UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE

MEETING #64

THURSDAY,
SEPTEMBER 26, 1996

The meeting took place in Versailles Rooms I and II, Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland at 8:00 a.m., Henry G. Bone III, MD, Chair, presiding.

MEMBERS PRESENT:

Henry G. Bone III, MD, Chair
Kathleen R. Reedy, Executive Secretary
Colleen A. Colley, PharmD, Consumer Rep
Cathy Critchlow, PhD
D. Roger Illingsworth, MD, PhD
Robert A. Kreisberg, MD
Robert Marcus, MD
Mark E. Molitch, MD
Maria I. New, MD
Robert S. Sherwin, MD

FDA CONSULTANTS PRESENT:

John M. Flack, MD, MPH
Joanna Zawadzki, MD

FDA REPRESENTATIVES:

Eric Colman, MD
Solomon Sobel, MD
Bruce Stadel, MD MPH
Gloria Troendle, MD

SPONSOR REPRESENTATIVES:

David Heal, PhD
Michael Lean, MA, MD, FRCP
Carl Mondel, MD
F. Xavier Pi-Sunyer, MD
Timothy Seaton, MD
Sylvia Smoller, PhD

PUBLIC COMMENTERS:

Richard Atkinson, MD
Kris Ernst
John Foreyt, PhD
Barbara Hanson, PhD
Lynn McAfee
Valerie Rochester

ALSO PRESENT:

Elliot Danforth, MD
Rodney E. Haddock, BSc, PhD, MRSC, CChem
Finian Kelly, MD
Damian McEntegart
Bramah Singh, MD, PhD
Michael Weber, MD

A G E N D A

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

8:08 a.m.

CHAIRMAN BONE: I just want to announce that this is the Endocrine and Metabolic Drugs Advisory Committee Meeting. If you are here for one of the other meetings that are occurring in the same facility, it's a good time to leave because we'll be starting the Endocrinology and Metabolic Drugs Advisory Committee Meeting in a few minutes.

Good morning. I'm Dr. Henry Bone. I'm the Chair and I'm calling into order the 64th meeting of the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee. As I mentioned earlier, if you're here for one of the other meetings that are occurring in this same hotel, they've probably just about started.

The topic for today is the new drug application for sibutramine. We'll be having presentations, of course, by the sponsor and by the Agency.

The first order of business will be the introductions by each of the people here at the front table. Then we'll have the meeting statement by Kathleen Reedy who is the Executive Secretary of the Committee.

If we could start at the far end on my right, please? If each person will introduce him or her self and their affiliation.

DR. ZAWADZKI: My name is Joanna Zawadzki. I'm an endocrinologist in private practice in this area. I'm a associate clinical professor at Georgetown University Medical Center.

DR. KREISBERG: Bob Kreisberg, endocrinologist, Birmingham, Alabama, clinical professor of medicine at UAB.

DR. CRITCHLOW: I'm Cathy Critchlow, epidemiologist, University of Washington, Seattle.

DR. MARCUS: Robert Marcus, endocrinologist, Veterans Affairs Medical Center, Palo Alto, professor of medicine at Stanford University.

DR. ILLINGSWORTH: Good morning. Roger Illingsworth, Department of Medicine in the Metabolism Division, Oregon Health Sciences University, Portland, Oregon.

DR. COLLEY: Colleen Colley. I'm a clinical pharmacist at the VA in Portland, Oregon.

DR. SHERWIN: Robert Sherwin, endocrinology professor of medicine, Yale University.

CHAIRMAN BONE: Henry Bone, the Henry Ford Hospital, Detroit, Michigan.

DR. REEDY: Kathleen Reedy, Executive Secretary of the Endocrinologic and Metabolic Drugs Advisory Committee for the FDA.

DR. MOLITCH: Mark Molitch, endocrinologist and professor of medicine at Northwestern University Medical School in Chicago.

DR. FLACK: John Flack. I'm associate professor of surgery, Madison Public Health Sciences and social director and medical director of the Hypertension Center at Bowman Gray School of Medicine.

DR. COLMAN: Hi, I'm Eric Colman. I'm a medical officer in the Division of Metabolism at the FDA.

DR. STADEL: Bruce Stadel, medical officer, FDA.

DR. TROENDLE: Gloria Troendle, Division of Metabolic and Endocrine Drugs, FDA.

DR. SOBEL: Sol Sobel, director of the Division of Metabolic and Endocrine, FDA.

CHAIRMAN BONE: Thank you.

Dr. Reedy?

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

meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exception. In accordance with 18 United States Code 208(b)(3), a full waiver has been granted to Dr. Mark Molitch. A copy of the waiver statement may be obtained from the Agency's Freedom of Information Office, Room 12A15 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Mark Molitch has an interest which does not constitute a financial interest within the meaning 18 United States Code 208(a), but which could create the appearance of a conflict. The Agency has determined, notwithstanding this involvement, that the interest of the government in Dr. Molitch's participation outweighs the concern that the integrity of the Agency's programs and operations may be questioned. Therefore, Dr. Molitch may participate fully in this meeting.

In the event that the discussions involve any other products or firms not already on the agenda

for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRMAN BONE: Thank you.

The next part of the meeting is the open public hearing segment. This is, as I remarked before, an extraordinary feature. If you look around the world at the way drug reviews are conducted, this is an exceptional characteristic of the United States that the opportunity is made available to people who are interested in making comments and who make arrangements in advance to be heard to do so.

We will have six presentations of five minutes each. I will make a signal when one minute is remaining. Then we take note of letters from five individuals or organizations, copies of which have been provided to members of the Committee and additional copies of which are also available outside along with the meeting programs.

The first speaker in the open public

hearing segment is Dr. Richard Atkinson. I will ask each speaker to state whether they have any affiliation with financially interested parties, and if so, what.

DR. ATKINSON: Hello. My name is Dr. Richard Atkinson. As for conflicts, I'm currently receiving no research funds from drug companies. In the past, I've served as a consultant, have given CME lectures sponsored by drug companies, and have gotten research funds. I've consulted for Knoll Pharmaceuticals in the past and given CME lectures sponsored by them.

As I said, I'm president of the American Obesity Association which is a lay advocacy group representing the interests of the 70 to 80 million obese American women and children and adults afflicted with the disease of obesity. The missions of the American Obesity Association are education, promotion of research and community action in the interests of obese people. I'm also a professor of medicine and nutritional sciences at the University of Wisconsin at Madison. My area of research is obesity, particularly in the use of drugs for the treatment of obesity. I'm currently participating in several studies evaluating drugs for obesity that involve more that 2,500

patients.

The American Obesity Association strongly supports the development of new treatments for obesity. The success rate of diet, exercise and behavioral modification of lifestyle has been very poor over the long-term. The data of Weintraub et al, our data and those of a number of other investigators demonstrate that the addition of pharmacologic agents enhances weight loss, the maintenance of weight loss, and reduces the major risk factors associated with obesity.

Obesity has a strong genetic component and there are compelling data to show that the biochemistry and physiology of obese people are different from those of lean people. Just as with other chronic diseases, we believe drugs will be necessary to alter the biochemistry of obese people towards that of lean people.

Dr. Claude Bouchard has identified over 20 genes that contribute to the etiology of obesity. Combinations of these genes make it likely that there are numerous different types of obesity. We know almost nothing about which drugs will be useful for which types of obesity, but it is naive to assume that all obesity will be treated with one or a few drugs.

There has been only one drug approved by the FDA for the treatment of obesity since 1973. Drug companies have devoted few resources to this serious health problem. The NIH devotes only about one-half of one percent of its budget to obesity research. For a disease that kills 300,000 Americans per year, affects more than one-third of the entire adult population, and affects about 25 percent of children in America, this lack of attention by the government and by industry is a national disgrace.

Clinicians and investigators need additional drugs and the research that will accompany the development and marketing of new drugs. Many obese patients respond poorly to the drugs currently available. Given the diversity of obesity, this is not surprising. Chronic diseases require chronic treatment. New agents, alone or in combination, must be tested to determine their utility for controlling obesity and its comorbid conditions. We urge the Endocrinologic and Metabolic Drugs Advisory Committee to carefully consider the evidence on sibutramine. Should the Committee find this drug to be safe and efficacious and to have an acceptable risk benefit profile, we believe the addition of a new agent for the treatment of obesity will be beneficial for

Americans who suffer from this disease.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Atkinson.

The next speaker is Dr. Foreyt.

DR. FOREYT: Good morning. My name is John Foreyt. I'm a professor of medicine at Baylor College of Medicine in Houston. I'm also the director of the Bakee Heart Center and Nutrition Research Center at Baylor. I'm also a clinical psychologist and have an active clinical practice.

My area of research expertise is in the behavior modification principles with obese individuals for the development of healthy lifestyle. I have in the past had funding from drug companies for research studies, also for presenting educational programs including from Knoll. I don't think I have any current conflict of interests. My thoughts and my words are my own. I paid for the trip here myself and this is what I wrote.

I believe that successful weight management really requires healthy eating and healthy physical activity, and the use of behavior modification principles to best maintain that healthy lifestyle. I also know very well the limitations of behavior modification principles. Behavior

modification does not work very well for most obese patients in the long run, with success rates for obese patients somewhere in the range of five percent to ten percent of individuals receiving the behavioral principles. I believe that we need things more than behavior modification, more than dietary advice, more than physical activity consultation if we're ever going to stem the increasing prevalence of obesity in our society. Last year, we published an article in the Lancet where we looked at current prevalent state and predicted by the year 2230, 100 percent of Americans will be obese.

Obesity is the number one public health problem in the United States. Obesity continues to kill Americans, disables increasing numbers every year. I think we need all the help we can get. Behavior modification works very well at helping adjust environmental behavioral affective cues.

I think anti-obesity drugs like sibutramine help regulate internal cues of hunger and satiety and help cognitively adjust people's thinking patterns in reducing their obsessiveness with thoughts about food and about eating. I think they help people push away from the table easier. I think they help enhance satiety and help them eat less. One of my

patients, for example, told me recently who was on a drug -- said "these drugs help me struggle like a normal person struggles." Before that time, she had been unable to control her eating. She still struggles even on the drugs, but I think the drugs help her make it more manageable in terms of dealing with her eating.

I don't believe drugs like sibutramine are magic bullets. I don't believe drugs like sibutramine are ever going to cure obesity. I think much like high blood pressure drugs don't cure hypertension or insulin doesn't cure diabetes or cholesterol drugs don't cure hypercholesterolemia but they help manage the condition. I think these drugs help, along with behavior modification, manage the condition. I think anti-obesity drugs are adjuncts and they're simply adjuncts to a healthy program of sensible eating and regular exercise. They help produce modest drops in weight, but those modest drops in weight lead to demonstrated medical benefits.

I think along with the limitations and side effects that all drugs have, you need to be sure to consider, very strongly, the benefits of producing modest weight losses. Although they're not cures, they certainly can help and they can help manage this

very terrible condition. As an active researcher and an active clinician in this field, I hope you'll approve sibutramine, given it's safe and efficacious. I think these drugs like sibutramine can really help manage this condition. We need all the help we can get.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Foreyt.

The next speaker is Kris Ernst.

MS. ERNST: Good morning. I have no conflict of interest.

My name is Kris Ernst. I'm a registered nurse practitioner and a certified diabetes educator. I work full-time teaching people how to live with the disease diabetes. I'm the immediate past president of the American Association of Diabetes Educators which is a multi-disciplinary association of health professionals. I'm here to talk today about what I've observed to be the impact of obesity on morbidity and mortality in people with diabetes.

Obesity is highly associated with hyperinsulinemia and insulin resistance. An increased relative weight has been implicated as an independent predictor of diabetes. According to the second

National Health and Nutrition Examination Survey, the prevalence of diabetes is 2.9 times higher in overweight people than in non-overweight people. In fact, according to Healthy People 2000 and the American Diabetes Association Clinical Practice Recommendations weight reduction is the treatment of choice in improving blood glucose control and in reducing hyperlipidemia, hypertension and proteinuria and may moderate other complications of the disease.

In 1986, the National Institute of Health consensus development conference on diet and exercise in non-insulin dependent diabetes concluded that there is an increased risk of non-insulin dependent diabetes in individuals who are 20 to 30 percent overweight. This risk increases with increased body weight and increased degree of obesity, and the distribution of excess of body fat.

Upper body obesity is associated with an even greater risk for non-insulin dependent diabetes. Non-insulin dependent diabetes is an important cause of morbidity and mortality in the United States. Half of all non-insulin dependent diabetes is estimated to be preventable by obesity control. In fact, in June of this year, a multi-center NIH funded trial, the diabetes prevention trial II was initiated. One arm

of treatment is aimed at preventing the onset of non-insulin dependent diabetes in high risk individuals by reducing body weight through dietary and exercise patterns.

Obesity has well established medical and psychological risk factors besides diabetes, including an increase in hypertension, hyperlipidemia, coronary artery disease, and general distress about weight. I see people every day that are struggling with weight control. The total proportion of disease attributed to obesity is quite high, with estimates ranging up to 92 percent.

Dietary factors and activity patterns that are too sedentary are together accountable for at least 300,000 deaths each year. Studies have associated dietary factors or sedentary lifestyles with 22 to 30 percent cardiovascular deaths, 20 to 60 percent of fatal cancers, and 30 percent of diabetes deaths. The combined effects of obesity and non-insulin dependent diabetes are deleterious. Consequently, the benefits of aggressive treatment of obese or overweight individuals with non-insulin dependent diabetes seems to be very well established.

Weight reduction is an indisputable goal in individuals with non-insulin dependent diabetes

improving metabolic functions and decreasing associated complications. This goal may seem relatively concrete and achievable, but weight reduction is actually a complex and illusive process to many. Studies have demonstrated that a combination of caloric restriction, behavior modification, a personalized exercise prescription, family support, recognition and avoidance of high risk situations, are all important components of a successful weight reduction program. However, even with all of these elements in place, relapse are a common problem. Consistently, the best predictor of long-term weight loss appears to be the long-term maintenance of exercise.

Obesity must be viewed as a chronic disease requiring a multi-faceted approach including ongoing clinical care and behavioral change. Behavioral change is motivated not by knowledge alone, but also by a supportive social environment and the availability of facilitative professionals, services and resources. The American Association of Diabetes Educators believe that sibutramine is one of the resources that should be available to persons seeking to reduce their weight.

Thank you.

CHAIRMAN BONE: Thank you, Ms. Ernst.

The next speaker is Dr. Barbara Hanson.

DR. HANSON: I'm the immediate past president of the American Society for Clinical Nutrition. I have no financial interest in any pharmaceutical firm. I have a conflict of interest with almost every pharmaceutical firm in this room having given educational lectures or received research support for the study of anti-obesity and anti-diabetes agents. I am firmly committed to the importance of expanding the armamentarium in the --

CHAIRMAN BONE: Specifically, did your financial support include the sponsor?

DR. HANSON: I have given educational programs in England for the sponsor on two occasions--

CHAIRMAN BONE: Thank you.

DR. HANSON: -- but I have not received financial support for research in my laboratory.

CHAIRMAN BONE: I'm sorry to interrupt. Go ahead.

DR. HANSON: We clearly are faced with an epidemic of obesity. I love John Foreyt's statistic that it's going to be 100 percent in the year 2030. Unfortunately, we all know how to lie with statistics and that's really not a projection I would adhere to.

But I would adhere to the fact that we are increasing in our degree of obesity even as the year 2000 goals set forth six years ago now were supposed to stem obesity. So, even as we were supposed to be stopping it and our national goals were to stop it, it has been increasing. If I were going to put my guess on it, I would guess we're heading toward the 40 percent level, not the 100 percent level. Even so, obesity is clearly the basis for a great deal of pathology in the American community.

One of the things I have studied is the effects of preventing obesity. We have studied it in non-human primates. We have shown unequivocally that if you can simply prevent the development of obesity, you can almost completely halt Type II diabetes. You can almost completely halt dyslipidemia and hypertension in large measure. So, I think the evidence is clear of the major contribution of obesity -- obesity, per se -- to morbidity and mortality among the American people.

Until very recently, we have not dealt with obesity in that way. In fact, my own upbringing was first in a department of psychiatry where we spent several years attempting to change behavior and attempting to admonish people who already were highly

motivated to lose weight. As John said, it is very clear that behavior alone will not solve the problem of reducing obesity. And so, we have had to turn to what the physiological and genetic bases of obesity are.

On that issue, it's also clear to those in the field of obesity that we're dealing with a heterogeneous disease. That many different agents are going to be needed, that agents one-at-a-time or in combinations will ultimately be needed to sufficiently attack the problem of obesity. So, we are strongly in support of research that will continue to enhance the development of anti-obesity agents or agents that will help with the mitigation or slow the development of obesity.

That's the area that the ASCN is concerned about. It's certainly one of the major nutrition problems in our country. So, obesity is an epidemic. It clearly can be and should be addressed with pharmaceutical means as well as behavioral and social means. We urge the Committee to consider obesity for the very high morbidity of producers and to look carefully at the benefits and the risks associated with its treatment.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Hanson.

The next speaker will be Ms. Valerie Rochester.

MS. ROCHESTER: Good morning. I'm with the National Council of Negro Women in Washington, DC. An organization that is dedicated to furthering the advancements and opportunities for African-American women and assuring quality of life.

One of the things that we are focused on primarily is health of African-American women and their families. Obesity is a major concern for African-Americans, particularly as it relates to African-American women. It's a concern, however it's not viewed widely as a concern among women. That's primarily due to the cultural differences in body image and body ideals when it comes to African-American women. Body size, attitudes and standards, as well as the rates of obesity, differ among African-American women as related to Caucasian women.

In a study comparing body images, body size perceptions and eating behavior among African-American and White college educated women, it was found that White women reported greater body dissatisfaction, more negative evaluations of

appearance in general, and more body image avoidant behaviors to control or conceal their weight. However, when we look at the rates of obesity among Black and White women, almost half of Black women, 46 percent, are overweight. Their average of being overweight is 24 pounds. That is a concern, especially when it is not viewed as being a major health condition.

We all know that obesity directly relates to high incidence of diabetes, high blood pressure -- excuse me, my voice is failing this morning -- heart disease and stroke, all conditions of which African-Americans are disproportionately represented. When it comes to addressing this issue in African-American communities, pharmaceuticals are important. However, we do need to combine those with education and behavior modification measures.

When it comes to addressing these conditions in African-Americans, again, the combined approach of pharmaceuticals, education and behavior modification methodologies will be very important. The National Council of Negro Women does support the advancement of these pharmaceuticals. We would be very interested in working further as far as developing the corresponding educational programs and

outreach programs to ensure that not only is obesity made a major health awareness problem among African-Americans, but that we also address it appropriately, culturally appropriately and sensitively.

Thank you.

CHAIRMAN BONE: Thank you very much.

The final speaker is Ms. Lynn McAfee.

MS. McAFEE: Good morning.

As to conflict of interest with the diet and pharmaceutical industries, I've given them plenty of money. They've never given me anything.

I'm Lynn McAfee from the Council on Size and Weight Discrimination. I'd like to take this opportunity to address a number of issues regarding anti-obesity drugs.

First, I'd like to suggest that a way be found to include the dropout rate in the effectiveness number. I find it very strange that a dropout rate for a supposedly successful drug is 50 percent while placebo was 40 percent, as was the case with redux. If the drug works so well, shouldn't it have a lower dropout rate than placebo, even taking into account side effects? It just seems so unlikely to me that people who were desperate enough about their weight to take an experimental drug and were successfully losing

weight, would wake up one morning and say "never mind. I've decided I'd rather be fat. Thanks, anyway." Something else is happening here.

I also would like to see the drug studied in varied populations. Past experience with other drugs such as anti-hypertensives have shown us that more representative distribution of ethnic groups and gender is important. Groups affected with comorbid conditions should be studied and analyzed as to effectiveness as well as improvement of comorbid condition. I would also like to see what happens to people with comorbid conditions as they gain back weight. It's possible they would be left worse off than if they had not taken the medication and lost weight.

My last point with regard to effectiveness is my concern with the necessity of people sticking to a low calorie diet for a lifetime. This has not proven possible until now. I wonder if even with medication it is truly realistic for people to keep up that level of dieting intensity indefinitely. The people in the Weintraub study pretty much dedicated their lives to dieting, yet even they had trouble maintaining weight loss by the end of the study.

The pharmaceutical companies are saying

that if we don't live the life of a Weight Watchers counselor, we have failed the drug. And while Weight Watchers has taken a lot of money from us over the years, I don't think even they can afford to hire all 34 million of us as Weight Watchers counselors. It seems to me the point of using medication is to make weight maintenance achievable. If people can not stay on this very restricted diet then the medication has failed, not fat people. This is an important point. Perhaps a group should be given medication and asked to eat more normally so if we can see if the medication has an effect on their caloric intake and weight over time. This might be a truer test of what will happen in the real world.

I'd also like to make a few comments about some of the morbidity, mortality and economic impact figures that are often used by obesity researchers. For example, Shape of America literature says "medical researchers have calculated the cost to society for obesity related diseases at more than $100 billion annually." But reading on you see that $33 billion of that money is for "weight reduction products and services." This number even includes diet soda. This is a classic case of misdirection. In fact, since Shape Up America is sponsored largely by various

weight reduction products and services, their goal is to increase this number not to decrease it.

Likewise, the widely touted Nurses Study takes what is a very small number of deaths and creates some rather sensational relationships that really need to be looked at with care. This study has been presented without criticism as obesity research gospel but there are criticisms of this work that should be heard. I am not saying the mortality figures for fat people are the same as for thin people. I am saying that while these sensational numbers may help to get much needed funded for obesity research, we should be certain that these are the right numbers to use when calculating the risks and benefits of these drugs.

Finally, I want to share with you some of my thoughts about sibutramine. I have had three conferences with the Knoll people since January and have been very pleased with their openness in showing me their data on effectiveness and safety and answering my many questions. The best thing to be said about this drug is that it's not redux. It's not a serotonin releasing drug so I've been told they won't have the problems with neurotoxicity and PPH that redux has. The main problems are hypertension

and pulse rate. While these are worrisome problems, they can at least be monitored.

The concern I have is regarding effectiveness. As a consumer advocate, this is important to me. For many decades, we've been paying billions of dollars a year for weight loss technology that just plain doesn't work. Because of the safety concerns I have about redux, I would have gladly accepted sibutramine as long as the effective rate was roughly equivalent. However, two days ago, I learned about a two-and-a-half year effectiveness study that concerns me greatly. The sponsor will undoubtedly be presenting to you shortly information on it. But based on the abstract published in Obesity Research last week, it appears that sibutramine's weight maintenance ability is not satisfactory. There was a mean weight loss of six kilograms at 40 weeks, but by 60 weeks there was a steady weight regain. At 96 weeks, the weight loss maintained was only 2.6 kilograms.

Of equal concern is the dropout rate. Only 15 percent of the subjects completed the study. This is quite serious. Are these people going to experience a worsening of their comorbid conditions when they regain weight? In the same journal, a paper

based on information from the Swedish Obesity Study states "all risk factors are improved by weight reduction, but when measured after one year of weight stability, five to ten kilogram reduction is required to detect the changes. The value of small weight reductions is thus questioned."

CHAIRMAN BONE: Thank you.

I want to thank all the speakers for their clear and concise comments.

As I said earlier, I mentioned that there are letters from the American Heart Association, the American Diabetes Association, Marion J. Franz, Denise E. Bruner, and the North American Association for the Study of Obesity which are provided in the way I described earlier.

The next stage in the proceedings will be the presentations by the sponsor, Knoll Pharmaceutical Company. The sponsor has asked if the Committee would be willing to ask questions in the following way. The sponsor would like to have questions -- not interrupt the presentations -- would like questions after each individual presentation, only those questions which are related to specific questions of fact or clarification, and discussion type questions deferred until after all the presentations.

Is that agreeable to the Committee? Any objection? No? Fine, then we'll proceed in that way.

The introduction will be given by Dr. Mel Spigelman from Knoll.

DR. SPIGELMAN: Thank you.

Dr. Bone, Dr. Bilsta, Dr. Sobel, Members of the Advisory Committee, Members of the FDA, ladies and gentlemen, my name is Mel Spigelman, Vice President of Research and Development at Knoll Pharmaceutical. I have the pleasure of introducing the programs that we will be presenting today on sibutramine.

As you are all aware, sibutramine has been submitted to the FDA for approval for the treatment of obesity, a disease which has become a virtual epidemic in this country. The magnitude of the problem can be seen from the results of the NHANES III study which documented that the prevalence of obesity, defined here as a BMI greater than 27.8 for men and 27.3 for women, was approximately one-third of the American adult population over the age of 20. Perhaps even more disconcerting however is the fact that this prevalence is increasing.

The ramifications of this finding are profound as obesity increases risk for a variety of

outcomes. Not only those that are commonly associated with obesity such as dyslipidemia, hypertension and Type II diabetes, but even those such as arthritis, gallstones, cardiovascular deaths, and even cancer deaths. It's noteworthy that weight loss is considered by most to be the primary therapy for the obese individual with some of these disorders, such as Type II diabetes, hypertension, or dyslipidemia.

With that brief introduction, I would like now to actually introduce sibutramine. Sibutramine is an SNRI, or seratonin-norepinephrine reuptake inhibitor. It was synthesized in 1980 by Boots Pharmaceutical Company and first went into men in 1984. Initially, this drug was being tested clinically for its anti-depressant activities. Although it failed to show activity in depression, it was noted that sibutramine produced consistent weight loss. Therefore, in 1990, the development program was focused on the area of obesity. With the acquisition of Boots Pharmaceutical by Knoll, the IND was transferred to Knoll and the NDA was submitted in August of last year.

Of note, the design of the clinical program was done in conjunction with the neuro-pharmacology division, as that group originally

reviewed the IND. Subsequently, all of the CD compounds were transferred to the endocrinology and metabolism division. Although the clinical program presented in the NDA was completed prior to the 1995 Committee Discussion on Guidelines for approvability of obesity compounds, our results are compatible with the criteria for approvability. Furthermore, the data that we will present will support the utility of sibutramine both in producing clinically significant weight loss and in maintaining that weight loss.

What I would like to do now is present the agenda for today's presentations. Dr. Xavier Pi-Sunyer, professor of medicine at the College of Physicians and Surgeons of Columbia University will give a brief presentation on the clinical and epidemiological importance of obesity. Dr. David Heal, head of CNS biology at Knoll Pharmaceuticals in Nottingham, England will present the pre-clinical pharmacology. This will be followed by Dr. Carl Mendel, who is director of endocrine at Knoll who will present the efficacy summary including discussion of pharmacokinetics. Dr. Timothy Seaton, senior director of endocrine metabolism at Knoll will then present the safety summary. We have asked Dr. Sylvia Smoller, professor of epidemiology and head of the Division of

Epidemiology and Statistics at the Albert Einstein College of Medicine to present the results of epidemiological evaluations of the benefit risk assessment of sibutramine.

Because of time constraints this morning, only one of the two epidemiological models, which I'll present in detail in your briefing package, will be formally presented this morning. Dr. Michael Lean, professor of human nutrition at the University of Glasgow and a sibutramine investigator, will then present the clinical benefit risk discussion. I will then discuss the present status of our proposed Phase IV post-marketing large simplified clinical trial, and conclude with a brief summary.

We have with us today several other representatives, both from Knoll as well as consultants and experts who have served as advisors. These individuals may be called upon to address questions from the Committee.

Prior to beginning the presentations, however, I would like to call your attention to the analytical processes which have been utilized to evaluate the efficacy and benefit of sibutramine. After demonstration of the efficacy of sibutramine in producing consistent and clinically meaningful weight

loss, we will proceed to evaluate the effect of sibutramine on risk factors such as blood pressure, lipids and glucose tolerance.

As clearly stated in the draft guidelines for the clinical evaluation of weight control drugs, risk factors are expected to improve if weight is lost. The logic is clear and persuasive. Risk factor improvement is expected to occur in patients who lose weight. Whereas, patients who do not lose weight are not expected to have improvement in their risk profiles. Therefore, the analytical question that we will continually pose in the presentations today is through patients who lose weight on sibutramine, derive the expected benefit from their comorbid parameter. This must be distinguished from a drug whose primary mechanism is to act as a direct modifier of a risk factor, wherein one would expect to treat a population as a whole to derive improvement in the risk factor.

For an anti-obesity compound, the treated population as a whole should show improvement and efficacy in the parameter of weight loss. Whereas, those who lose weight would be expected to show benefit in the evaluation of their risk factor.

I would also like to call your attention

to three areas in which our proposed labeling for sibutramine has been changed from that originally presented in the NDA. Based on discussions with the FDA, we have recently concluded that the maximum daily dose should be limited to 20 milligrams per day. The recommended starting dose is five to ten milligrams per day, which may be titrated upward in five milligram increments every four weeks if there is evidence of inadequate weight loss as measured by less than four pounds over the four week period and good tolerability. Treatment should not be continued in patients who either have unacceptable side effects or who, after an adequate trial of therapy, will most likely not achieve clinically significant weight loss. Data supporting this titration scheme will be presented in the efficacy presentation.

Finally, in addition to not being recommended for patients with a history of coronary artery disease and/or arrhythmias, we also present that sibutramine should not be used in patients with inadequately controlled hypertension.

I would now like to introduce our first speaker, Dr. Pi-Sunyer, who will present an overview of the significance of obesity and the need for pharmacotherapy.

DR. PI-SUNYER: Good morning. It's a pleasure to be here and be able to continue the discussion on health risks of obesity and benefits of weight loss. You've heard during the open hearing, a number of speakers allude to the relationship of obesity to a number of conditions which are some of the greater killers in America today. I just want to go over three or four of the epidemiological studies that deal with this and then go on to talk briefly about some of the benefits with regard to these comorbid conditions that occur with weight loss.

You can see in this first slide, the study from the Nurses Health Study of hundreds of thousands of women who have been followed over the 16 year periods in this particular report with a BMI from below 22 to a BMI greater than 35, and the relative risk of developing Type II non-insulin dependent diabetes which you can see begins to rise steeply after a BMI of 27. It very rapidly increases up to a relative risk that is close to 100 percent of the original.

If you look at the risk of hypertension -- this is a study taken from Witteman in Circulation published in 1989 of a number of American individuals. Again, you see the direct relationship of increasing

BMI from below 23 to greater than 32 with an increased relative risk of developing hypertension or having hypertension. So, the relative risk of individuals with a BMI above 32 goes up five-and-a-half fold.

With regard to lipids, we also have an increased risk with primarily, a manifestation of hypertriglyceridemia with increased chylomicron remnants, increased VLDL remnants, decreased HDL and particularly important, the production of small, dense LDL particles which are significantly atherogenic.

With regard to gall bladder disease this, again, is taken from the study by McClure & Colditz, you can see that the BMI -- the relative risk increases at a point of a BMI of 25 and essentially triples. Then at the BMI of 32 and above, goes up six-fold. So, the increase risk of gall bladder disease is greatly increased with increasing weight. This is particularly true of women.

Now, finally, I just want to mention the data from the American Cancer Society study which shows the mortality ratios for cancer sites at which incidence of overweight is greater than for average weight. This is the weight index calculated from the Metropolitan Life tables of 1959. The group that was 110 to 119 percent above ideal, the group that was 120

to 129 percent, 130 to 139 percent, and greater than 140 percent. That is 40 percent above ideal body weight. In males, there is an increased prevalence of colon and rectal cancer and of prostate cancer. In females, the particularly important cancers that are at a greater prevalence with regard to mortality is the endometrial cancer, uterine cancer, cervical cancer and breast cancer. Breast cancer particularly important in post-menopausal rather than pre-menopausal women.

Now, with regard to the benefits of weight loss, I just want to show you a couple of studies. This first one is a study done by Dr. Henry of the University of California, San Diego in which he measured fasting plasma glucose before and during each block of a diet, of a very low calorie diet, that was followed over a period of a month. Each of these bars is a four day period. This is a group of non-diabetic matched obese individuals. This is a group of diabetic obese individuals. You can see the blood sugar began at a level of about 290 milligrams per deciliter. It dropped by the end of the third, fourth day period -- this is 12 days after the beginning of the diet -- to about 120 milligrams percent.

Thereafter, it remained at a level of the

normal individuals showing the important effect of decreased food intake and beginning of weight loss on glucose disposal. This is shown here. This is the glucose disposal of the diabetic individuals before the diet. This is after the diet, a very significant increase in glucose disposal rate. You get the same effect on non-diabetic obese individuals whose glucose disposal rate greatly improves. This is a group of normal individuals for comparison.

If you look at systolic and diastolic blood pressure before and after weight reduction, this is a study published by Staesson et all in hypertension in 1989. Each bar is an individual. The red arrow is the combined group. You can see that -- this is before weight loss and after weight loss. This is systolic pressure, diastolic pressure -- that there is a consistent drop in blood pressure in individuals as their weight measured shown here drops in terms of kilogram. So that we have a very significant drop in blood pressure with drops in body weight.

Finally, if you look at lipid lowering -- this is from a study of McMahon published in a group of young adult Americans -- you can see here with a weight loss, there was about six to seven kilograms on

average. There was a change in total cholesterol from baseline of minus 5.6 percent. There was an increase of HDL cholesterol of plus 6.1 percent. There was a decrease of the ratio of total cholesterol to HDL cholesterol of ten percent. There was a decrease in triglycerides of 7.7 percent.

Now, we know on the basis of studies like the ones that I've shown, that we no longer need to bring a person's, an individual's weight down to normal, to ideal body weight. We know that in a sense, this is futile because they begin to escape from such a pattern of treatment. We are now becoming more and more satisfied with a partial normalization of weight with risk factor reduction. I think all of the trials, all of the clinical programs that are going on today with regard to diet, exercise and behavior modification, are aiming at a partial normalization with risk factor reduction.

So that for the past two decades, the components of effective weight management programs has been diet, physical activity combined with a strong behavior modification program that will change lifestyle behavior for these individuals, hopefully, permanently.

We have found more recently, however, that

if you look at data of the net weight loss over time in behavioral studies with follow-ups of more than one year that the results are not very good. This is the post-treatment result. This is at one year, two years, three years, four years, five years. This is the number of studies that have been carried out over that period of time. One year, eight studies. You can see at the end of four or five years, very few studies are available. But you also see that at post-treatment, the average weight loss is about 16 pounds. By the time you get out to four and five years, a good two-thirds of that weight has been regained.

So, we have a handle on how to get people to lose weight. We have a very poor handle on how to get people to maintain that loss of weight. Because of this, we believe that, essentially, we need a new paradigm for treatment. We have to understand that obesity is a chronic disease. It will not be cured. It is a lifelong condition and probably needs to be treated as such. That state-of-the-art treatment is comprehensive and includes the behavior modification, dietary change and increased physical activity but that there is an appropriate role of pharmacological management of obesity. This is based on evidence of safety and efficacy of the anti-obesity agent or

agents.

So, we feel that at this time, at this state in the American health scene, that the new paradigm for treatment allows for the addition to diet, exercise and behavior modification, of effective and safe anti-obesity agents. Thank you very much.

CHAIRMAN BONE: Specific questions related to Dr. Pi-Sunyer's presentation?

Dr. Marcus?

DR. MARCUS: Yes. I was very interested in the graph that showed a linear and inexorable rise in weight among people who are not treated whereas, I had assumed that people would generally be in some sort of stable equilibrium. Actually, how good is the evidence that weight gain continues in a linear fashion essentially forever shown on the slide?

DR. PI-SUNYER: The data in the American epidemiological scene is that essentially, the average American gains a half-a-pound a year from age 20.

DR. MARCUS: But your slide wasn't the average American, it was --

DR. PI-SUNYER: No, no. This --

DR. MARCUS: -- obese people.

DR. PI-SUNYER: Obese people.

DR. MARCUS: Are they also, left to their

own devices, gain in a linear fashion essentially forever the way the graph looks?

DR. PI-SUNYER: There is not good data following long-term obese people in that kind of a slide. So, I can't tell you that every obese person -- certainly, many obese persons plateau off at certain weights. But there is a good natural history for suggesting that many of them continue to inexorably rise slowly over time from age 25 or 30 -- or 20, whenever they have their problem, up to the age of 60. After age 60, there tends to be a plateau and a downward falling away.

DR. BONE: Thank you.

DR. PI-SUNYER: I'd like to present, if I could have the next slide, Dr. David Heal who will present the pre-clinical pharmacology.

DR. HEAL: Good morning, Dr. Bone, Dr. Sobel, Dr. Bilsta, ladies and gentlemen.

The presentation on the pre-clinical pharmacological of sibutramine is divided into four sections. In the first part, I will demonstrate that in vivo sibutramine is a seratonin or 5-HT, a norepinephrine reuptake inhibitor, an SNRI.

Sibutramine is aylcylcobutyl alkylamine. It is a tertiary amine and when it is administered to

either animals or man, it is rapidly deanimated to form the secondary amine metabolite 1 and the primary amine metabolite 2. Metabolites 1 and 2 are the predominant active species in animals and man.

When sibutramine is given repeatedly to animals, we can see that there is a profound reduction in their body weight gain. The divergence of the two curves indicates that there is no tolerance to the drug while the animals are receiving treatment, in this case 30 days. Upon drug withdrawal, we can see that there is only a very, very gradual increase of body weight back to control levels. There is no evidence that withdrawal induces profound rebound hyperphagia leading to very, very rapid weight gain with rebound above control levels.

In the next 11 slides, I will discuss the mechanisms underpinning this weight loss fact.

The monoamine neurotransmitters norepinephrine, seratonin and to a lesser extent dopamine, are intrinsically involved in the regulation of food intake and energy expenditure. There are three principle presynaptic mechanisms whereby drugs can enhance central and peripheral monoaminergic function.

Monoamine releasing agents enter the

presynaptic terminal by the high affinity reuptake carrier. There, they displace monoamines from storage granules and this leads to massive reflux of monoamines into the synaptic cleft. Monoamine releasing agents like dexamphetamine and dexfenfluramine bypass the physiological control mechanisms of inhibition of neuronal firing and negative order receptor feedback.

The major route of inactivation for monoamines in the CNS is to be taken back up into the presynaptic terminal again by the high affinity carrier. Reuptake inhibitors like sibutramine block this carrier protest. This leads to enhanced concentrations of monoamines in the synaptic cleft. Monoamine reuptake inhibitors do not bypass physiological control mechanisms. Monoamine oxidase is the major affecter for the catabolism of monoamines. Its inhibition by drugs leads to enhanced concentrations of monoamines in the neurone and enhances release on neuronal activation. Sibutramine and dexfenfluramine are not inhibitors of MAO. Dexamphetamine is a weak inhibitor of this enzyme.

In rat brains, sibutramine is a weak inhibitor of norepinephrine reuptake. However, its metabolites 1 and 2 are potent inhibitors of

norepinephrine reuptake being approximately as potent as the selective norepinephrine reuptake inhibitor, desipramine. They are also moderately potent inhibitors of 5-HT reuptake being approximately as potent as the SSRI fluoxetine. In vitro metabolites 1 and 2 are also moderately potent inhibitors of dopamine reuptake.

However, as I will show on the next slide, this pharmacological action is not expressed in vivo at pharmacologically relevant doses. The pharmacological profiles of metabolites 1 and 2 contrast markedly with those of dexamphetamine which is a moderately potent inhibitor of norepinephrine reuptake and a weight inhibitor of dopamine reuptake, and with those of dexfenfluramine which is a weak inhibitor of both norepinephrine and 5-HT reuptake.

Evidence from in vivo experiments demonstrates a clear potency separation between sibutramine's actions as a reuptake inhibitor of norepinephrine and 5-HT compared with dopamine. This figure shows the doses at which there is efficacy in four rat behavioral models. The widths of the lines indicates the dose ranges for efficacy and the lines are color-coded to demonstrate the neurotransmitters involved. Thus, norepinephrine and 5-HT is shown in

blue, norepinephrine alone is shown in green, and dopamine is shown in red.

Effective doses for prevention of reserpine induced ptosis yield an ED50 of 0.6 milligrams per kilogram. Inhibition of food intake between three and five milligrams per kilogram, and induction of thermogenesis between three and ten milligrams per kilogram. These doses are between two and two-fold lower than those required to induce even minimal dopamine reuptake inhibition in vivo as shown by the induction of circling in the unilateral nigrostriatal lesion graphs. And this is a very well established model for assessing enhanced central dopaminergic function.

This slide compares the in vivo effect of fluoxetine, sibutramine, and dexfenfluramine on extracellular 5-HT concentrations in rat brains measured by the sophisticated technique of in vivo microdialysis. At ten milligrams per kilogram, the SSRI fluoxetine produces an approximately 400 percent increase in 5-HT eflux. The SNRI sibutramine produces a 200 percent increase at this dose. However, the 5-HT releasing agent, dexfenfluramine at ten milligrams per kilogram, produces a massive 2,300 percent increase in 5-HT eflux.

Differentiation of sibutramine's mode of action from that of fenfluramine is emphasized by this follow-up study. 5-HT releasing agents like fenfluramine and dexfenfluramine into the presynaptic nerve terminal by the high affinity reuptake transporter and this slide shows the effect on eflux which are ten milligrams per kilogram fenfluramine has. However, pre-treating the rats with a monoamine reuptake inhibitor blocks this process. We can see that when the rats are being pre-treated with either sibutramine or fluoxetine, we can ablate the effects of fenfluramine treatment in these animals.

In this part, I will deal with sibutramine's actions to reduce food intake by enhancing satiety. When given acutely to rats, sibutramine produces a dose-dependent reduction in food intake. The ED50 for the inhibition of 24 hour food intake is approximately five milligrams per kilogram. Sibutramine and dexfenfluramine both reduce food intake by enhancing post-ingestive satiety, the natural physiological response. However, dexamphetamine disrupts the satiety response and reduces food intake only at behaviorally activating doses.

A synergistic interaction of

norepinephrine and 5-HT reuptake inhibition on food intake is shown by this next slide. We have used the selective norepinephrine reuptake inhibitor nisoxetine and the selective 5-HT reuptake inhibitor fluoxetine. When given alone at high dose, neither drug has any affect on drug intake. However when these drugs are given in combination, it blocked both 5-HT and norepinephrine reuptake equivalent to administering sibutramine. We can see that there is a profound reduction in food intake and the magnitude of this response is identical to that observed with sibutramine.

This section deals with sibutramine's action to increase energy expenditure or thermogenesis by enhancing central sympathetic to brown adipose tissue. Oxygen consumption is a good indicator of increased energy expenditure or thermogenesis. Sibutramine given at ten milligrams per kilogram produces a profound 31 percent and prolonged increase in the energy expenditure of rats.

Thermogenesis is a norepinephrine mediated response and this is demonstrated by the fact that it is blocked by high and combined doses of atenolol and ICI 118,551 which block the atypical or beta 3 receptor, in addition to blocking beta 1 and beta 2

receptors. This response was not affected however by low doses of atenolol or ICI 118,551 which blocked beta 1 and beta 2 adrenoceptors respectively. This effect is mediated by a norepinephrine reuptake inhibition because neither sibutramine nor its active metabolites have affinity for the beta 3 adrenoceptor.

In this section, sibutramine is clearly shown to be different in pharmacological terms, from the monoamine releasing agents dexamphetamine and dexfenfluramine. Sibutramine and dexamphetamine are pharmacologically different because sibutramine does not release dopamine or norepinephrine. Whereas, dexamphetamine is a potent releaser of both catecholamines. Sibutramine reduces food intake at non-stimulant doses, whereas dexamphetamine reduces food intake only at behaviorally activating doses. Sibutramine enhances satiety, whereas dexamphetamine does not. And Sibutramine inhibits food intake by inhibition of norepinephrine and 5-HT reuptake. Dopaminergic mechanisms are not involved. Dexamphetamines effects on food intake are mediated partly through dopaminergic activation.

Sibutramine is pharmacologically different from dexfenfluramine. Sibutramine's metabolites are potent seratonin and norepinephrine reuptake

inhibitors. Dexfenfluramine is a weak reuptake inhibitor of both monoamines. Sibutramine is not a seratonin releasing agent. Dexfenfluramine is. Sibutramine is not a norepinephrine releasing agent. Dexfenfluramine is at high concentrations.

Thus, in conclusion we can say that sibutramine potently inhibits norepinephrine and seratonin but not dopamine reuptake in vivo. It is the first SNRI to be developed as an anti-obesity drug. Sibutramine reduces food intake by enhancing satiety, a central effect mediated by norepinephrine and seratonin reuptake inhibition. Sibutramine increases energy expenditure by enhancing central sympathetic drive to brown adipose tissue. Sibutramine's mode of action is different from that of the monoamine releasing agents, dexamphetamine and dexfenfluramine. As an SNRI, we believe that sibutramine will lack potential for primary pulmonary hypertension, abuse and neurotoxicity.

Thank you very much.

CHAIRMAN BONE: Thank you.

Are there specific questions?

Dr. Kreisberg?

DR. KREISBERG: Yes. I wonder if it would be possible to go back to your first slide? I think

it's comparable to your Figure 214 in your handout. Second slide -- no, keep going. That's it.

You explain in your material that these are lean and growing rats.

DR. HEAL: That is correct.

DR. KREISBERG: Although the major portion of your presentation was not on the actual response of the animals to the drug -- you introduced the subject -- these are lean growing rats. I wonder whether that really is a satisfactory experimental model for obesity since it would seem to me that the best model would be a rat that had already achieved a stable body weight?

The second question that I have, since it looks like the effect appears so promptly within the time period of drug administration -- that is, it's almost maximum by five days or virtually most of the difference is at five days. Then the lines are either parallel or slightly diverging -- whether this is a smaller animal or a compositionally more lean animal? In other words, could the introduction of the drug lead to some stunting in the size of the animal that allowed it to weigh less, or is it actually a same sized animal that just has less body fat?

DR. HEAL: That's a very interesting set

of questions. Although this diagram here shows our effect in the growing animals, we can actually demonstrate a weight loss in Zucker rats, cafeteria-fed rats, and other types of obese animals.

What you see here is from the run-in period that, in fact, the growth rates of the animals is identical in this period here leading up. So, they're just pair matched animals. So, in fact, what you see here is initially the marked drop in animals caused by, obviously, acute administration of the drug. But I would point out quite clearly that the difference here is smaller than the difference here, indicating there is a divergence and the animals are continuing to lose weight.

I take your point entirely that this obviously demonstrates lean growing animals. However, these are adults weighing in at 260 grams. We're not talking about effects which occur in animals which are still in their pre-adult stage.

CHAIRMAN BONE: Dr. Marcus?

DR. MARCUS: I'd like to revisit the question of thermogenesis. Certainly, the rat has a larger component of brown adipose tissue activity than humans and I'd like to ask about the effect of this drug on other categories of thermogenesis.

Specifically, can you show whether there are differences in basal metabolic rate in food induced thermogenesis or in activity induced thermogenesis by this drug?

DR. HEAL: We have not looked in any detail at activity-induced thermogenesis. There does not seem from some preliminary experiments that we have done to be any affect on food-induced thermogenesis, as you will see in your pack. The actions of sibutramine to increase thermogenesis in rats by brown adipose tissue is highly selective. It seems to increase central sympathetic drive to brown adipose tissue. And in fact, it leads in terms of glucose utilization studies to an increase of 18-fold in glucose utilization specifically in brown adipose tissue.

CHAIRMAN BONE: Dr. Sherwin, you had a question?

DR. SHERWIN: Yes. I was just wondering how well does this drug cross the blood brain barrier?

DR. HEAL: That is a question which will have to be handled by one of my colleagues.

I'd like to call on Dr. Rod Haddock from the Pharmacokinetics Department to take the stand please?

DR. HADDOCK: We have some information on the transfer of material from plasma into the brain. From the data that we have in the rat, it seems that the concentrations are twice as high in the brain than they are in systemic plasma.

DR. SHERWIN: So, it's concentrated. It's actively transported to the brain, you're saying? Am I getting that straight?

DR. HADDOCK: The concentrations are twice as high which would indicate that there is a preferential rate of transport, yes.

DR. SHERWIN: I'm just curious. Obviously then the drug is having central effects.

DR. HADDOCK: Indeed.

DR. SHERWIN: How much of a peripheral effect? I mean, if you locally delivered desipramine for example, you can increase norepinephrine tissues. Do you think this drug also works peripherally as well as centrally?

DR. HADDOCK: May I defer to my colleague, Dr. Heal?

DR. HEAL: In terms of the two pharmacological actions which we have demonstrated, they are both centrally mediated in origin. In the case of the effect on food intake, we can demonstrate

that central injection of the metabolites of sibutramine leads to a dose related reduction in food intake. In terms of the effects on brown adipose tissue and glucose utilization, if we pretreat the rats with the ganglionic blocker chlorisondamine, then in fact, we can abolish sibutramine's actions to induce thermogenesis. This appears to be due to activation specifically in the paraventricular nucleus of the hypothalamus.

Obviously, as a reuptake inhibitor, there is no difference physiologically in the site in the central and the peripheral nervous system. As a reuptake inhibitor, one would expect that sibutramine would inhibit the reuptake of catecholamines into tissues where reuptake is a major component of inactivation of transmission. We can certainly show that it inhibits 5-HT uptake in platelets.

DR. SHERWIN: I just wonder will it have then an amplification effect on the periphery only because now you're activating the central system outflow and then you're blocking reuptake peripherally. That's sort of what I'm getting at.

DR. HEAL: Sure. That's a very interesting hypothesis and, in fact, it's one that has been put forward by Professor Stock who did the

thermogenesis experiments. Where, in fact, what we observed was that the magnitude of the effect which we saw with sibutramine was greater than that observed with a direct beta 3 agonist. So, assuming that it was 100 percent efficacious -- and we don't know that it is a full agonist -- then it could indicate that peripheral uptake inhibition does play some part.

Interestingly, reuptake inhibition in the periphery was not sufficient to elevate glucose utilization in most of the other tissues. The only other two tissues were one skeletal muscle, gastrocnemius and diaphragm. And that was almost certainly due to increased respiration. Here, the changes were only 20 or 30 percent. So, in tissues like the heart, there was no increased glucose utilization.

CHAIRMAN BONE: Thank you.

Yes, Dr. Molitch?

DR. MOLITCH: I have three questions related, actually, to prior questions by people, from Dr. Kreisberg's question. I didn't hear the answer to the carcass analysis of the rats as to whether there's a selective decrease in the fat compared to other tissues. Number two, I presume, therefore, that the metabolites also have uptake into brain tissue

actively transported as well. Therefore, is there any serial data looking at the brain transport to see if there is accumulation of drug or does it achieve a steady state at a low level and then continues at the same level in the brain?

DR. HEAL: I can answer one of those questions, certainly. The question concerning the analysis of body composition, that has been done. It is not due to a loss of lean mass. It is due to a loss of fat.

With regards to questions on kinetics and drug metabolism, then I once again have to hand over to my colleague, Dr. Haddock.

DR. HADDOCK: In terms of transport of the metabolite and the sibutramine, it is certainly true that the active metabolites are indeed transported into the brain and the concentrations are some twice-as-high as they are in plasma. In terms of time course, we don't have specific studies analyzing time course extensively in brain and plasma. But certainly from our radio tracer data we can say that the time course is relatively short within the 24 hour period. So, at the end of 24 hours, there is no accumulation or no significant accumulation of material in the brain.

CHAIRMAN BONE: Thank you.

Dr. Kreisberg has a question.

DR. KREISBERG: One last question getting back to this issue of thermogenesis. Can you account for the differences in weight between the treated animals and the placebo animals strictly on quantification of differences in food intake?

DR. HEAL: No. There is definitely, as time goes on, a contribution. When we do energy balance equations there is definitely a contribution of thermogenesis in these animals.

CHAIRMAN BONE: Just to clarify a point that came up with Dr. Kreisberg's earlier question and your comment on carcass analysis. Is the difference in weight between the animals shown in the growing animal study entirely accounted for by fat?

DR. HEAL: There is no loss of lean growing mass in those animals.

CHAIRMAN BONE: Bob, does that answer your earlier question? Thank you.

All right, I think we're ready to go ahead.

DR. HEAL: The following presentation on pharmacokinetics and efficacy will be given by Dr. Carl Mendel, the director of endocrine with Knoll

Pharmaceuticals.

DR. MENDEL: Good morning Dr. Bone, Dr. Sobel, members of the Advisory Panel and guests.

I'm here to tell you about sibutramine, its pharmacokinetics, its weight loss efficacy, and the effects of sibutramine induced weight loss on comorbidities and risk factors associated with obesity.

To start, a very brief summary of what we know about the pharmacokinetics of sibutramine in humans. Sibutramine is efficiently absorbed from the GI tract. It has a large first pass metabolism. This generates two metabolites which mediate the pharmacological response of sibutramine. These metabolites are formed by the cytochrome p450 enzyme system and are further metabolized to inactive products before being excreted in the urine as glucuronides.

Here we see the pharmacokinetics in healthy volunteers of a single oral dose of sibutramine. Sibutramine itself has a short half-life, approximately one hour whereas the half-lives of the active metabolites are much longer, approximately 14 and 16 hours. Although not shown on this slide, the pharmacokinetics of sibutramine are similar in

obese subjects and in non-obese subjects, in men and in women, and in the elderly and in the young. On repeat daily dosing, steady state plasma concentrations of the active metabolites are achieved within three to four days with an approximately two-fold accumulation.

I'd now like to direct your attention to the weight loss efficacy of sibutramine. The data will show that sibutramine is an extremely effective weight loss agent. Listed here are the eight major placebo controlled studies in obesity which have been conducted and completed to date with sibutramine. In each and every one of these studies, sibutramine was found to produce statistically and clinically significant weight loss in a dose dependent manner. The degree of weight loss was remarkably consistent from study to study. Highlighted in yellow are the two pivotal efficacy studies: BPI 852 and SB 1047, the first of six months' duration, the second of one year duration. If you read down further to the left on the slide, you'll see SB 1049. This is a third long-term study and was of one year duration. In all, more than 2,500 patients were studied in these trials.

Shown here is the design of BPI 852, the pivotal dose ranging and efficacy study of six months'

duration. More than 1,000 patients were randomized to placebo or sibutramine in doses ranging from one to 30 milligrams. Ancillary therapy in the form of dietary counseling, recommendations for an exercise program and suggestions for behavioral modification was provided. Patients completing the study were allowed to enter an open label, long-term extension study that allowed additional monitoring of safety.

The inclusion and exclusion criteria are shown here. As you can see, patients with major comorbid diseases were excluded in this study. The baseline demographics indicate that the groups were well matched at baseline. The majority of patients were female and the BMI was approximately 35 kilograms per meter squared. The median weight was almost 100 kilograms. Therefore, please keep in mind as we looked at weight loss curves, a five percent decrease in weight would equal approximately a five kilogram decrease in weight. Mean percent change of body weight in this study is shown in this slide for the last observation carried forward or LOCF analysis.

The amount of weight lost increased with dose and was marked. At the 20 milligram dose, for example, mean weight loss approached seven percent in this analysis, whereas weight loss on placebo was

minimal. The rate of weight loss was most marked during the first three months of therapy. For the five to 30 milligram doses, weight loss was statistically significantly greater for sibutramine than for placebo at all time points.

In this slide, we see the weight loss curves for completers. These data appear even more compelling. At the 20 milligram dose, for example, there was a mean weight loss of almost nine percent, again, with only minimal weight loss in the placebo group. In the interest of time and to be conservative, I will present only LOCF data from this point on.

Now, an analysis of the data in this study -- and I'll show you the slide in a minute -- suggests that we can predict early-on which patients will achieve clinically significant long-term weight loss on a given dose of sibutramine. In particular, those patients who lose four pounds or more in the first four weeks of treatment generally went on to achieve clinically significant long-term weight loss.

Now, if we look at the ten milligram dose here, for example, more than 60 percent of patients lost more than four pounds in the first four weeks. Of these, almost 70 percent went on to achieve

clinically significant -- that is greater than or equal to five percent weight loss -- by week 24. Conversely, of those who did not lose four pounds in the first four weeks, the vast majority -- over 80 percent -- did not go on to achieve more than five percent weight loss at week 24.

Data from our other long-term studies, SB 1047 and SB 1049 confirm this paradigm. Thus, subjects who will not respond well to a given dose of sibutramine can be identified early and taken off that dose of sibutramine. Patients on sibutramine in this study also experienced marked dose related decreases in body mass index or BMI. In the interests of time, BMI slides for other studies will not be shown in the primary presentation but of course, in all of our studies, the observed changes in BMI paralleled the observed changes in weight.

If we look at the percentages of patients losing at least five percent of their baseline weight, we see that already at a ten milligram dose, approximately half the sibutramine treated patients lost more than five percent of their weight. This compares to only 13 percent in the placebo group. And at the 15 milligram dose, approximately one-quarter of the sibutramine treated patients lost more than ten

percent of their body weight as compared to none in the placebo group.

Now, changes in waste circumference are generally thought to reflect changes in visceral fat and visceral fat is associated with many of the comorbidities of obesity. Sibutramine induced reductions and waste circumference were marked dose related and commensurate with the amount of weight lost. Overall, in BPI 852, sibutramine doses of five to 30 milligrams produced marked weight loss, marked decreases in body mass index, and marked decreases in waste circumference. Observed decreases in serum lipids and passing blood sugar will be discussed later in the presentation.

I now want to turn your attention to the second pivotal efficacy trial. Shown here is the design of SB 1047, the one year placebo controlled efficacy study. Almost 500 patients were randomized to treatment with sibutramine, ten or 15 milligrams or placebo for one year. Ancillary therapy consisted of dietary counseling. The inclusion and exclusion criteria were similar to those of BPI 852 except that stable hypertensives were allowed in this study. More than 100 hypertensives were, in fact, enrolled, approximately half of them on anti-hypertensive

medication. The baseline demographics in this study were similar to those of BPI 852. The treatment groups were well matched at baseline.

Statistically and clinically significant weight loss was observed in this study with the magnitude of weight loss very similar to that seen at comparable doses in BPI 852. As you can see, the rate of weight loss again was greatest during the first three months of treatment. Active weight loss continued out to six months and then was maintained out to one year. More than half the patients at the 15 milligram dose lost at least five percent of their body weight. Fully one-third of the patients at this dose lost at least ten percent of their body weight compared with only seven percent in the placebo group.

Marked reductions in waste circumference were observed in the sibutramine treated patients as compared to placebo. Although not shown on this slide, the waist to hip ratio also declined statistically significantly in sibutramine treated patients compared to placebo. To summarize, in both pivotal studies, BPI 852 and SB 1047, marked reductions in body weight, BMI and waste circumference were observed.

Now let's look at an additional one year

efficacy study, SB 1049. The purpose of this study was to examine the efficacy of sibutramine in conjunction with a very low diet or VLCD. Patients who lost at least six kilograms of body weight on a VLCD were randomized to 12 months of therapy with sibutramine 10 milligrams or placebo. The groups were well matched at baseline. Of note, the mean weight exceeded 100 kilograms and the mean BMI approached 40 kilograms per meter squared.

Marked weight loss was seen during the VLCD phase of the study before drug therapy. Treatment with sibutramine then resulted in substantial additional weight loss by month six with maintenance of that weight loss out to month 12. Thus, patients who combined a VLCD with a ten milligram dose of sibutramine lost on average more than 12 percent of their body weight. This study demonstrates the significant additive effects of sibutramine and effective non-pharmacological therapy.

More than half the sibutramine treated patients in this study lost at least ten percent of their body weight. Almost one-third lost 15 percent of their body weight and there were even a significant number of 20 percent responders. As in other trials, waist circumference also declined markedly and

significantly in the sibutramine treated patients. All-in-all, the results of this study show just what sibutramine can do when combined with effective non-pharmacological therapy.

I now want to turn your attention very briefly to two studies designed to compare sibutramine with dexfenfluramine, the only agent approved in this country for long-term weight loss. SB 1052 shown on the left was a small pilot study. The largest study, SB 2053, was designed as an equivalence trial. In both these studies, a relatively low dose of sibutramine, ten milligrams, was compared with the full recommended dose of dexfenfluramine, 30 milligrams per day for 12 weeks. The yellow is a sibutramine curve; the green is the dexfenfluramine curve. In both studies, the observed placebo subtracted weight loss on dexfenfluramine was similar to that reported in the literature. In both studies, weight loss on sibutramine was numerically superior. Furthermore, in the larger study SB 2053, the appropriate equivalence analysis showed that sibutramine was at least as good as dexfenfluramine.

I'd now like to deal with a slightly different subject, the effects of sibutramine induced weight loss on the comorbidities of obesity, including

serum lipid profiles, diabetes, hypertension, and serum uric acid. In the presentation that follows it is important to keep in mind that sibutramine is not being evaluated here as a lipid luring drug, an anti-diabetic drug, or an anti-hypertensive drug. Rather, sibutramine is being evaluated here today as a weight loss agent.

In the presentation that follows, we will examine the effects of sibutramine induced weight loss rather than the effects of sibutramine itself on these comorbidities of obesity. Some of the analyses that I will present in this section were completed only recently, the result of questions generated in our ongoing discussions with the FDA.

Changes in fasting serum lipids in sibutramine treated patients in BPI 852, our single largest study, are shown in this slide. This is a difficult slide and I'll help you through it in a minute. But what it shows is that there were marked statistically significant differences between the all-sibutramine group and the all-placebo group for triglycerides, cholesterol, and HDL cholesterol. More importantly, the improvements in serum lipids in sibutramine treated patients who lost significant amounts of weight were even more pronounced.

And if I can just help you through the slide, the all-placebo group is shown on this slide for triglycerides, cholesterol, LDL and HDL. The all-sibutramine group is shown on this line with the significant changes shown. As we go down on these columns, we see more weight loss. We have the no change, zero to five percent, five to 10, 10 to 15, more than 15 percent weight loss, and we see the lipid changes increasing as the weight loss increases. Now, in general, we see the same thing in the placebo group. We have no 10 and 15 percent responders in the placebo group.

Thus, serum lipids improve as weight loss increases on sibutramine just as on placebo. Within a given category of weight loss, there were no differences between sibutramine and placebo. Of course, since more weight was lost on sibutramine, serum lipids improved more on sibutramine than on placebo. Overall, these data suggest that sibutramine itself, independent of weight loss, does not positively or negatively affect serum lipids. But that sibutramine induced weight loss results in the full measure of lipid changes expected on the basis of weight loss alone. A meta-analysis of the serum lipid changes in our entire database resulted in very

similar findings.

Another way of looking at this issue is to examine the weight changes and corresponding lipid changes in our database and ask whether the lipid change associated with the given weight change is similar in sibutramine treated patients and in placebo treated patients.

Turning to this slide, the percentage of weight change is shown on the X-axis and the percentage lipid change is shown on the Y-axis. And I'll just focus you here. If we take a point here, this would mean that for a 20 percent decrease in weight, we would be getting a ten percent fall in cholesterol shown here. A steeper slope indicates a greater lipid change for a given weight change and that would look something like this. If sibutramine induced weight loss results in the lipid changes expected on the basis of weight loss alone, then the slopes of the sibutramine curves and the placebo curves should be identical. Certainly, the slopes of the sibutramine curve should not be flatter than the slopes of the placebo curves.

Turning back to this slide, looking at the data collected from our placebo controlled obesity studies comprising more than 2,000 patients, it can be

seen that sibutramine and the placebo slopes are virtually identical for both cholesterol and triglycerides indicating that for a given amount of weight loss on sibutramine, the improvement in serum lipids expected on the basis of weight loss alone is obtained in full measure.

And in this slide, we see the corresponding findings for LDL and HDL -- LDL here, HDL here -- with the slopes of the lines, again, statistically similar but even favoring sibutramine numerically. Thus, we conclude from these data that sibutramine induced weight loss results in the full measure of improvement in serum lipids expected on the basis of weight loss alone.

There is one sibutramine study that was conducted specifically in dyslipidemic patients. That study, SB 2059, was a short-term trial conducted in Spain in mild dyslipidemic subjects who met the Spanish criteria for mixed lipidemia shown here on the slide. The study duration was four months. Patients taking hypolipidemic agents were excluded. Weight loss is shown in this slide. Compared to our other studies, the placebo group lost a great deal of weight with the mean weight loss on placebo approaching six percent. As in other studies, however, the

sibutramine group did lose significantly more weight.

The serum lipid changes observed in that study are shown in this slide and are consistent with the weight loss achieved. As expected, since both groups lost significant amounts of weight, both the sibutramine treated patients and the placebo treated patients experienced improvements in their serum lipids with the expected numerical superiority of sibutramine. Those patients on sibutramine who lost more weight tended to have greater improvements in their serum lipids. The same was true for placebo treated patients but, of course, more sibutramine treated patients lost significant amounts of weight. This study shows that sibutramine can be used effectively in patients with dyslipidemia.

Now let me direct your attention to SB 3051, a study that compared sibutramine 15 milligrams and placebo in obese diabetic patients. The study was 12 weeks in duration. It contained an open label extension that allowed additional monitoring of safety. There was a larger proportion of males in this study than in most of our other trials and the patients were somewhat older. The mean fasting blood sugars approached 200 milligrams per deciliter and mean hemoglobin A_1 levels approached ten percent.

Approximately 75 percent of the patients in this study were on either insulin or sulphonyureas.

Statistically significant weight loss was obtained on sibutramine as compared with placebo, although weight loss in both the placebo and the sibutramine groups was somewhat smaller than that seen in other studies. The weight loss in sibutramine treated patients was accompanied by numerical decreases in fasting blood glucose with a treatment effect of -30 milligrams per liter for glucose shown here, and -0.4 percent for hemoglobin A_1. Patients who achieved weight loss on sibutramine experienced greater treatment effects in fasting blood sugar and hemoglobin A_1, although all of the changes shown represent numerical trends rather than statistical superiority. In addition, a significantly greater number of patients on sibutramine than on placebo experienced hemoglobin A_1 declines of more than one percent as shown here.

Serum lipids also improved on sibutramine as compared with placebo. These improvements were greater in those sibutramine treated patients who lost significant amounts of weight. Although most of these findings represent numerical trends that did not reach statistical significance, they remain consistent with

our findings that sibutramine induced weight loss results in the full measure of improvement in serum lipids expected on the basis of weight loss alone.

We also examined retrospectively the effect of sibutramine induced weight loss on fasting blood glucose in patients with mildly abnormal fasting blood glucoses above 110 milligrams per deciliter in BPI 852, our single largest study. Patients on sibutramine, and particularly those who lost significant amounts of weight shown here, experienced significant decreases in their fasting blood sugar as compared with the all-placebo group. These findings suggest that sibutramine induced weight loss results in the changes expected on the basis of weight loss alone, not only for serum lipids but also for serum glucose.

Lastly, let me direct your attention very briefly to a study conducted in obese hypertensive patients. This study, SB 2057, examined the effects of sibutramine ten milligrams compared with placebo over a 12 week period. The treatment groups were well matched at baseline. Approximately one-third of the patients were receiving anti-hypertensive medication. As expected, sibutramine induced significant weight loss in this group.

Treatment related changes in blood pressure are shown in this slide. Blood pressure declined in sibutramine treated patients as a whole and in placebo treated patients as a whole, but declined more in the placebo treated patients despite a significantly greater weight loss in the sibutramine group. And I'll come back and help you look at the numbers in a second. Nevertheless, in the sibutramine treated patients who lost significant amounts of weight, blood pressure declined more than in the placebo group as a whole, although less than in placebo treated patients who lost similar amounts of weight.

So, if we look at systolic blood pressure, for example, the placebo/sibutramine difference 0.4 when we look at the group of entire patients. In those sibutramine treated patients who lost weight, the blood pressure effect is less. Actually, the blood pressure is lower even compared to the all-placebo group although it's not lowered as much as in the placebo patients who lost similar amounts of weight. The effect of sibutramine on blood pressure will be examined in more detail in the safety presentation, but these data indicate that controlled hypertensives can be treated safely and effectively

with sibutramine.

Finally, serum uric acid is another more recently recognized risk factor for cardiovascular disease and was identified as an independent risk factor in the NHANES study. This slide shows the highly statistically significant improvements in serum uric acid in sibutramine treated patients compared with placebo treated patients in our database as a whole and in each of our three long-term studies. As expected, those sibutramine treated patients who lost significant amounts of weight did even better.

To summarize, sibutramine produces pronounced weight loss in conjunction with diet and exercise clearly fulfilling the criteria of a successful weight loss agent as established in the FDA draft guidance for weight control drugs. A significant number of sibutramine treated patients achieved more than ten percent reduction in body weight. Waste circumference, an indicator of visceral fat declines proportionately with weight loss in sibutramine treated patients. The dose response curve for sibutramine is broad and efficacy is maintained for at least one year. Sibutramine also produces significant weight loss in patients with dyslipidemia, Type II diabetes and hypertension. Although blood

pressure does not improve commensurate with weight loss on sibutramine, serum lipids, glycemic control and serum uric acid improve markedly in patients who lose weight on sibutramine.

Thank you.

CHAIRMAN BONE: Specific questions? I'm sure there will be several.

Dr. Zawadzki?

DR. ZAWADZKI: I have a couple of questions to start. Number one, what was the diet these patients were placed on?

DR. MENDEL: In the different studies, it was somewhat different. In the BPI 852, there were individualized diets depending on whether patients were males or females. It was basically a diet, a diet-she. Women were given a 1,500 kilocalorie diet. Men were given an 1,800 kilocalorie diet.

DR. ZAWADZKI: So, there was basically a weight reduction diet imposed in all the studies?

DR. MENDEL: Yes. All studies were conducted in conjunction with some form of dietary intervention.

DR. ZAWADZKI: In the study that you described with individuals with hypertension, were beta blockers excluded as anti-hypertensive agents?

DR. MENDEL: In that study, beta blockers were not excluded. In all of our database, we have only about 30 patients who were treated with beta blockers while receiving sibutramine in obesity studies.

DR. ZAWADZKI: And in terms of looking at those data, was there a similar weight loss?

DR. MENDEL: Yes. The numbers of patients were small but looking at the data weight loss was essentially identical to those not on beta blockers.

DR. ZAWADZKI: Now when one looks at the data from the animal study which showed that there was some blocking of thermogenesis with beta blockers, how do you explain the weight reduction in these clinical studies?

DR. MENDEL: I think in terms of the pre-clinical studies, I'll let Dr. Heal comment on those.

DR. HEAL: From the pre-clinical studies, it's important to point out that neither beta 1 nor beta 2 antagonists actually prevented the thermogenic effects of sibutramine. It was only when these drugs were given at very, very high dose to block beta 3 receptors that we saw a blockade of thermogenesis.

In terms of actions on food intake, beta 1 antagonists have only a very, very small attenuation

of this affect of sibutramine. This is predominantly reversed by alpha 1 antagonist and 5-HT 2A, 2C antagonists. So, from the animal studies, we would predict that this should not actually block sibutramine's effects in people.

CHAIRMAN BONE: Dr. Kreisberg, I think, is next. We'll go around and make sure everybody gets a chance.

DR. KREISBERG: The majority of the patients that you studied were women. I don't know what the exact overall breakdown was, but maybe perhaps 500 of the 2,500 that you cited at the outset as participating in these trials were men. I wondered if you've looked at the pattern of weight loss in men and contrasted that to women, and whether your generalizations in terms of efficacy refer to men as well?

DR. MENDEL: Yes, we've looked separately. There are between 300 and 500 males in the database. We've looked separately at their weight loss. It is quite similar to the weight loss of the group as a whole.

CHAIRMAN BONE: All right, I think Dr. Flack had a question.

DR. FLACK: I have several questions and

a comment. Can you explain how the dosing sequence, titration sequence of four weeks was arrived upon? Because when you look at those curves, the rapid fall occurs early-on but there's still a lot of weight loss ongoing at weeks eight and 12. I'm afraid that we're about to march down to the same thing we did with blood pressure drugs, titrating them far too fast.

Can you explain why four weeks was chosen?

DR. MENDEL: Yes, this was essentially an empirical observation. I mean, we did look at different time periods as well. Four weeks seemed to be a reasonable predictive time period. Again, the predictability really at all doses -- I focused you on the ten milligram dose but the predictability was, you know, in the range of 60 to 70 percent of those patients that did go on to achieve long-term weight loss. Of those who didn't -- I mean, really, about 80 percent didn't.

Now, clearly, the longer out you go, you do increase the predictability a little better. If you wait until six months, you're at endpoint. So, this is really an empirical observation on which this is based.

CHAIRMAN BONE: Dr. Flack, weren't you referring to the interval for adjusting the dose, not

this interval for determining whether the patient is likely responding.

DR. FLACK: Right. I'm talking about the interval that a physician would be asked or a practitioner would be asked or told that they could increase the dose, the titration interval. Because you're leaving a lot on the table there. I understand the model. I've reviewed that model. But the average change after that, for two months after that, is still very impressive.

DR. MENDEL: Yes, and in terms of dose titration, let me ask Dr. Spigelman to come up.

DR. SPIGELMAN: Yes, I think what we're really looking at here is a question of risk benefit, in essence, when we look at the dose titration scheme. The empiric observation is there that at four weeks, one has high predictability to say whether, in fact, the dose that the patient is on will or will not be successful in achieving the desired weight loss aim.

What we're saying is that in that time period over four weeks, one can make a clinical decision at that point in time as to whether or not that dose is going to be an effective dose. If it is not going to be an effective dose probabilistically, then what we're saying is that it is not worth the

further risk of exposure at that dose for the probability of benefit. Therefore, to move on.

DR. FLACK: I guess I would view it differently in that the benefit of achieving weight loss in a faster than a one or two month period really is going to confer probably no long-term benefit over the lifetime treatment of the patient and that you probably ought to wait and slow the titration down.

CHAIRMAN BONE: We can go into that in more detail this afternoon.

DR. FLACK: One final issue is the lipid effect. Really, the lipid effect, when it is displayed by weight loss, is really different than what it is by dose because the dose and the weight loss are related but not perfectly with one another. Looking at the overall compilation of data here, my conclusion, certainly, under 15 milligrams a day is that the lipid changes are relatively inconsistent. They're not consistent across dose. There's really no dose effect. They are there at certain doses in a positive way, but it seems like they're really more inconsistent.

DR. MENDEL: Yes. We actually don't believe that the proper way to look at it is by dose. Really, the question is whether in sibutramine treated

patients who lose weight, do we get the expected lipid effects? In order to answer that question, we have much greater power if we pull the data across doses. We believe that's the appropriate way to look at these data.

CHAIRMAN BONE: Are there other questions from members of the Committee?

I think Dr. Marcus?

DR. MARCUS: Yes, I would like first to get some clarification on Dr. Zawadzki's question with particular respect to study 1049. After the very low calorie diet phase, what was the diet that the patients was on for the duration of the drug treatment phase? It's never stated in any of the documents so far.

DR. MENDEL: You're right.

Dr. Kelly, can you answer that question please?

DR. KELLY: Finian Kelly from Knoll Pharmaceuticals in Nottingham of the United Kingdom.

After the very low calorie diets, these patients continued to attend specialist obesity centers on a monthly basis as the study was carried out. They had a low calorie diet prescribed and the low calorie diet tended to be in the region of 1,500

cataclories per day.

DR. MARCUS: Thank you.

Can you tell me anything about ethnicity or racial characteristics of the subjects of these various studies? Have you done any analysis to see whether there is a differential response according to racial group?

DR. MENDEL: Yes. Again, the vast majority, about 80 percent, were Caucasian throughout these studies. We have approximately 150 African-Americans in the database. When we look at their weight loss separately, it's very similar to the weight loss in the group as a whole. In terms of orientals and other ethnicities, we really have too few patients in the database.

DR. MARCUS: I am particularly concerned about the last observation carried forward strategy in your pivotal study number 1047 because it suggested -- it stated here that 49 percent of the placebo group and 55 percent of the sibutramine groups are those who completed the study. That means you essentially had as many people drop out as complete the study. Although you say it's typical completion rate for a year long study in obesity, nonetheless, it can be highly confounded if they dropped out at some point

after a weight loss -- for whatever reason they dropped out, if you're carrying the observation forward to the end of the year. On one hand, it could be a conservative guess that they wouldn't be losing more. On the other hand, they could have been regaining. You give us no opportunity in the data that you've submitted to understand what really went on. I wonder if you can clarify some of that?

DR. MENDEL: We have three different types of analyses. All yield very similar curves. Basically, a true intent to treat where patients are followed for the duration of the time after they drop out really wasn't feasible in these studies. So, the three different ways of looking at the data are a completer's analysis, the last observation carried forward analysis, and an observed analysis. All three analyses on the curves for all the studies looked very, very similar. In general, the completers analysis looks best.

CHAIRMAN BONE: Well, let's see -- did you have any further questions?

DR. MARCUS: Well, I'm just trying to process the answer to that question.

DR. MENDEL: Would you like to see some of the other curves?

DR. MARCUS: Yes, I think so.

DR. MENDEL: Okay.

CHAIRMAN BONE: I think the other correlated question --

DR. MENDEL: With the chairman's discretion here.

CHAIRMAN BONE: Well, the other correlated question would be whether, in any of your studies, you in fact had a true intent to treat analysis by rounding up the dropouts at the end of the planned observation period?

DR. MENDEL: No, we didn't. That's very hard to do in these studies.

CHAIRMAN BONE: Yes. Could we make an arrangement to have those --

DR. MENDEL: Surely.

CHAIRMAN BONE: -- slides shown in the beginning of the afternoon session? Would that be all right?

DR. MARCUS: Yes. I have one final question that just addresses what would seem to be a rational strategy for the use of this drug, but your analysis doesn't show what would happen if you modeled it that way. That is, a physician prescribes up to your maximum dose, 20 milligrams. And at the end of

a period of time on that drug, the patient has not lost weight, then you would think that the physician would then stop the drug. For those that did meet that, then you would have anticipation that the amount of weight loss would even exceed what your mean weight loss that you've shown in your curves would indicate.

Now, your non-pivotal studies actually give some hint as to how many patients would actually have lost 20 or more percent. It looks pretty good, but I'd like to know whether you can give us some similar information about the much larger pivotal studies to see whether that degree of weight loss in so-called responders is actually what you observed.

DR. MENDEL: I'm not aware of specific analyses that have been done on that question.

Do the statisticians have -- Bob?

MR. McENTEGART: Damian McEntegart, Hattert Statistics from Nottingham in the United Kingdom.

Could I have statistic slide number two, please?

CHAIRMAN BONE: While that slide is being put up, I think for the rest of the time here, perhaps what we'll do for things that require more extended discussion or information that wasn't actually

presented in the talks is we can perhaps set aside a little time immediately after lunch to review those points. We'll deal directly with the content of the talks for now just to make sure we keep following here. That way, all those can be put together by the company and be ready.

Well, it's up now, let's go ahead. I think that's fine.

MR. McENTEGART: Okay.

When we planned the analysis for study SB 1047, we were very aware of the kind of issues that have just been raised. Our primary analysis was what determined outcome analysis. We called it this because it's based on the patients' response outcome in the trial. This outcome analysis was identified as our principle measure of efficacy in the study protocol. It was based on an article by Larry Gould in the 1980 Biometrics paper.

In the analysis, patients are ordered according to their outcome in the trial. The best outcome is considered to be withdrawal due to treatment of success whereby either the patients or doctor does not consider it beneficial for the patient to receive any more weight. Patients who complete the trial are then ordered below this best outcome of

treatment success withdrawal according to their actual month 12 weight loss or gain. So, the highest weight loser has the second best outcome. The next highest weight loser has the third best outcome and so on, until the outcome of highest weight gain is reached.

Patients who withdraw from the trial for reasons other than treatment success are then assigned outcomes below that of the patient with the highest weight gain. Definite treatment related withdrawals due to adverse events and/or lack of efficacy are assigned to the worst outcome. Other withdrawals are assigned the next worst outcome on the grounds that they may be related to treatment. In these set of ordered actions that we've compiled is then compared between treatments using the Kruskal Wallis test overall and Wilcoxon rank sum tests for pairwise comparisons.

So, in effect, what this outcome analysis is doing is just giving us a different way of handling the dropouts than last observation carried forward. We didn't present this in our presentation for consistency with the other studies. The FDA statistical reviewer herself quotes a view that no single analysis can be taken as a valid comparison of efficacy. Rather, what we're looking for is

consistency of results across approaches that use different ways of handling withdrawals. Indeed, the results for 1047, which I can show if you'd like to see, do have this consistency for sibutramine.

If I could have statistic slides number three and four, please?

So these, then, are the ordered outcomes in the trials defined as I've just described. At the top, we have the one or two withdrawals due to treatment success. And the next best outcome is the patients who lose more than 20 percent weight loss. We can see there is a supremacy for sibutramine in that category and so on through the completers of the trial, down to the patients at the bottom who withdrew due to lack of efficacy and/or adverse events. They are assigned the worst outcome in the analysis.

If I could have the next slide, please?

Comparing the treatment groups overall by Kruskal Wallis test, the pairwise comparisons by Wilcoxon and Rank sum tests, we can see that indeed, overall, there is a significant difference between the treatment groups and in the pairwise comparisons. Sibutramine 10 milligram and sibutramine 15 milligrams are very superior to placebo.

CHAIRMAN BONE: Thank you.

Let's see, I think Dr. Illingsworth had a question.

DR. ILLINGSWORTH: In your study SB 1049 --

CHAIRMAN BONE: Excuse me, Roger.

Dr. Zawadzki, did your question pertain to this exactly? No? All right, we'll come back to you. You started so we'll give everyone else their first chance.

DR. ILLINGSWORTH: In your study SB 1049, the slides indicate there was a three month follow-up. What happened to the patients in whom the drug was stopped? Did they regain weight? If so, do you have data on this?

DR. MENDEL: Yes. Can I have backup slide 22, please?

Essentially, what this slide will show is that when drug is stopped, patients do regain weight. We interpret that to mean that the drug is continuing to be effective out to at least one year. This slide only shows the weight regain out to one month. It continues up with the weight regain out to three months. You can see the placebo subjects also regain weight, but the sibutramine subjects regain more weight.

CHAIRMAN BONE: Thank you.

Did you have another question, Dr. Illingsworth? No.

I think Dr. Colley had a question, did you? No?

Dr. Flack had a question. We'll come back to him. Dr. Zawadzki -- if no one else -- actually, the Chair had one or two questions and hasn't had a chance yet. So, I'll take a turn.

Would you discuss what occurred during your run-in periods? Exactly what was done during the run-in periods and what were the criteria for the patients going into the randomized study?

DR. MENDEL: The run-in periods were very short, usually only about two weeks. What was done during the run-in periods was simply initiation of the ancillary therapy. In some cases, that was diet only. In other cases, it was diet, exercise, and behavioral modification.

CHAIRMAN BONE: And were there criteria for the patients to be entered into the randomized phase at all?

DR. MENDEL: No, there were no criteria based on what they did during the run-in period.

CHAIRMAN BONE: And how many people

entered the run-in period but didn't go into randomization, typically?

DR. MENDEL: In some cases, actually, the randomization occurred before the run-in period. So, typically, most patients entering the run-in period entered the randomization. Even in the VLCD study where patients had to lose six kilograms to enter the protocol, more than 90 percent of the patients did, in fact, lose six kilograms. Of those, a total of about 80 percent were randomized.

CHAIRMAN BONE: Thank you.

Dr. Zawadzki and then Dr. Flack.

DR. ZAWADZKI: Were there any quality of life measures done in any of these studies?

DR. MENDEL: No, there were not.

CHAIRMAN BONE: Dr. Flack?

DR. FLACK: It would seem that the drug would be an ideal drug to use in diabetics, yet the weight loss threshold didn't really exceed five percent for the treated group over the placebo group in the one diabetic study.

My question is, one, do you have an explanation for that? Two, are there any studies ongoing, or perhaps additional data you have, demonstrating better efficacy in diabetics?

DR. MENDEL: I think in terms of the diabetic population, it's well recognized that diabetics are quite resistant to losing weight. So, both the placebo group in the diabetic study and the sibutramine group did not do as well as groups in other studies.

In terms of whether or not -- and so, it is possible that in diabetics as a whole, they will respond more poorly in terms of weight loss than the population as a whole. However, the key to using this drug will be to use it and continue using it only in those patients who are responding to the drug. Even if there are fewer diabetics who respond well to the drug, those that do respond should have a good outcome on sibutramine.

CHAIRMAN BONE: Dr. Sherwin had a comment.

DR. SHERWIN: Yes, I would differ with you in terms of benefit to people with diabetes. Since this drug seems to work through increasing sympathetic outflow, that produces insulin -- impairs beta self function. So, one would not anticipate that a drug that would increase sympathetic outflow would benefit people -- there would be confounding factors both ways.

DR. FLACK: I think that's the issue on a

number of disease conditions and I was speaking simply from the narrow focus of weight. Because there are a number of conditions --

DR. SHERWIN: Well, you said ideal, and that's the reason --

DR. FLACK: Well, they're ideal in the sense that many of the diabetics are overweight. But your point is well taken and I appreciate that.

DR. MENDEL: We actually don't believe that the pre-clinical pharmacology indicates that there should be any adverse effects on diabetes control.

I'd like Dr. David Heal to comment on that.

DR. HEAL: Once again, I'm going to have to ask for two slides for this. So, if you would like this to be deferred to this afternoon's session, I will present it then. But if you want the issue dealt with now --

CHAIRMAN BONE: Well, why don't we do this? Let's go on to the next question while you're getting those slides ready, if there is a next question.

Any other questions or comments from members of the Committee?

DR. HEAL: I'm not by training, someone that is skilled in the art of diabetes and its management. However, I present this information to you. It's in very preliminary form and it has been experiments which have been conducted by Dr. Cliff Bailey who is very eminent in this field.

What it shows is the effect of 24 hour incubations of L-6 cells with sibutramine and metabolite 2 which is the primary amine on the uptake of 2-deoxyglucose. The study used 2-deoxyglucose as a measure of glucose uptake by L-6 rat muscle cells. The cells were exposed to increasing concentrations of either sibutramine or metabolite 1.

In the absence of added insulin, you can see that there is a clear increase in the uptake of glucose by these cells. The L-6 muscle cells are also sensitive to insulin, and as a submaximal stimulation 10^{-8} molar, we can see that this increases glucose uptake by about 50 percent. This effect is actually significantly increased by sibutramine at 10^{-8} molar and metabolite 2 at all doses. These concentrations are very similar to the concentrations which are circulating in plasma at steady state. Thus they argue that sibutramine and the metabolite 2 have a direct action to improve insulin sensitivity in

cultured muscle cells.

This slide shows the effects of sibutramine on body weight, food intake and plasma glucose concentration in the ob/ob mouse. This slide shows you effects of sibutramine 10 milligrams per kilogram on these three parameters when given daily for a period of 28 days. The ob/ob diabetic mouse produces a model of severe insulin resistance and hyperinsulinemia. During the treatment period, this dose of sibutramine did not significantly affect either food intake or body weight. However, it significantly decreased plasma glucose concentrations as you can see here, without significantly altering plasma insulin levels. This study provides evidence to show that sibutramine also improves insulin sensitivity in vivo.

DR. SHERWIN: That's very interesting. I'm surprised. Do you have -- well, I guess we can discuss it later in terms of the clinical.

As far as the isolated muscle cells, I would think that since this drug is working on the nervous system, an isolated muscle cell wouldn't be terribly relevant or may not be the best approach. But the animal study is interesting and surely is unexpected for me from my perspective anyhow.

DR. MENDEL: Right, we also have -- I'm sorry.

DR. HEAL: It seems that this may be actually a direct structure effect of sibutramine as a molecule because those muscle cell cultures wouldn't be expected to contain catecholamines.

DR. SHERWIN: Right.

DR. MENDEL: We also have looked at the data in the diabetes study and we have a presentation prepared that show that trends actually favor increasing insulin sensitivity rather than decreasing it. I don't know whether you'd like to present that now or later?

CHAIRMAN BONE: Certainly not. Let's talk about that later. Otherwise, we're going to compromise the rest of your presentation. That was a point that Dr. Spigelman asked me to avoid.

Are there further questions?

Dr. Critchlow?

DR. CRITCHLOW: Yes, just one, a clarification on the titration. I just want to be sure I understand this. You would propose that people be started on the five milligram dose. If they don't lose sufficient weight, they would increase to ten? Otherwise they stay on five or what?

DR. SPIGELMAN: The starting dose of the vast majority of the patients -- and we can get into this in a discussion or now, as Dr. Bone prefers -- would be ten milligrams with five reserved for special populations. Then the schema would be as I described it earlier. For those patients who do not lose the four pounds over four weeks but who do have very good tolerability of the drug, the dose would be escalated. But those patients who do lose four pounds in four weeks, they would continue with good tolerability on that same dose.

CHAIRMAN BONE: I think that's a little bit contrary to the suggestion that was made earlier and we're going to have to discuss that extensively this afternoon, I'm sure.

Further questions or comments before we go on to the next speaker?

DR. MENDEL: I'd like to then introduce Dr. Timothy Seaton who will deliver the safety presentation.

DR. SEATON: Good morning, Dr. Bone, Dr. Sobel, members of the Advisory Panel and guests.

The safety presentation will demonstrate that sibutramine is a safe and well tolerated drug. The presentation will include a description of the