONE: Is that seven-and-a-half
13 kilograms from baseline or from entry or --
14 DR. HAUPTMAN: Seven-and-a-half kilograms
15 from entry until the identification of the tumor.
16 CHAIRMAN BONE: I see. So there wasn't an
17 unusual amount of weight loss in those patients?
18 DR. HAUPTMAN: No, it wasn't. But again,
19 one of the potential thoughts was that the weight loss
20 that occurs is sufficient to change breast architec-
21 ture and pick up on standard mammography findings that
22 otherwise wouldn't be seen being hidden by the excess
23 breast and actipose tissue.
24 CHAIRMAN BONE: I understood that; that's
25 why I was asking the question, to see if these were

1 patients who had had very large amount of weight loss
2 that would sort of reinforce that argument. But if
3 it's sort of useful but not an exceptional amount of
4 weight loss, it doesn't really help one way or the
5 other, I guess.
6 I have one further question about the
7 vitamin issue and I think it bears on this finding of
8 the rise in oxalate in the second year. Presumably,
9 the fact that the urinary oxalate rises in the second
10 year is due to the fat content going up in the second
11 year in the diet. I mean, that's the obvious reason.
12 It might not be correct, but it's the obvious reason.
13 And have these questions about loss of fat-
14 soluble nutrients been investigated in relation to the
15 actual dietary fat content? I mean, the implication
16 of the question is the following.
17 If people, as they may do in clinical prac-
18 tice, take the medication in conjunction with a diet
19 which is not so strict as study subjects in terms of
20 its fat content, will they actually be at potentially
21 higher risk of developing fat-soluble vitamin defi-
22 ciency, because the amount of fat not absorbed is
23 greater?
24 And with this, so to speak, the same
25 partition coefficient, a larger amount of solid

1 passing through, would they tend to absorb less of
2 these vitamins? Was that looked at in relation to the
3 dietary fat?
4 ACTING CHAIR SHERWIN: We'd like the company
5 to comment, and maybe the FDA's consultant.
6 DR. HAUPTMAN: First of all, the amount of
7 fat that's inhibited was within a very narrow window.
8 Generally, it's between 20 and 25 grams. Once you get
9 above 30 grams per day it's just not going to be
10 tolerated. So it's not thought there's going to be a
11 tremendous loss.
12 And there's a direct relationship between
13 the amount of at you eat, and of course the amount of
14 fat that's left in the stool. So in a 90 gram fat
15 diet you have 30 grams; 60 gram fat diet, 20 grams.
16 The amount of free fatty acid which is probably the
17 more important predictor of if there's an absorption
18 of oxalate, is very, very small -- on the range of
19 maybe 5 grams per day.
20 This data for the oxalate absorption, that
21 is of concern for people who are from the old intesti-
22 nal bypass operations where they had tremendously
23 increased amounts of free fatty acids. They were up
24 to 30, 40 grams per day binding to the calcium,
25 preventing the calcium from binding to the oxalate,

1 given hyperoxylurea.

2 So mechanistically, any increase in oxalates

3 -- and the combined data 161 and 185 we didn't see it

4 -- is going to be limited to a very, very small amount

5 because the amount of free fatty acids in the colon is

6 extremely small.

7 CHAIRMAN BONE: Well, point taken, although

8 presumably they're -- within the range of tolerable

9 fat intake there's some -- there would be some

10 relationship. What about the relationship between the

11 amount of steatorrhea or the amount of fat ingested

12 either one, and the decline in fat-soluble vitamins?

13 DR. HAUPTMAN: I didn't talk about the

14 steatorrhea and the -- I think it was steatorrhea and

15 increased complaints -- was that the first part?

16 CHAIRMAN BONE: No, I'm talking about the

17 fat-soluble vitamins. I'm trying to get a little bit

18 of a handle on if there's a particular risk group or

19 if there's a relationship here, particularly as people

20 may take a larger fat intake in practice than they

21 would in the study.

22 DR. HAUPTMAN: I think they -- still, one-

23 third of the fat is inhibited but two-third of the fat

24 in fat-soluble substances are still absorbed. So our

25 feeling is that still, two-thirds of whatever you take

1 is getting in, regardless of the total amount of fat
2 you may be ingesting.
3 ACTING CHAIR SHERWIN: Dr. Gallo-Torres.
4 DR. GALLO-TORRES: If I may. Actually
5 calling this a malabsorption syndrome is a very
6 conservative way of looking at things. Because it is
7 mostly lipid is absorbed, malabsorbed, number one.
8 The second comment I would like to make is,
9 whatever is occurring is occurring with physical
10 chemical compounds which are normally offered to the
11 colon. The chemical structure is the same. The
12 policy is normal. We're not talking about different
13 structure of triglycerides, monoglycerides, and so on.
14 And the additional comment which is in my
15 consult is that, after administration of the recom-
16 mended dose, 120 milligrams t.i.d. for six weeks, and
17 looking into colonic events, such as cell prolifera-
18 tion -- and I realize that cell proliferation was
19 controversial -- there were no findings of concern.
20 The most important finding was that actual-
21 ly, a decrease in the oxycholic acid, and this is a
22 very interesting finding because there are two or
23 three multi-center clinical trials in the United
24 States, almost exclusively based on this pharmacody-
25 namic finding. Decrease in the oxycholic acid in both

1 the solid and the liquid phase of the stool, and this
2 is supposed to be a very good parameter of anti-cancer
3 compounds.
4 In other words, sulindac, piroxicam,
5 aspirin, and ursodeoxycholic acid are undergoing
6 trials based on these findings. So if anything, this
7 compound may prevent cancer if one was to use the data
8 to more studies in that regard. So there are no
9 findings of concern.
10 ACTING CHAIR SHERWIN: And the issue of fat
11 in the diet relative to vitamin malabsorption?
12 DR. GALLO-TORRES: I'm going there. I'm
13 sorry
14 ACTING CHAIR SHERWIN: Oh, I'm sorry.
15 DR. GALLO-TORRES: Well, we all heard
16 comments about the effect of diet on cancer, and
17 specifically, we're talking about colon cancer I
18 suppose, because cancer of the small intestine is an
19 extremely rare condition. We don't see cancer of the
20 small intestine.
21 Now, there are certain specific conditions
22 that are supposed to epidemiologically increase the
23 risk, such as a low fiber diet for example. Now
24 again, the -- what is the specific question that you
25 would you like me to answer, please? Because I can go

1 -- but I don't want to do that.

2 ACTING CHAIR SHERWIN: You can give us a

3 lecture -- but the question was, the amount of fat in

4 the diet and how -- in the context of this drug --

5 would that influence fat-soluble vitamin absorption?

6 DR. GALLO-TORRES: Yes. I think there's no

7 doubt there is some malabsorption with -- Dr. Coleman

8 said -- some malabsorption of lipid-soluble vitamins.

9 There's no doubt about that. And I think the supple-

10 mentation should perhaps --

11 ACTING CHAIR SHERWIN: But if you increase

12 the amount of fat in your diet, within the context of

13 this drug, would that help or hurt or not affect, fat-

14 soluble vitamin absorption?

15 DR. GALLO-TORRES: It will alter the

16 absorption of vitamins --

17 ACTING CHAIR SHERWIN: Which way? That's

18 what I'm trying to get at.

19 DR. GALLO-TORRES: Usually when you decrease

20 the fat content in the lumen you could decrease the

21 absorption of the vitamin.

22 ACTING CHAIR SHERWIN: You --

23 DR. GALLO-TORRES: Decrease, decrease. Yes.

24 That has been shown, actually, on some of my early

25 publications with vitamin E, and it is true for, I

1 should say, all the other vitamins -- lipid-soluble
2 vitamins.
3 But the other point I wanted to make is
4 that, having done that, again referring to colonic
5 events, that is the case of the absorption of lipo-
6 soluble vitamins in the upper part of the intestine,
7 but often more of these vitamins to the colon, may
8 again be, at least theoretically, beneficial. At
9 least theoretically. So there's no points of concern
10 that I can find regarding these matters.
11 ACTING CHAIR SHERWIN: Dr. Molitch.
12 CHAIRMAN BONE: Could increasing the fat
13 content make the vitamin absorption better or worse?
14 DR. GALLO-TORRES: Yes well, first of all
15 you see, the lipo-soluble vitamins depend on bile, on
16 bile secretion, on bile acid for absorption. If there
17 is no bile in the lumen there will no absorption of
18 vitamin E, D, and K. And so -- that's number one.
19 Number two, the amount, the presence of the
20 fat in the lumen is directly proportionate to the
21 amount of lipo-soluble vitamin being absorbed.
22 Therefore, if there is less fat, lipid, in the upper
23 small intestine, there's going to be less absorption
24 of these vitamins.
25 The extent to that depends upon a lot of

1 factors. It is a very complex situation, but I don't
2 -- you know, you have seen the clinical data. They
3 are not pronounced decreases in the levels. At least
4 if we are going to use those levels, as Dr. Coleman
5 said, organ levels such as liver levels, may be more
6 interesting. But from what we see, there are no
7 findings of concern.
8 ACTING CHAIR SHERWIN: Henry, are you
9 satisfied?
10 CHAIRMAN BONE: I think that's as far as
11 we're going to get.
12 DR. GALLO-TORRES: Me, too.
13 ACTING CHAIR SHERWIN: Okay. Dr. Molitch.
14 MR. MOLITCH: I have two, I hope, quick
15 questions with quick answers. The first is for Dr.
16 Coleman. When you recalculated the weight loss data
17 and the percent weight loss in these various studies,
18 were you doing that from the beginning at the -4 week
19 period, or at the zero time, at the time of randomiza-
20 tion?
21 DR. COLEMAN: We did both, but I had focused
22 my energies on the change from baseline weight.
23 MR. MOLITCH: Which is -4 weeks, correct?
24 DR. COLEMAN: No, that's initial.
25 MR. MOLITCH: Oh, from zero week, time of

1 randomization?

2 DR. COLEMAN: Yes.

3 MR. MOLITCH: Okay, and so it still didn't

4 quite reach the 5 percent level, even at that point?

5 DR. COLEMAN: Right.

6 MR. MOLITCH: And my second question is

7 really to the sponsors. The finding that 90 percent

8 of post-menopausal women were taking estrogen, this is

9 truly an extraordinary number compared to the popula-

10 tion at large. Would suggest that many of these women

11 have also suggested that they take calcium supple-

12 ments. And was the question of them taking calcium

13 supplements, were they all stopped as part of the

14 vitamin stopping, or were some of them taking calcium

15 or not taking calcium? Do we know that answer?

16 DR. CANNOVATCHEL: Of the post-menopausal

17 women, of which there were 50 on placebo and 70 on

18 orlistat, the total number of post-menopausal women

19 taking estrogen. We did not stipulate to discontinue

20 their calcium. If they were on it they continued; if

21 they were not in it, we didn't stipulate to start.

22 We would have to check our database to

23 confirm what percentage were on it, if that's of

24 interest.

25 MR. MOLITCH: Could that possibly confuse,

1 or at least affect some of the DEXA findings and some
2 of these other findings that we're talking about, with
3 these measurements of PTH and the like? And they were
4 also probably getting vitamin D with some of those as
5 well, is my guess, since some of those calcium
6 supplements have vitamin D in them if they're over-
7 the-counter preparations.
8 DR. CANNOVATCHEL: Again, the majority of
9 patients were not post-menopausal --
10 MR. MOLITCH: Right.
11 DR. CANNOVATCHEL: -- and of those, they
12 were comparable between treatment groups in terms of
13 the percentage of each.
14 CHAIRMAN BONE: Mark, I think it would be
15 extraordinary if you did see an affect on bone mass or
16 vitamin D metabolism over the interval. I would think
17 it would take a long time to see a sufficient degree
18 of vitamin D depletion to cause secondary hyperpara-
19 thyroidism and have this eventually reflected in the
20 bone mass.
21 MR. MOLITCH: Oh, I think so, but I think it
22 may have masked perhaps other changes that might have
23 been seen due to the drug, were they not taking
24 calcium supplements.
25 CHAIRMAN BONE: I wouldn't argue with you

1 about that.

2 ACTING CHAIR SHERWIN: Yes, go ahead. I

3 just had one question for you, too.

4 DR. CANNOVATCHEL: I'm sorry. If I may just

5 make one clarification on the answer regarding the

6 calcium supplements. In the one study where we

7 monitored the calcium parathyroid hormone levels in

8 the 2-year studies in the U.S., because of measure-

9 ments of parathyroid hormone and calcium, we did

10 discontinue calcium supplements in that population.

11 MR. MOLITCH: Thank you.

12 CHAIRMAN BONE: Thank you.

13 ACTING CHAIR SHERWIN: I'm just curious

14 because I just don't know. If you seriously take out

15 part of the small bowel so that you impair that

16 absorption, how long does it take for fat-soluble

17 vitamin levels to be affected?

18 DR. GALLO-TORRES: I believe that Dr. Olson

19 may be more qualified to answer that question, but

20 I'll give you a little try. Studies done 25, 30, 35

21 years ago, show that in order to get depletion of the

22 vitamin one needs at least one-and-a-half, two years,

23 in some instances, for example, of vitamin E. Vitamin

24 E -- diets that contain no vitamin E in the diet took

25 that long to produce --

1 ACTING CHAIR SHERWIN: Two years, did you --

2 DR. GALLO-TORRES: One-and-a-half years,

3 yes, 18 months. These are old data. But as I said,

4 Dr. Olson perhaps would like to comment more on this

5 matter.

6 DR. HIRSCH: Those were actually -- I can

7 quote -- those are the studies of M.K. Horwitt in

8 which --

9 DR. GALLO-TORRES: Horwitt, exactly.

10 DR. HIRSCH: Exactly. In which no vitamin

11 E was fed to people at the Elgin State -- whatever it

12 was -- for years, and nothing happened to them. They

13 had increased dialuric acid hemolysis of erythrocytes,

14 but there were no clinical findings of any kind and

15 there was -- no levels of vitamin E were found after

16 several years.

17 DR. GALLO-TORRES: Correct.

18 CHAIRMAN BONE: Remember that if you have

19 fat-soluble vitamins in your fat stores and you're

20 depleting your fat stores, you essentially have an

21 internal source of that vitamin for quite a while.

22 ACTING CHAIR SHERWIN: Well yes, that's sort

23 of the point I'm trying to make. Is that my one

24 concern is that where you have subtle changes in

25 absorption it may take a long time to manifest.

1 Any other questions before we break?

2 DR. CARA: Just a follow-up question to Dr.

3 Coleman. I think I may have misinterpreted something

4 that you had said earlier. Did you in fact say, that

5 when you analyzed all seven studies there was enough

6 power in each one of those studies to essentially

7 demonstrate the beneficial effect of the drug on the

8 comorbidities?

9 DR. COLMAN: On balance, that's true.

10 DR. CARA: Thank you.

11 ACTING CHAIR SHERWIN: Okay. I'm happy to

12 say that it's time for lunch. We'll reconvene in 45

13 minutes, just so we can end at an appropriate time.

14 So 1:45.

15 (Whereupon, at 1:04 p.m., a brief luncheon

16 recess was taken.)

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

2 1:53 p.m.

3 ACTING CHAIR SHERWIN: Just before we began,
4 Dr. Hauptman asked if the Hoffmann-LaRouche Company
5 could just summarize in five minutes, how they feel
6 about the vitamin issue and vitamin supplementation,
7 and to clarify a few issues. And I agreed to exactly
8 five minutes because we really want to get moving.
9 But I'll give you five minutes.

10 DR. CANNOVATCHEL: Thank you. Dr. Cannovat-
11 chel from Clinical Development. To make two clarifi-
12 cations amongst the discussion we had this morning.
13 Of those patients treated with orlistat over a 2-year
14 treatment period, who had two consecutive low values
15 at some time during that time course, of those who
16 received a vitamin supplement of any of the vitamins,
17 at their lowest level, then given a vitamin supple-
18 ment, post-supplementation, their levels were as high
19 or higher than their baseline levels at the time of
20 randomization. And that's, as I showed with vitamin
21 D, is consistent in A, D, and beta carotene.

22 Second point, the question about those
23 patients who have lost more than 5 percent of their
24 body weight and the change in their mean levels. As
25 also with D, where there was no significant difference

1 in their levels, compared to placebo, similar findings
2 are true for both vitamin A and vitamin E, where they
3 were not significantly different between treatment
4 populations.
5 To interpret the bone metabolism and vitamin
6 D data presented today, we have an independent expert
7 that I'd like to invite to comment on these findings.
8 Dr. Bess Dawson-Hughes, professor of Medicine at Tufts
9 University School of Medicine, Chief of the Calcium
10 and Bone Metabolism Laboratory at the Jean Mayer, U.S.
11 Department of Agriculture, Human Nutrition Research
12 Center on Aging at Tufts University, whose areas of
13 interest includes calcium, vitamin D, and bone
14 metabolism.
15 DR. DAWSON-HUGHES: Thank you. I wanted to
16 make three points that had to do with the interpreta-
17 tion of the overview of, at least from my perspective,
18 of what we've seen today.
19 I think we can agree that there's a modest,
20 around 8 percent decline in vitamin D levels, 25
21 hydroxy D during the treatment period of two years
22 with oral stat. Is there any evidence for clinical
23 consequences of this decline?
24 Vitamin D deficiency causes poorer or less
25 effective calcium absorption. One then sees a very

1 subtle lowering of the circulating ionized calcium
2 concentration and a rise in parathyroid hormone. In
3 over 400 patients we have seen no change whatsoever in
4 ionized calcium concentration or in parathyroid
5 hormone levels.
6 What about the implications for the skele-
7 ton? The effect of D deficiency on the skeleton is
8 felt to be mediated by its effects on parathyroid
9 hormone. Parathyroid hormone increases the bone
10 remodeling rate and this induces bone loss. We saw no
11 increase in parathyroid hormone, so there's no reason
12 to think that there would be an effect on the skele-
13 ton.
14 We do have a modest amount of bone data;
15 very modest indeed -- I think 37 patients altogether.
16 That is not enough to draw any conclusions about the
17 effect on bone mineral density. We know that there
18 was no significant difference there, but the power of
19 that negative statement is quite limited because of
20 the sample size.
21 Second point. Would a longer treatment
22 period of orlistat have been likely to have caused a
23 further reduction in the vitamin D level? Because of
24 the interesting and unique physiology of vitamin D,
25 wherein most of our D reserves come from skin synthe-

1 sis promoted by sun exposure, every summer we get
2 boosted up -- our stores are returned. And so I would
3 see no likelihood of ongoing and aggravated loss.
4 Finally, does a multi-vitamin fix or reverse
5 the subtle decline in 25 hydroxy D? In subjects who
6 were initiated on there by other vitamins during
7 treatment, the deficit was systematically reversed.
8 It's only in those patients who started out on the
9 vitamin, who in fact were taking the vitamin at the
10 time they were taking orlistat in their breakfast, did
11 they show some subtle decline in the vitamin D levels.
12 So it looks like for all weight-reducing
13 programs, including the program with orlistat, that a
14 supplement is a reasonable approach. It would seem
15 prudent and wise not to take it with the orlistat, but
16 to take it apart -- physically apart.
17 Thank you.
18 ACTING CHAIR SHERWIN: Would the effects or
19 potential effects on bone be greater in a developing
20 or growing bone? If children, adolescents, you
21 interfered with absorption of vitamin D, would that in
22 fact, be a higher risk group?
23 DR. DAWSON-HUGHES: It's not clear that it
24 would be. We don't have strong data in terms of D
25 requirements for children. It is interesting that at

1 very high latitudes, children will have very low
2 vitamin D levels in the winter and then yoyo by
3 season.
4 These children do not have any distinguish-
5 ing bone growth pattern, compared with children who do
6 not have striking deficits in their 25 D. That's a
7 semi-analogy, but I think I would not especially worry
8 about that group.
9 CHAIRMAN BONE: Hello, Bess?
10 DR. DAWSON-HUGHES: Yes.
11 CHAIRMAN BONE: First of all, hello. Bess,
12 thanks for your comments. I had a couple of ques-
13 tions. Presumably the people who had the decline in
14 vitamin D were not getting much in the way of sun
15 exposure. I mean, I would take it that that's part of
16 the group.
17 Do you know whether any analysis or effort
18 was made to capture that information, about whether
19 the people who did not have much sunlight exposure
20 were in the fact, the ones who had the vitamin D
21 declines?
22 DR. DAWSON-HUGHES: I have been shown
23 analyses of seasonal changes in 25 hydroxy D levels in
24 this enormous data set, and they mimic those changes
25 seen in our data and other people's. D levels vary by

1 40, 50 percent, according to time of year.

2 CHAIRMAN BONE: Well, that's what you'd

3 expect, but I was wondering if the patients who fell

4 into the low range were distinguishable on that basis

5 or whether that's really --

6 DR. DAWSON-HUGHES: They were distinguish-

7 able in that when they would become low it would be

8 winter most of the time.

9 CHAIRMAN BONE: I see. So you think that's

10 just the tail of the curve, and the whole curve is

11 moving up and down?

12 DR. DAWSON-HUGHES: Yes.

13 CHAIRMAN BONE: I see. And the other thing

14 -- I mean, that's plausible. The other thing was, the

15 mean PTH values didn't change much. Was there any

16 categorical analysis to look to see if there were a

17 group of patients in whom PTH values were significant-

18 ly changing?

19 DR. DAWSON-HUGHES: We saw -- you couldn't

20 see, unfortunately -- the analysis of the subset of

21 subjects considered to be at highest risk. Those

22 would be people who started low in their 25 hydroxy D

23 and had two consecutive low values. That subset of

24 patients did not have any excursion in their parathy-

25 roid hormone levels, as did not the larger group.

1 So even in the high risk group there
2 appeared to be no threat from a rise in their parathy-
3 roid hormone levels.
4 CHAIRMAN BONE: Thank you very much. That's
5 a big help. I think that was from the part of the
6 presentation I was having difficulty hearing. Thank
7 you.
8 ACTING CHAIR SHERWIN: Thank you. I think
9 now we can begin our general discussion, and would
10 like to entertain any questions from the panel at this
11 point.
12 DR. HIRSCH: Maybe I can start with a
13 comment and a question. I'll try to be very brief.
14 I think Dr. Hauptman very correctly told us this
15 morning that clearly, obesity has to do with intake
16 and output, and that's obviously the situation. And
17 it's also clear now, abundantly, that individuals who
18 are obese store more fat and maintain the same
19 intake/outgo relationship but just at a different
20 level of fat storage.
21 And we now know also that the likelihood is
22 very great that there's some molecular genetic input
23 to a story which somehow reacts with psycho-social
24 influences to promote this situation in man. And
25 we're in a kind of funny situation at the present time

1 because we're probably on the brink of being able to
2 get a sufficient understanding so that we can have
3 more directed therapy for obesity and drug or inter-
4 vention of some kind, that will be vastly better than
5 we've ever had before.
6 But until that time, what we're doing -- and
7 I think this should be made clear -- is not really
8 intervening with any basis mechanisms that produce
9 obesity, but somehow setting up a counter-irritative,
10 or whatever you want to call it, situation. In some
11 respects what we're doing is something like jaw-wiring
12 used to be years ago but now in a more bio-chemical
13 sense we're making part of this regulatory system work
14 badly in order to promote fat loss.
15 The ingenuity of the body, or the wisdom of
16 the body as Cannon said, is so great that it almost
17 always beats down these efforts, and therefore we see
18 a little bit of weight loss, and finally the weight
19 comes back up over a year or two or three. This is
20 not to say that one shouldn't try to do this -- and as
21 a matter of fact, this Agency has already gone on
22 record as saying that a drug or intervention that will
23 drop the weight 5 percent, etc., is a suitable thing
24 to have.
25 So here we are. But now let's look at the

1 mechanism of how this drug acts. What does it do,
2 exactly? It seems rather clear, to me at least, that
3 if you make the calculation of how much fat is lost in
4 the stool, that's probably inadequate to explain the
5 weight loss. That what is happening is that there's
6 better compliance with the diet in the group receiving
7 the drug and the group not receiving the drug.
8 I'm led to believe, therefore, that although
9 there is some caloric drainage, that probably there is
10 a kind of intestinal aversive conditioning of some
11 variety developing whereby the patient learns that
12 there are consequences to eating more and therefore
13 learns to not eat more over time. And that this works
14 for a while until other mechanisms come into play.
15 Note that in the second year, for example,
16 the patients who were still on the drug have many
17 fewer GI adverse effects. This probably comes about
18 by virtue of this kind of aversive conditioning and
19 learning the mechanism of staying on the diet, but
20 eventually, another set of learned phenomena seem to
21 occur whereby the weight goes back up even though the
22 drug probably still has the same anti-pancreatic
23 lipase effect.
24 So I just want it made clear that what we're
25 dealing here with is something that works through the

1 central nervous system, although the afference to it
2 happens to be in the intestine. And I suppose
3 everything works through the CNS, but this is also a
4 CNS-active drug in the sense of being a way of
5 teaching aversive conditioning.
6 Having said that, I don't think that denies
7 the usefulness or potential utility of doing this, but
8 I just wanted to go on record in believing that that's
9 probably the way this thing works, and is not getting
10 at any fundamental mechanism underlying obesity.
11 ACTING CHAIR SHERWIN: Thank you. Any other
12 comments? Dr. Illingworth.
13 DR. ILLINGWORTH: In the background informa-
14 tion it's mentioned that you measured fatty acid
15 composition, assuming lack of proteins or erythro-
16 cytes, but the data wasn't actually in the background
17 information -- hasn't been presented. Is there any
18 change in fatty acid composition and is there any risk
19 of patients becoming deficient in arachidonic acid,
20 thereby affecting platelet function, things like that?
21 DR. HAUPTMAN: We did specifically look at
22 essential fatty acids in our 14161 study, which was
23 our 2-year study in a general practice situation in
24 the United States. And we looked at omega 6 is there,
25 including arachidonic acid and triene to tetraene

1 ratios.

2 The next slide, please. Take a look at the

3 N6 fatty acids. There are no difference -- the total

4 N6 fatty acid and the arachidonic acid, there's no

5 significant difference. And the triene to tetraene

6 ratio, there's also no -- and those are the three key

7 parameters.

8 DR. ILLINGWORTH: What are these in? Red

9 cells, or --

10 DR. HAUPTMAN: This is cells.

11 DR. ILLINGWORTH: -- lipase?

12 ACTING CHAIR SHERWIN: Any other questions?

13 My assumption about the fact that HDL tends to rise

14 less in the people treated with the drug, relates to

15 absorption of cholesterol, or is it possible that it

16 has something to do with lipoprotein lipase? Roger,

17 do you have any feelings about that?

18 DR. ILLINGWORTH: I suspect, although it

19 hasn't been actually examined, the drug must block or

20 interfere with cholesterol absorption, and by analogy

21 with patients given a very low fat diet, with reduc-

22 tion in both fat intake and cholesterol intake, you

23 actually get a decrease in HDL.

24 So what I think we're seeing with the small

25 change in HDL is probably opposing effects of a

1 reduction to fat intake of the diet and effects linked
2 to stimulation, probably, of vLDL production with
3 probably an increase in A1 synthesis, perhaps.
4 I suspect that's why we don't see a drop in
5 triglycerides is because the drug is behaving sort of
6 analogous to bile acid sequestering, but by a differ-
7 ent mechanism. You're blocking cholesterol absorption
8 rather than bile acid absorption, and the liver has
9 compensated for this perceived low intake of choles-
10 terol by making more lipoproteins.
11 Is that your review?
12 DR. HAUPTMAN: Yes.
13 DR. CARA: I have a question to the sponsor.
14 You've obviously built up a very impressive database
15 of patients that have been both followed prospectively
16 using placebo medication and orlistat. Is there any
17 thought to continuing those patients? Have the
18 studies completed? Are you continuing to monitor
19 these patients to evaluate long-term efficacy of
20 therapy?
21 DR. HAUPTMAN: All our studies were termi-
22 nated in order to put together the NDA, and they're
23 all designed for 2-year studies. But we're going to
24 initiate in Phase IIIB and Phase IV, other studies
25 that will be two or three years in duration, including

1 a study in Sweden looking at the prevention of the
2 development of diabetes in obese people, which might
3 go on longer term than that.
4 And clearly, if the drug gets approved and
5 on the market, we would do subsequent evaluation of
6 long-term use of the drug.
7 ACTING CHAIR SHERWIN: I have another
8 question for you. It relates to data about body
9 composition that was in the document provided by the
10 company. My impression was that in the DEXA studies,
11 fat-free mass was maintained and fat mass decreased in
12 comparing the drug to placebo, whereas in the radioac-
13 tive potassium studies there was a significant fall in
14 fat-free mass.
15 And so I was a little -- I mean, I don't
16 have any reason to expect that fat-free mass would
17 diminish, but I didn't see that data commented on, or
18 any of the data on body composition.
19 DR. HAUPTMAN: We can show some body
20 composition data, but first to the study that you
21 looked at, total body potassium. It was, I believe,
22 an aberrant study because what it shows was a total
23 weight loss of about 9 kilograms, but there's actually
24 a gain in lean body mass in the placebo group.
25 Which just didn't make sense -- that why,

1 losing weight you would have an increase in lean body
2 mass. Because normally, for every kilogram of weight
3 loss that you lose, 75 percent of that is fat mass and
4 25 percent fat-free mass.
5 Well, we can show you some of the data that
6 we have done, again, in small studies. This is a
7 study done by Dr. Lars Sjostrom in Sweden, in which we
8 used DEXA in our 1-year and at the end of two years of
9 our study.
10 This is the total weight loss, and the
11 placebo and the orlistat -- the white is lean and the
12 black is fat-free mass. And because the total amount
13 of weight loss is greater in the orlistat group, you
14 have a greater total amount of lean mass, but the
15 percentages are, for the first year, very similar.
16 In the second year, there's actually
17 slightly greater lean body mass lost percentage-wise
18 on the people on placebo versus the people on orlis-
19 tat.
20 Next slide, please. This is a very small
21 study, again done by Dr. Sjostrom, in which we used
22 equations that he calibrated based on CT evaluation,
23 to be able to come up with ways of evaluating differ-
24 ent types of fat tissue -- subcutaneous, visceral, and
25 lean body mass -- based on anthropomorphic measure-

1 ments.

2 And the caveat is, it's a small study. But

3 what it shows here in this study is that compared to

4 placebo, the orlistat people have a greater percentage

5 of their visceral adipose tissue.

6 Next slide, please. Oh, there isn't? Okay,

7 slide off. So again, these are small studies, but the

8 bulk of the data show that what you get is loss of

9 mostly fat mass and in that same study where they have

10 the total body potassium, they also measured it by, I

11 believe, DEXA, and it was in the correct direction.

12 So we think that that one study which showed

13 actually an increase in lean body mass instead of a

14 decrease in the placebo group causing the statistical

15 difference, is an aberration.

16 ACTING CHAIR SHERWIN: What's the effect on

17 bowel transit time? Would fat malabsorption or fat

18 alterations in absorption affect transit time in the

19 bowel?

20 DR. HAUPTMAN: We did studies in which we

21 looked at -- with scintigraphic evaluation of GI

22 transit time, and we saw no difference following a

23 mixed meal with the orlistat and the placebo group.

24 So there wasn't any significant difference there.

25 ACTING CHAIR SHERWIN: And you, at least to

1 some extent, either in these clinical studies or pre-
2 clinical studies, looked at protein and carbohydrate
3 absorption? Even though there shouldn't -- I'm not
4 sure that you'd have any reason to suspect that it
5 should change, I'm just curious whether there is any
6 data.
7 DR. HAUPTMAN: We don't have data on that
8 for the specific reason that you mentioned, based on
9 the fact that we don't inhibit, you know, trypsin or
10 amylase, we didn't measure that.
11 DR. HIRSCH: But you probably have stool
12 nitrogens, do you?
13 DR. HAUPTMAN: No, we don't. We will. We
14 don't; we will.
15 ACTING CHAIR SHERWIN: Dr. Illingworth.
16 DR. ILLINGWORTH: We haven't actually seen
17 the structure of the drug. Is that feasible?
18 DR. HAUPTMAN: Yes, we can get that up. Our
19 drug metabolism people have a slide of that.
20 DR. ILLINGWORTH: And while you're doing
21 that, a second question. One percent of the drug is
22 absorbed. Is there any effect on other lipases?
23 Hepatic lipase in the liver?
24 DR. HAUPTMAN: We did a very detailed study
25 specifically looking at that -- that was Dr. Eccle's

1 group -- and we did -- so we can show you briefly,
2 exactly what we looked at and what we saw in terms of
3 lipase, if you'd like to. Okay.
4 DR. GUERCIOLINI: Dr. Guerciolini from
5 Clinical Pharmacology. Let's review the structure, or
6 the clinical structure of orlistat. Slide J-5,
7 please. This is the standard chemistry we're going to
8 go through today. There is the structure of orlistat
9 which is, basically is a large molecular weight
10 substance with a very high liposalicytic characteris-
11 tic, which makes it very unlikely to be absorbed
12 through the gastrointestinal tract.
13 In fact, the main backbone of the structure
14 is a long anaphoratic chain, very similar to a free
15 fatty acid chain. There are two additional constitu-
16 ents of the molecule -- the beta latone ring which is
17 the molecule actually interacting on a one-to-one
18 basis with the sereine residue of the gastrointestinal
19 lipases. And amino acid, and formalucin.
20 As I said, this structure resembles very
21 much the triglyceride in order to act as an inhibitor,
22 has to resemble and to somehow fool the enzyme in
23 order to inhibit it.
24 It's important, specific, and slow to
25 reverse, an inhibitor of gastrointestinal lipases, but

1 since pancreatic and since system lipases are also
2 very similar in structure, the possibility exists that
3 the orlistat will innervate the non-system-lipases.
4 Orlistat though, is very small and very
5 small amount absorbed systemically, so the amount of
6 absorption is unlikely to affect systemic lipases.
7 Nevertheless, in order explore this opportunity, a
8 specific study was being designed to actually eluci-
9 date whether these events occur.
10 Slide on. Systemic lipases are extremely --
11 the two enzymes more importantly involved in the
12 disposition, and distribution, and metabolism of
13 lipoproteins. While lipoprotein lipases prefer larger
14 and less dense molecules like triglycerides, rich
15 chylomicron and vLDL, the peri-lipases also act upon
16 more dense particles -- intermediate and high density
17 level proteins.
18 The way to measure the activity of those two
19 enzymes is constantly referring in the post-heparin
20 lipase, since the vast majority of the enzyme is
21 anchored to the endothelial cell, heparin is capable
22 to release such a molecule into the plasma.
23 Another way to measure recently become
24 available, is pre-heparin lipase. The small amount is
25 a small fraction of the lipidic activity of the

1 plasma, which is actually circulating, bound to
2 lipoproteins.
3 The objective of the study we conducted in
4 the B subject was to evaluate it, whether the thera-
5 peutic doses of orlistat could have an effect on post-
6 heparin hepatic lipase activity. Secondary objective
7 was also to evaluate the effect on pre-heparin lipase
8 activities.
9 Next slide, please. The study was conducted
10 in a single center, double-blind, placebo-controlled,
11 randomized design, in a single center in Colorado.
12 Twenty-four healthy subjects were enrolled into the
13 study and they went through a 10-day treatment with
14 orlistat at the recommended daily doses of 120
15 milligrams three times a day.
16 During the study period there were two test
17 meals. A fat-rich breakfast containing 28 grams of
18 fat was administered either on day-5 as well as day-
19 10. The main parameter was to evaluate the post-
20 heparin hepatic enzyme activity, which represented
21 vast majority of the lipolytic effect on the plasma.
22 Next slide, please. Please appreciate the
23 scale of the unit which is expressed in terms of
24 micromoles of free fatty acids produced over one hour
25 by one milliliter of plasma. This is a very large

1 amount of enzyme activity as delivered by the heparin
2 administration to the subject.
3 If an inhibition by the practice, a small
4 fraction of orlistat is systemically absorbed, with
5 that being occurring, it would be represented by a
6 decrease in the orlistat group in enzyme acuity. And
7 certainly appreciable that such a decrease did not
8 occur, after they view the two groups, due to the same
9 enzymatic activity level.
10 The secondary parameter was to evaluate the
11 pre-heparin enzyme acuity level. The small fraction
12 and highly variable enzyme activity which are circu-
13 lating on the plasma.
14 Next slide. Again, please, check the scale.
15 In this case we are measuring nanomoles of free fatty
16 acids reduced over one hour, per millimeter of sample.
17 This scale is virtually a 6th order of magnitude lower
18 than the previous one, and of course represents report
19 of variability of results, either individual variabil-
20 ity as well as time point variability.
21 Plasma level of pre-heparin lipase, acuity
22 was measured at hourly intervals after the meal, up to
23 12 hours. Either point-to-point comparison or the
24 area under the effect curve, where the two treatments
25 -- were not significant difference between the two

1 treatments.

2 Next slide. Same comment is valid also for
3 pre-heparin lipoprotein and lipase acuity, which
4 again, very small actual amount -- about 7 nanomoles
5 per milliliter per hours. Again, a 6th order of
6 magnitude lower than the post-heparin lipase acuity.
7 And again, point-to-point comparison as well as area
8 under the curve were no different between treatments.

9 One consequence of a division of system
10 lipases will be the tremendous increase of trigylicer-
11 ides observed after a meal, fat meal. And if I have
12 the next slide, that's the post-prandial triglyceride
13 curve observed with the two groups. As suspected, in
14 absence of any inhibition of enzymatic activity by
15 orlistat, the two curves were virtually overimposable.
16 And actually, if any, the orlistat curve was marginal-
17 ly lower than the placebo group.

18 But virtually there was no significant
19 difference between the two treatments. Next slide.
20 Our study demonstrated that the repeated dose of
21 orlistat has no effect on the larger amount of enzyme
22 activity present and anchored in the cell, as well as
23 the smaller amount of enzyme activity which is
24 circulating.

25 Next slide. On the basis of the result of

1 this study, it's possible to conclude that orlistat
2 therapeutic doses have no effect on hepatic and
3 lipoprotein enzyme activities.
4 DR. ILLINGWORTH: Thank you.
5 ACTING CHAIR SHERWIN: If you could stay at
6 the podium for a few minutes.
7 DR. GALLO-TORRES: Going back to the lumen
8 of the intestine, do you test for activity on lipases
9 produced by bacteria? Bacteria lipases?
10 DR. GUERCIOLINI: It has been reported in
11 the literature that a small amount of enzyme material
12 remaining to the colon, deriving from colonic floor.
13 We did not assess such an opportunity in terms
14 evaluating the extent of inhibition of -- enzyme
15 activity present to the colonic floor.
16 ACTING CHAIR SHERWIN: By the way, is the
17 drug metabolized in the gut?
18 DR. GUERCIOLINI: The disposition metaboling
19 of all this has been extensively evaluated in either
20 in vitro, in pre-clinical, in clinical setting.
21 There's a wealth of information converging toward the
22 indication that orlistat has marginally metabolized.
23 Is mostly excreted intact and unchanged into the
24 feces.
25 Eighty-three percent of the dose is recov-

1 ered in the fecal material as intact orlistat.
2 Ninety-seven percent of the intact dose, administered
3 is directly into the feces.
4 ACTING CHAIR SHERWIN: Thank you. Do I see
5 any more comments? Looks like we've been talked out.
6 CHAIRMAN BONE: I'd just like to add a
7 congratulatory note to the sponsors on having done
8 extensive comorbidity studies. I think that we're
9 seeing a series of drugs with modest efficacy on
10 actual weight loss. As Dr. Hirsch has pointed out
11 it's extremely helpful when we have some questions --
12 about issues like the vitamin that's been discussed --
13 it's extremely helpful to have the additional informa-
14 tion on comorbidities which the sponsor has provided.
15 ACTING CHAIR SHERWIN: If there's no more
16 questions I think we can go to the questions posed by
17 the FDA for this committee. And we'll begin -- when
18 I ask the question we'll ask Henry Bone in absentia to
19 give us his response.
20 Is orlistat, when dosed at 120 milligrams
21 t.i.d., an effective weight loss drug?
22 CHAIRMAN BONE: I would say yes based on the
23 secondary categorical criteria.
24 ACTING CHAIR SHERWIN: Dr. Illingworth.
25 DR. ILLINGWORTH: Yes.

1 DR. CRITCHLOW: Yes.

2 DR. HIRSCH: Yes, but with diet, etc. That
3 is, I think it should be clarified that the drug
4 itself has not been tested on people on a random diet
5 and not otherwise treated. So I would only -- have to
6 amend that to say, as given by the sponsor which was
7 in a circumstance of a 30 percent fat diet and
8 whatever other things were done.

9 MR. MOLITCH: Yes.

10 DR. COLLEY: Yes.

11 ACTING CHAIR SHERWIN: Dr. Cara.

12 DR. CARA: Yes, with the same issues that
13 Dr. Hirsch mentioned, and also I'd like to clarify
14 that it's an effective weight loss drug for adults.

15 ACTING CHAIR SHERWIN: I would echo Dr.
16 Cara's comments. Yes.

17 Okay. The next question: Do the data
18 indicate a need to provide vitamin supplements to all
19 patients taking orlistat?

20 I'll go around the other way. Dr. Cara.

21 DR. CARA: Yes, although I think one of the
22 issues that we need to be aware of is the continuous
23 monitoring of vitamin supplementation. I'm particu-
24 larly concerned about the issue of vitamin overload,
25 especially if patients tend to regain initial weight

1 perhaps related to decreased efficacy of the drug.

2 So yes, but with that qualifier.

3 ACTING CHAIR SHERWIN: Dr. Colley.

4 DR. COLLEY: Yes, and there should be some

5 guidance in the labeling as to when to take the

6 vitamin supplement. One of the consultants suggested

7 it be given not with the drug, so that the absorption

8 is better.

9 And one other comment. Although the effect

10 on vitamin K did not manifest in their data, I would

11 also like the labeling to reflect that there may be a

12 potential for interaction with oral anti-coagulants.

13 MR. MOLITCH: Yes. I think that a multi-

14 vitamin, as indicated previously, is probably part of

15 standard substantial weight loss regime in general.

16 And I think it certainly should be given with this

17 medication. We're a little bit less concerned about

18 if the patients aren't losing so much in the second

19 year or even regaining a little bit, that we have to

20 be worried about stopping one multi-vitamin pill.

21 DR. HIRSCH: Yes, as Dr. Colley mentioned

22 though, with the addition of giving it at the appro-

23 priate time, etc.

24 DR. CRITCHLOW: Yes, as well.

25 DR. ILLINGWORTH: Yes, as well, with the

1 suggestion that they, in the package insert, define
2 some recommended doses and emphasize, don't take too
3 much. We don't want to get patients to be taking
4 excess amounts of vitamin A ending up with vitamin A
5 toxicity.
6 ACTING CHAIR SHERWIN: Dr. Bone.
7 CHAIRMAN BONE: Well, I don't think people
8 are in much danger of getting vitamin A toxicity from
9 a standard multi-vitamin if that turns out to be
10 sufficient. But I think it's appropriate to have some
11 fairly specific guidance. I think it's not proven
12 that all patients will require supplements, but I
13 think that there's sufficient proof that the right
14 thing to do is to give the supplement to everyone and
15 not worry so much. So I would say yes.
16 ACTING CHAIR SHERWIN: I would say yes, too.
17 Okay, now the last question is: Taking into
18 consideration the overall risks and benefits of
19 orlistat, do you recommend that the drug be approved
20 for marketing for the management of obesity?
21 I'll ask Dr. Bone to begin.
22 CHAIRMAN BONE: Taking into account particu-
23 larly, the comorbidity information, I would say yes.
24 ACTING CHAIR SHERWIN: Dr. Illingworth.
25 DR. ILLINGWORTH: My answer would also be

1 yes, used in the context of, in addition to dietary
2 measures as we would all recommend, as been used --
3 CHAIRMAN BONE: I certainly would agree with
4 those remarks.
5 DR. CRITCHLOW: Yes, I think there is a role
6 for this drug.
7 DR. HIRSCH: But, but I would again empha-
8 size diet, and it's been shown to be effective for a
9 period of two years, and like with all drugs, it's
10 going to vanish thereafter. So however that can be
11 indicated is it's not going to be that -- I mean, the
12 effectiveness will wane over time.
13 MR. MOLITCH: Yes, with the same provisos.
14 DR. COLLEY: Yes.
15 ACTING CHAIR SHERWIN: Dr. Cara.
16 DR. CARA: Yes, with the same provisos that
17 have been mentioned, but also I would encourage the
18 FDA to provide some very strict labeling regarding
19 potential use and abuse in children. I think that's
20 going to be an especially critical issue.
21 DR. HIRSCH: If I could add, I think also --
22 I mean, we're not going to get into the issue of
23 labeling now, but there are some obvious things like
24 the carcinoma of the breast issue has to be dealt with
25 in some way, at least to state that it has been

1 observed or something, so there may be particular
2 attention to those with known high susceptibility or
3 whatever.
4 And I would have thought it prudent, too,
5 that people with intestinal disorders of any kind,
6 inflammatory disease of the intestine, would be
7 excluded from using this, and there may be other
8 medical exclusions, too. But this is -- I guess this
9 is getting into another area.
10 In general what we're saying, yes is
11 conditionally with a very carefully thought-out set of
12 instructions and restrictions, etc., to go with it;
13 the details of which we're going to have to either
14 leave to you or discuss at some other time or whatev-
15 er.
16 ACTING CHAIR SHERWIN: You took the words
17 out of my mouth. I was going to end with those,
18 Jules, but I --
19 DR. HIRSCH: I'm sorry.
20 ACTING CHAIR SHERWIN: -- would say yes --
21 no, you don't have to be sorry. But I feel strongly
22 that this study was conducted in people without GI
23 disease, without gallstones, without kidney stones.
24 It was an ideal population, and the toxicities may be
25 greater in special circumstances.

1 So that I do believe that it's incumbent on
2 the FDA to be very careful about the labeling of this
3 drug, and also about the use of it in children,
4 because I still think that since no children were
5 studied that there is some potential risk.
6 I'd also like to now -- now that we've
7 completed the vote -- yes?
8 DR. HIRSCH: I just would like to ask my
9 colleagues whether they'd like to make any additional
10 statement about a level of BMI or a level of obesity
11 at which use of this is recommended? I would have
12 some feelings, myself, about that, but I don't know
13 whether it's even appropriate or whether the FDA
14 wishes us to comment on that, or get into it.
15 ACTING CHAIR SHERWIN: Well, why don't you
16 make some comments first, Dr. Sobel, and Dr. Bilstad
17 --
18 DR. HIRSCH: We'd like to help you with any
19 other issues --
20 ACTING CHAIR SHERWIN: -- and then we'll
21 respond to your comments.
22 DR. SOBEL: Well, we can start with Jules'
23 suggestion. I think, does the committee want to
24 recommend the target population as far as BMI as we
25 have with another agent?

1 ACTING CHAIR SHERWIN: I think -- my guess
2 is, knowing this committee, yes.
3 DR. ILLINGWORTH: Roger Illingworth. Yes,
4 with the same criteria that we've applied to previous
5 drugs for the treatment of obesity.
6 DR. CRITCHLOW: I agree that previous
7 criteria would apply here as well. That is, 30 in the
8 --
9 ACTING CHAIR SHERWIN: Without comorbidity
10 --
11 DR. CRITCHLOW: -- without comorbidity; 27
12 with.
13 ACTING CHAIR SHERWIN: Twenty-seven with
14 comorbidity -- it's 30 without, 27 with comorbidities.
15 DR. HIRSCH: I think it's very arbitrary but
16 that sounds reasonable to me. What I'm trying to get
17 across is it should not be used by people who want to
18 lose, you know, three pounds after Thanksgiving Day or
19 something of that sort. So that there has to be a
20 serious illness because we don't understand all the
21 potential of this drug for mischief as well as for its
22 good, and therefore, something like a BMI of 30, and
23 27 if there are comorbidity, seems a reasonable thing
24 to recommend at this time.
25 DR. SOBEL: In addition, we usually ask at

1 this point, does the committee recommend any post-
2 marketing studies in any specific area that you would
3 like to see?
4 DR. HIRSCH: Well, we've already touched on
5 the carcinoma of the breast thing, and I mentioned
6 briefly earlier, the issue of feeding to animals known
7 carcinogens or mutagens and looking further at in
8 animal, the effects of the drug coincidentally.
9 Because the issue was raised of, this could even be a
10 chemopreventive. We simply don't -- it could work one
11 way or another, but it would be nice to use animal
12 models in which there are a lot of large intestinal
13 malignancies and feed the drug and see the effects of
14 it.
15 ACTING CHAIR SHERWIN: Dr. Bone, do you have
16 any comments?
17 CHAIRMAN BONE: Yes. I think that -- you
18 know, I voted in favor of approval but with some
19 disquiet, and I sense that throughout the committee,
20 because this is -- it's inducing such -- it's a little
21 bit like a condition we've heretofore regarded as a
22 disease state.
23 And I think it would be appropriate for the
24 labeling to express caution about use beyond the two
25 years, because some of these effects, as we've

1 discussed, may be cumulative and may actually only be
2 manifest with prolonged usage, but might nevertheless
3 become significant.
4 Tied to that, I would make a very strong
5 argument for a very long-term Phase IV study being
6 agreed to, actually prior to the final approval, which
7 would -- in a substantial cohort, a rather large
8 cohort -- look for treatment, emergent problems of the
9 kind that we've discussed, and plan to follow those
10 patients for, perhaps four or five years anyway. And
11 I think this is well within the means of the sponsor
12 and should be quite practical in view of the wide-
13 spread use of drugs which are designed to treat
14 obesity.
15 We really looked here at something with a
16 modes benefit reinforced by the comorbidity data, and
17 it would be very important to be aware of a subtle
18 problem that wasn't manifested in the course of the
19 clinical trial. So I think that's extremely impor-
20 tant.
21 ACTING CHAIR SHERWIN: Roger, anything else?
22 Yes, I feel very strongly about duration of the
23 studies. I think that, given the fact that a lot of
24 the changes we see are going to be very subtle for a
25 very long time, I would urge, I echo Henry Bone's

1 comments that I believe long-term studies focused on
2 the issues of breast cancer and the issue of osteopo-
3 rosis in women over an extended period of time -- that
4 would be a particular concern of mine, despite the
5 data that we've been presented.
6 It is a little disconcerting that we are
7 creating somewhat of an illness -- bad malabsorption
8 -- and the benefit is a modest reduction in weight.
9 So we have to balance the two. I think that we
10 haven't surprisingly, seen much evidence of severe
11 toxicity. It may be just the duration, but at least
12 it -- I think that even though the drug did not have
13 a dramatic effect, we felt compelled to approve it
14 given the benefit with comorbidities.
15 On the other hand, I do believe that there
16 may be things that we don't know about yet -- the
17 specter of breast cancer is one that I don't under-
18 stand, but I do believe is extremely important since
19 it was statistically significant, and therefore, one
20 has to be very vigilant in the next two years.
21 And I think that a study focused on that is
22 essencial, and that the FDA is going to need to insist
23 on that issue before allowing the drug to be approved.
24 That they approve a study to examine this.
25 DR. CARA: If I can make one other comment.

1 I think the other thing -- I mean, I agree with what
2 you and Henry Bone were saying, but what disturbs me
3 a little bit about the studies that the sponsor has
4 shown us is that essentially have been done in a very
5 homogenous population. And I think that we really
6 need to be vigilant and look at long-term efficacy and
7 long-term morbidity and mortality data in other
8 populations: African-Americans, Hispanics, specifi-
9 cally.
10 I don't know that there will be any signifi-
11 cant differences, but on the other hand, we don't know
12 that there won't. So I think that is another issue
13 that I'd like to see addressed as these Phase IV
14 studies are being designed and implemented.
15 ACTING CHAIR SHERWIN: Any other comments?
16 CHAIRMAN BONE: I have a question, probably
17 for Dr. Sobel. It has to do with this breast cancer
18 question. This is really nagging. I think that the
19 Agency and the sponsor clearly have beaten this
20 problem as hard as they can for the time being, with
21 the available information, and really haven't been
22 able to resolve it. There doesn't seem to be any
23 mechanistic basis for this, but it's an improbable
24 observation to have had by chance. Will this be of
25 sufficient concern to constitute -- require a warning

1 in the labeling?

2 DR. SOBEL: Well, on the -- let me just say

3 that I don't think we've explored the database as

4 completely as we might have. We have to recognize

5 that we have looked at the concert data that arose

6 from the seven major studies. There is an exposure of

7 some 7,000 patients. There is a differential exposure

8 which we haven't fully accounted for in looking at the

9 figures.

10 The 9:1 or 8:0 or however you do it, is a

11 ratio that has not been accounted for by the differen-

12 tial exposure. So there are a lot of other things

13 that we have to do at this point to refine the

14 epidemiologic data in additional to the longitudinal

15 approach that I suggested.

16 Now, in regard to a warning, that's a

17 question I think perhaps, we'll readdress that after

18 we've refined the database a bit more.

19 CHAIRMAN BONE: Excuse me. I got the

20 impression that the reviewers did not have additional

21 questions. If there are additional questions to be

22 explored from your perspective about this, I really

23 think that that should be satisfactorily resolved

24 before --

25 DR. SOBEL: Yes, I think so. I think we do

1 have to do a more rigorous exploration. Certainly
2 we're going to proceed. Perhaps Dr. Stadel would want
3 to comment or -- because we've initiated some discus-
4 sions on doing more with the data that are available
5 to us.
6 DR. STADEL: Only to the extent when this
7 issue first came up I looked at the incidence in the
8 trials on an intent-to-treat basis, looked at the
9 distribution of cases from time starting drug to time
10 of diagnosis, and looked at whether this was account-
11 able on differential dropout. And then at that point
12 recommended through Dr. Coleman, to recommend to the
13 company that they seek a consultation for further
14 workup of the data since I could not account for it in
15 a straightforward way.
16 What's been presented today is there workup
17 of the data. I have not seen and would like to see,
18 a written report on the workup thus far, and then see
19 if there's in fact, more that can be extracted from
20 the existing resources of data.
21 CHAIRMAN BONE: Do I understand then that
22 that response has not actually been reviewed by the
23 Agency?
24 DR. STADEL: I have not seen a report on
25 their work -- a written report, no. Today is -- you

1 know -- I heard their presentation, that's correct.

2 CHAIRMAN BONE: Then I would certainly

3 reserve my vote pending that information being

4 settled.

5 ACTING CHAIR SHERWIN: Dr. Troendle.

6 DR. TROENDLE: I had two more questions

7 about further study. One of them is to do with

8 further vitamin studies. You have certainly talked

9 about doing a bone study. There is still the question

10 of an adequate evaluation of vitamin K, I guess. That

11 might fit into the bones since some of the K-dependent

12 proteins are bone proteins.

13 Then the other thing I wanted to ask about,

14 what studies in children do you recommend that those

15 be done, and to what age?

16 ACTING CHAIR SHERWIN: We lost our Pediatri-

17 cian. But I don't know that we have enough data. I

18 mean, surely -- my own view would be that you would

19 need a study before you could possibly recommend it

20 for children. And --

21 DR. TROENDLE: Well, I was asking about a

22 study.

23 ACTING CHAIR SHERWIN: Do we want a study in

24 children?

25 DR. TROENDLE: Yes. Do you want to recom-

1 mend a study?

2 ACTING CHAIR SHERWIN: Well, I think it's

3 likely, knowing that obesity is becoming a problem

4 among certain populations in this country. That drugs

5 for weight loss are going to be used, and I would

6 think it would be a very reasonable thing to do. But

7 the criteria would have to be very strict with respect

8 to, you know, the criteria for pharmacologic treatment

9 in childhood. But I think that we're getting to that

10 point where that's going to -- I would say yes. I'll

11 stop there. I would like to see that.

12 DR. HIRSCH: I would like to comment on

13 that. This drug probably works by virtue of, at least

14 in part, the kind of conditioning mechanism that I've

15 mentioned to you. In that respect I find it a very

16 favorable thing because it's sort of pushing people to

17 eat a lower fat diet, which may be an advantageous

18 thing.

19 On the other hand, there are times during

20 adolescence, particularly in women, where there's a

21 great sensitivity to any kind of dietary manipulation,

22 and it waits to be seen whether this is at all safe.

23 I'm thinking of the anorexia/bulimia sort of situa-

24 tion, which could get somehow, confounded with all of

25 this. I'm not sure that we ought to be in a position

1 of recommending this for anyone under age 18, let's
2 say.
3 ACTING CHAIR SHERWIN: At this point no,
4 definitely not.
5 DR. HIRSCH: It may be fine, but I think
6 there has to be more understanding and more work with
7 it before that's done.
8 DR. TROENDLE: Dr. Hirsch, do you recommend
9 studies in children?
10 DR. HIRSCH: Oh yes, I certainly think it
11 should be studied, because the --
12 ACTING CHAIR SHERWIN: Before one can make
13 a recommendation?
14 DR. HIRSCH: Before one can make a recommen-
15 dation, the --
16 DR. TROENDLE: What ages?
17 DR. HIRSCH: Well, I think certainly down
18 to, you know, puberty, post-pubertal children into
19 adolescence, because obesity has its roots deep down
20 -- the prevalence of obesity is growing very rapidly
21 in our childhood populations, so I think it's very
22 important to extend therapeutic options there, but we
23 do have to do the studies first. I believe.
24 ACTING CHAIR SHERWIN: Dr. Illingworth.
25 DR. ILLINGWORTH: One other area that I'd

1 like to see a little bit more information about, and
2 that is potential drug interactions or effects on
3 absorption of other drugs, particularly lipase drugs
4 -- cyclosporin, drugs that are lipophilic.
5 I noticed in the background information that
6 the area of the curve and efficacy of prevastatin was
7 enhanced when they're on this drug. That's a fairly
8 water-soluble drug. What about more lipophilic drugs?
9 Are they influenced?
10 DR. GUERCIOLINI: Dr. Guerciolini again. I
11 think it will be just much lighter. It will address
12 all the list of drug interaction we absolutely have.
13 J-3, please. Actually, the approach to drug interac-
14 tion was, according to the guideline that the FDA was
15 proposing, was a sort of rational approach.
16 Is the drug dependent on fat absorption in
17 order to be inhibited? Second, is the drug a narrow
18 -- if there's marginal changes in the absorption could
19 result in toxic effect on one side, in efficiency
20 therapeutic effect on the other side. So there was
21 the choice of our selection of drug interaction,
22 rather than checklist interaction.
23 These are the criteria -- the group with
24 narrow interpret in this drug are represented by
25 digoxin, phenytoin, and warfarin. The other group is

1 a concomitant likely to be used drug in the target
2 population. Of course there are anti-hypertensive,
3 there is a oral hypoglycemic agents, or a contracep-
4 tive. Women are the largest representation in our
5 population, and from our study is the only one at that
6 time, ever able among the -- available among the staff
7 and family, and with an assay which was validated at
8 that time.
9 You can notice that virtually there is no
10 pharmacokinetic or pharmadynamic interaction in the
11 vast majority of the drug interaction study. Alcohol
12 is not really a drug but was a source of European
13 concern since alcohol consumption is typical with the
14 meals, and we want to make sure that either alcohol
15 absorption was not enhanced, nor the pharmacodynamic
16 effect of -- also was reduced by concomitant adminis-
17 tration.
18 If you look at those list of drugs, most of
19 them are high lipophilic drug. In other words, they
20 fit into the process that they require a certain
21 amount of fat likely to be absorbed. Water in
22 particular, is a very lipophilic drug. Nifedipine is
23 a log or partition coefficient of about 4. So it's
24 very like a lipophilic drug.
25 No interaction were observed, which seemed

1 to indicate it up to a coefficient or partition
2 coefficient of about 4, there is not likely it would
3 make nth degree onto an interaction.
4 The prevastatin study was a surprise to us.
5 As I said, the assay was just available at that time,
6 it was the only assay. The expected pharmadynamic
7 enhancement of lipid lowering effect of prevastatin
8 was confirmed. Also add an additional 10 percent
9 effect on cholesterol reduction.
10 But the pharmacokinetic prevastatin was
11 largely increased -- about 30 percent there, you see
12 about 20 of Cmax. We actually don't have a rational
13 explanation for that phenomena. Certainly, prevas-
14 tatin is not a lipophilic drug, and if any -- certain-
15 ly they will not be affected in terms of inhibition of
16 absorption.
17 DR. ILLINGWORTH: Thank you.
18 ACTING CHAIR SHERWIN: Thank you. Dr.
19 Bilstad, do you have any comments that you'd like to
20 make?
21 DR. BILSTAD: I just want to say that I
22 think that the committee has explored the issues of
23 the safety and effectiveness of this drug in some
24 detail and very thoroughly. It's been a good discus-
25 sion and we certainly appreciate the comments and

1 recommendations from the committee. Thank you.

2 ACTING CHAIR SHERWIN: Okay. Well, before

3 I adjourn this meeting I'd like to thank the company

4 for putting together a nice packet for us. It was

5 clear and easy to read and it was very straightfor-

6 ward. It made our job easier.

7 And I'd also like to thank Dr. Colley who's

8 ending her tenure on our committee, and thank her for

9 her companionship over the last few years. Thank you.

10 And we're ready to adjourn.

11 (Whereupon, the meeting of Advisory Commit-

12 tee on Endocrinologic and Metabolic Drugs was conclud-

13 ed at 2:54 p.m.)

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CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Endocrinologic and Metabolic Drugs Advisory Committee Meeting #67

Before: DHHS/PHS/FDA/CDER

Date: May 14, 1997

Place: Bethesda, MD

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

Irene Gray