UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

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MEETING #61

OPEN SESSION

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THURSDAY,

NOVEMBER 16, 1995

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The Committee met in the Plaza Ballroom of the Holiday Inn Silver Spring, 8777 Georgia Avenue, Silver Spring, Maryland at 1:00 p.m., HENRY G. BONE, III, M.D., Chairman, presiding.

COMMITTEE MEMBERS PRESENT:

HENRY G. BONE, III, M.D., Chairman
NEMAT BORHANI, M.D., M.P.H.
JOSE FRANCISCO CARA, M.D.
COLLEEN A. COLLEY
CATHY W. CRITCHLOW, Ph.D.
ROGER D. ILLINGWORTH, M.D., Ph.D.
(Telephonically)
ROBERT A. KREISBERG, M.D.
ROBERT MARCUS, M.D.
MARIA I. NEW, M.D.
ROBERT S. SHERWIN, M.D.
JOANNA K. ZAWADZKI, M.D.

COMMITTEE MEMBERS PRESENT (Continued):

KATHLEEN R. REEDY, Executive Secretary

FDA REPRESENTATIVES PRESENT:

JAMES M. BILSTAD, M.D.
LEO LUTWAK, M.D., Ph.D.
SOLOMON SOBEL, M.D.
BRUCE STADEL, M.D.

PUBLIC PARTICIPANTS PRESENT:

PAUL ERNSBERGER, Ph.D.
ARTHUR FRANK, M.D.
LYNN McAFEE
JOE McVOY
BARBARA MOORE, Ph.D.
JAMES O'CALLAGHAN, Ph.D.
ERIC ROSE, M.D.
JUDITH S. STERN, ScD., Ph.D.

SPONSOR REPRESENTATIVES PRESENT:

JOHN BLUNDELL, B.Sc., Ph.D.
GLENN L. COOPER, M.D.
MARC DEITCH, M.D.
GERALD A. FAICH, M.D., M.P.H.
RICHARD GAMMANS, Ph.D.
ARTHUR RUBENSTEIN, M.D.

ALSO PRESENT:

BRUCE CAMPBELL, Ph.D.
JOHN CONTRERA, Ph.D.
ED NEVIUS, Ph.D.
LYNDSEY ROSENWALD, M.D.
BOBBY SANDAGE, Ph.D.

I-N-D-E-X

I-N-D-E-X (Continued)

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

(1:05 p.m.)

OPEN SESSION

CALL TO ORDER, INTRODUCTIONS

CHAIRMAN BONE: Good afternoon, everyone. It's a pleasure to be here, as opposed to some other places I've been lately.

I'm Dr. Henry Bone. I'm the Chairman of the Endocrinologic and Metabolic Drugs Advisory Committee. I'll bring the meeting to order, just to outline the plan for this afternoon. After that, I think we'll introduce the Committee, have a conflict of interest statement, then opening remarks by Drs. Bilstad and Sobel. I'll give a short summary of what brought us to this point with this particular question. And then we will start the open public hearing.

If I could ask the Committee members and the FDA personnel who are present to identify themselves, starting with Dr. Critchlow? Please everybody speak distinctly into the microphone. Our audiovisual people have asked us to make a point of that.

DR. CRITCHLOW: Cathy Critchlow, Department of Epidemiology, University of Washington,

Seattle.

DR. BORHANI: Nemat Borhani, University of California at Davis and University of Nevada in Reno.

DR. ZAWADZKI: Joanna Zawadzki, Division of Endocrinology and Metabolism, Georgetown University.

DR. SHERWIN: Robert Sherwin, Department of Medicine, Yale University.

DR. KREISBERG: Bob Kreisberg, Birmingham, Alabama.

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

EXECUTIVE SECRETARY REEDY: Kathleen Reedy, Executive Secretary of this Committee, FDA

DR. MARCUS: Robert Marcus, Department of Medicine, Stanford University.

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

DR. CARA: Jose Cara, Department of Pediatrics in Henry Ford Hospital.

DR. SOBEL: Sol Sobel, Division of Metabolism and Endocrinology, FDA.

DR. BILSTAD: Jim Bilstad, FDA, Office of Drug Evaluation II.

DR. LUTWAK: Leo Lutwak, FDA.

DR. STADEL: Bruce Stadel, FDA Division of Metabolism and Endocrinology.

CHAIRMAN BONE: In addition, we will have participating by teleconference joining us a little later Dr. Roger Illingworth of the University of Oregon. The participation is a little bit unusual, but because of Dr. Illingworth's participation in the prior hearing and the fact that he has been actively prepared for the meeting and his availability by teleconference, the General Counsel of the FDA has determined that this is an appropriate arrangement.

Next will be the conflict of interest statement, which will be read by Dr. Reedy.

CONFLICT OF INTEREST STATEMENT

EXECUTIVE SECRETARY 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 for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of 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. Joanna Zawadzki. A copy of the waiver statement may be obtained from the agency's Freedom of Information Office, Room 12A-3 in the Parklawn Building.

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, Dr. Reedy.

Next we'll have some opening remarks and summary by Dr. Bilstad, who is the Director of the Office of Drug Evaluation II. Dr. Bilstad will, in addition, make some remarks of a background nature which will be germane.

OPENING REMARKS, SUMMARY OF SITUATION

DR. BILSTAD: Good afternoon. Could we have the first overhead, please? I just wanted to put into some perspective why we're having this meeting

today and review some of the events of the September 28th Advisory Committee meeting.

Regarding the discussion of efficacy, the Committee members seemed to be quite persuaded by the evidence provided and, in fact, in response to the question regarding efficacy, "Is the evidence of efficacy sufficient to warrant approval of dexfenfluramine for long-term indefinite use, as proposed?"; the Committee voted seven yes and one no.

Could I have the next overhead? The discussion of safety was focused primarily on two issues; one, of course, being the occurrence of primary pulmonary hypertension and the other being the neurologic findings in animal studies. With regard to the primary pulmonary hypertension, I think that the Committee members were concerned that this was an event that did appear to be related to the drug based on the data presented, but that it also was a rare event.

There was much more discussion of the neurologic findings in animals and much more concern about this area. To some extent, the discussion of the findings was hampered by the paucity of background material on this issue that was provided to the Committee before the meeting.

Presentations on the animal neurologic findings were made by two investigators who were invited to FDA because they had conducted research in this area. And those were Dr. Molliver from Johns Hopkins University School of Medicine and Dr. Seiden from the University of Chicago. Any views expressed by these speakers regarding the approvability of dexfenfluramine were their own and were not intended to reflect views of the FDA.

The voting on the safety question, "Is the evidence of safety sufficient to warrant approval for long-term use, as proposed?"; the initial vote was two yes and six no, but that was later changed to three yes and five no.

During the discussion of the question related to a Phase IV study, there appeared to be some misunderstanding of what the FDA had intended in the wording of the questions and whether the discussion of an additional study pertained to a pre-approval study or a post-approval study.

Next overhead. Because of some uncertainty on my part that we were correctly understanding the recommendations of the Committee, near the end of the meeting I asked the remaining five members to express their views on the question, "In

evaluating the benefits and the risks of this drug, would the Committee recommend approval based on the data presented?"

Recognizing that the five Committee members remaining did not constitute a quorum, initially we planned to ask the three members who had left the meeting prior to the last question for their response to the question as soon as was feasible. After that we had further discussions internally. And it was decided that, rather than to poll the Advisory Committee members by telephone, that dexfenfluramine should be represented at this Advisory Committee meeting.

Today's meeting is intended to focus primarily on the animal neurotoxicity issue with some further discussion of co-morbidities and, finally, on the overall benefit risk analysis.

Additional background material has been provided to the Committee members, including the complete transcript of the previous meeting and additional information on the animal neurotoxicity issue. The questions for the Committee, which Dr. Sobel will discuss shortly, have been worded to take into consideration and extend the discussion from the last meeting.

Dr. Bone had asked me to comment briefly on criteria for drug approval, what it means when we approve a drug, and procedures for removing a drug from the market in Phase IV studies.

The FD&C Act requires NDAs to contain full reports of information demonstrating that the drug is safe and effective under the conditions of use in the product's proposed labeling and there is no conditional approval for drugs of this class. What this means is that when we approve a drug, we have to make the judgment that there is sufficient evidence of safety and effectiveness to feel comfortable in the approval. Basic safety and effectiveness data have to be established.

Next. If after approval information becomes available in which the determination is made that the benefits no longer outweigh the risks, there are really two procedures that we can take legally to remove a drug from the market if the sponsor does not choose to do so voluntarily. One is the eminent hazard provision of the act, in which case the Secretary of HHS can make the determination to remove the drug. That's invoked very rarely and, in fact, has been invoked only once. And that was for the drug fenfluramine because of the concern about the adverse

event lactic acidosis.

The other procedure that we can go through is to publish a notice of opportunity for a hearing in the Federal Register documenting in some detail the reasons why we think the drug should be removed. And there follows a series of events that can lead to an administrative hearing before an administrative law judge in which that issue is decided. This process can take many, many months. It is not a rapid process.

Finally, I would like to make some comments on Phase IV. In approving a drug, while I mentioned before that we cannot have a conditional approval, we certainly can receive a commitment from the sponsor to conduct a Phase IV trial; that is, a post-marketing trial. While the sponsor usually does conduct such a trial, that's not always been the case, certainly in all circumstances, in the past.

I think in recent years our experience at FDA has been quite encouraging from this standpoint. And in cases where the results of a Phase IV study are unfavorable to the drug, this probably is the situation where we would present it to an advisory committee and get the recommendations of the advisory committee on how to proceed.

And that concludes my comments.

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

Next remarks will be the charge to the Committee from the Division Director, Dr. Solomon Sobel.

OPENING REMARKS, CHARGE TO COMMITTEE

DR. SOBEL: I think that the best way to go about this is to put up the questions that you will eventually be asked to answer and to clarify points in these questions so that when you're listening to today's discussion, this can be a framework for your thoughts. You do have the questions already, but I'll project them for the audience, essentially.

The first question is: Based on currently available safety and efficacy data and considering the overall benefits and risks of the use of dexfenfluramine, the dexfenfluramine as proposed by the sponsor, do you recommend approval for marketing? This question addresses the conventional issue in drug approval. Essentially this is a question about risk-benefit.

The Committee is being asked whether the risks which may be encountered with this drug are of sufficient magnitude to outweigh the projected

benefits that will accrue to those patients who have a weight loss in the ranges demonstrated in the various analyses which you have had presented to you.

I am referring, of course, to the degree of weight loss that we discussed at the last meeting was considered from several standpoints. And there was one analysis, a response analysis, which identified a subset which did have an appreciable weight loss, but today's Committee will address this question based on their feelings about the ranges demonstrated. As Dr. Bilstad said, there was a feeling of the Committee that a sufficient degree of efficacy had been demonstrated based on the responder analysis.

The phrase "use of dexfenfluramine as proposed by the sponsor" may in the course of today's discussion be clarified by including such considerations as continued use only in those who have responded to an adequate degree at some time point, such as one month or perhaps three months.

Also the Committee may wish to discuss limitations on the long-term use beyond one or two years. I think that that subject was not broached, but it's something that you may wish to keep in mind in your deliberations whether long-term use should

have some limitation placed upon it.

Question Number 2, "If dexfenfluramine were approved for marketing, should approval be contingent on a commitment from the sponsor to conduct post-marketing studies? If so, what should be the objectives and essential features of those studies?"

Dr. Bilstad has discussed the meaning of Phase IV post-marketing studies and their regulatory consequences. The Committee may wish if approval is recommended to define in a general way which issues they desire to be clarified in a Phase IV study. These issues may include both efficacy and safety issues.

The Committee should give consideration to issues of numbers of patients, timetables for the completion of protocols for the study, and the time for the inception and completion of the study.

Particular emphasis should be given to recommendations for the duration of the study; for example, one or two years or perhaps some other time period, and for recommendations concerning interim analyses.

The question of Phase IV may still be answered individually, even if the Committee vote on the approval is negative. Committee members are asked

to express views on the nature of what would constitute a desirable Phase IV study.

Question Number 3, "If dexfenfluramine were not to be approved for marketing based on currently available information, what additional data should be obtained before reconsidering approval?"

In the event of non-approval, the Committee is asked to recommend what type of information should be obtained before reconsidering approval. This may include, among other approaches, various reanalyses and new studies. This is somewhat reiterative a question, too, in the event of a negative vote, but may be more or less expansive than the responses you may make to the latter part of Question 2.

Question Number 4, "If dexfenfluramine were to be approved, do you have any recommendations regarding labeling?" This may include recommendations such as continued use contingent on early response; limitations on the length of use and other matters, such as use only as monotherapy, rather than combined therapy with drugs such as phentermine; and also warnings concerning combined use with other serotonin-active agents.

I hope this clarification will give you

some guidance as you are listening to the discussion. However, if further clarification is needed, I will be glad to answer questions.

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

SUMMARY OF SEPTEMBER 28 MEETING ON DEXFENFLURAMINE

CHAIRMAN BONE: I will attempt to avoid redundancy with the previous very well-chosen remarks by Drs. Bilstad and Sobel in reviewing some of the results of the September 28th meeting. The meeting we're conducting today is a follow-up to that meeting for the reasons that Dr. Bilstad stated.

There were two prior meetings concerning FDA guidelines for the consideration of drugs for long-term or indefinite treatment of obesity, as opposed to short-term treatment, which has been the limitation on all drugs for that indication up until now.

So a distinguishing issue is that we are contemplating specifically long-term treatment, as opposed to short-term treatment, with this or other drugs which would be considered for this new indication. The agency has made this an important priority to look into longer-term treatment.

At the guideline meetings we discussed

what was sufficient criteria. Those have been discussed in detail. I'll refer to those briefly as we go along.

At the last meeting the sponsor presented data regarding weight loss from a number of studies, one of which was a one-year study and several of which were shorter term.

The Advisory Committee had previously recommended in the guidance for new applications that the period of randomized double-blind treatment be one-year and a follow-up year be included. The sponsor studies were completed prior to the guidance being presented and discussed. So obviously that has to be taken into account and has been.

The one-year study that the sponsor presented did not meet the primary efficacy criterion which had been outlined in the guidance which was a difference of five percent of initial body weight between subjects who were in the placebo group and subjects in the treatment group over the period of the study.

However, two alternative methods of analysis were discussed and contemplated in the course of developing the guidance. The basic idea was that if an identifiable subgroup could be delineated which

had benefit of the magnitude described or if a significantly higher percentage of subjects met the 5 percent or a 10 percent difference criterion, that those could be alternative ways of regarding a drug as effective. The Committee had recommended that these analyses be planned from the beginning of the study.

The sponsor's application did show a significantly greater percentage of patients falling in the greater than 5 or greater than 10 percent weight loss categories.

In addition, the Advisory Committee had recommended that analysis of co-morbidity data, such as effects on lipid metabolism, glucose metabolism, et cetera, effects on body fat, mean body mass, and so on, be considered.

These were not considered absolutely essential to the approval of the drug but were strongly recommended. And the Advisory Committee had in previous discussions suggested that when a drug had not quite met the primary criteria, the successful effect, demonstration of a beneficial effect on co-morbidities, would be something to take into account in evaluating a marginally less efficacious drug.

The sponsor's studies, of course, had been

completed prior to the development of the guidance, did present some rather limited information on co-morbidities, but this was not a major feature of the studies.

The first part of the discussion about safety focused on the well-recognized problem of primary pulmonary hypertension. The manufacturer of the drug, in fact, had participated in the study of this problem, which we will hear more about, I believe, as far as its frequency and likely effects on mortality but which is, fortunately, an infrequent but, unfortunately, rather serious event.

As Dr. Bilstad commented earlier, the major part of the discussion focused on the issue of neurotoxicity, perhaps in part because of the fact that we were less clear about that. It may or may not have been a question of how seriously this was regarded but a question of the lack of clarity.

I think it would be fair to say that there was a considerable difference in approach and perspective and impressions on the part of various eminent neuroscientists speaking at the behest or support of approval and those who came to express concern and reservations.

We're going to hear a lot more about that

today I hope on the part of the Committee members that at least closure or meeting of the minds about what the issues exactly are can be elicited so that this will be easier for the Committee to evaluate. And there will be I'm sure additional discussion about the safety, clinical safety, information bearing on these issues as well.

I think with that, if you will, supplement to the previous remarks by Drs. Bilstad and Sobel, we can go forward to the open public hearing component of the meeting.

Now, I will comment that the agency and I'm sure other Committee members and myself have received a large number of letters from members of the public. Those letters which the agency had in hand in sufficient time to make copies have had copies made and distributed to all of the Committee members. In addition, some letters which I have received and perhaps others have received in the last day or two are here available for anyone to look at amongst the Committee.

We will have nine speakers. When the original seven speakers in the open public hearing made arrangements with Dr. Reedy for time, she advised them of four minutes each because we had half an hour.

We will ask everyone to stick within the four-minute time period. And we will further greatly appreciate it if anyone's remarks can be made slightly shorter so that the overall time is not greatly extended by the effort of the agency to accommodate all of those who wish to make presentations here.

We will ask that each individual identify themselves and state their affiliation as well as any financial connections or other connections they may have to either the sponsor or other commercial entities with an interest in this issue.

The first of the open public hearing speakers will be Lyn McAfee from the Council on Size and Weight Discrimination.

OPEN PUBLIC HEARING

MS. McAFEE: My name is Lyn McAfee. And I'm from the Council on Size and Weight Discrimination.

Although I realize people my size are not the target market for this drug, one advantage to my size is that I have been every weight there is. And so I feel I have a unique perspective to offer. I also may be one of the few people in the room who has actually taken fenfluramine.

First let me say that there is no one in

this room today who wants and needs this drug more than I do. I weigh well over 500 pounds and have serious size-related physical ailments.

I believe that in the future drugs will be developed that will be of great use to fat people. I believe this strongly enough that for many years I have acted as an unpaid consultant to the University of Pennsylvania's Behavioral Genetics Department, helping them locate appropriate fat subjects and sensitizing them to our accommodation needs. But dexfenfluramine is not the drug I've been working for.

It is my position that not enough is known about the safety of this drug to warrant its approval for indefinite use at this time. There are two outstanding safety issues: primary pulmonary hypertension and the tangled axon problem.

Since we know that people gain back their weight once they stop taking anorectic agents, this is a drug one would have to be on for their entire lives. We also know that the risk for PPH increased dramatically for those few people who have taken it for more than a year.

The European experience the company often alludes to is largely very short-term, but it is clear that the duration of use increases risk. Since a

pathogenic mechanism is not known, it seems impossible to evaluate properly to what extent usage of 20, 30, 40 years would increase risk. Since this is a terminal disease, I think this fact alone should keep you from approving it for lifetime use.

The tangled axon problem is a more difficult one for me to evaluate as a lay person. When I saw that very dramatic slide of the tangle at the last meeting, I thought to myself, "I don't want tangles like that in my hair, let alone my brain."

Since that meeting, I have come to know that problems like this have been observed for many years. As long as controversy remains, I believe the risk of irreversible brain damage outweighs any potential weight loss benefit.

This is a drug that is really based on the old willpower model. We need something to keep them on their diets, to be compliant, to eat less than their bodies tell them they should. It doesn't solve the problem. It merely redefines it so that it becomes once again a personal problem, a personal failure of will. Our willpower needs a shot of serotonin, although there's no way to test whether, in fact, we are deficient in serotonin.

This is no magic pill. Fat people will

have to face a lifetime of continuous dieting and exercise just to maintain whatever weight one can lose until the six-month plateau hits.

Fat people will have to come up with a considerable amount of money every month of our lives for a drug whose long-term risks have not truly been established and a weight loss that may be barely noticeable to others.

And while a five percent weight loss may save lives, it would probably save as many lives if we could rid ourselves of prejudice affecting medical care. We are routinely told that everything that is wrong with us is because we are fat and are told to go home and lose weight. Often no serious attempt at diagnosis is made. Important tests are not done. And our first line of treatment is dieting, a treatment for which there is a 95 percent failure rate.

Developing first-line treatments that don't include diet could save lives. We could probably save many lives a year if we would remove the very serious barrier to exercise that fat people experience. Physician prejudice against fat people, well-documented, and avoidance of medical care by fat people seriously affects our morbidity and mortality. Yet, no attempt is made to tackle these big pieces of

the puzzle.

This drug is not the last, the only for fat people. It may be that the safety concerns will be satisfactorily resolved some day, but that day is not today. Today fat people need and deserve safety first.

Thank you.

CHAIRMAN BONE: Thank you.

The next of the open public hearing speakers will be Dr. Paul Ernsberger, Associate Professor of Medicine and Pharmacology from Case Western Reserve School of Medicine.

DR. BORHANI: Mr. Chairman?

DR. ERNSBERGER: Yes. I'd like to --

DR. BORHANI: Mr. Chairman, can I ask a point of order, please? I'm sorry, but I do not know how the distinguished public speakers were invited, who invited them, and what is the description of their -- because this lady, I never had the pleasure of meeting her.

CHAIRMAN BONE: Yes. I can answer that question for you, I think.

DR. BORHANI: Please.

CHAIRMAN BONE: The open public hearing is a period of time allotted for any person who wishes to

make a comment and who makes arrangements in advance with the agency. There is no selection. These are people who have asked to make comments as part of the open public hearing commentary. These are people who are just members of the public or may or may not have a scientific or other interest.

DR. BORHANI: They called the agency?

CHAIRMAN BONE: Yes.

DR. BORHANI: But their presentations are not distributed to the Committee for purpose, --

DR. ERNSBERGER: You can have a copy of mine.

DR. BORHANI: -- for a reason?

CHAIRMAN BONE: They may.

DR. BORHANI: May I have a copy of this lady's presentation? Because some of the comments she made are very pertinent, and I would like to think about them.

CHAIRMAN BONE: Certainly. Thank you.

We'll go ahead now with the comments by Dr. Ernsberger.

DR. ERNSBERGER: Thank you. You have a copy of my comments.

I would like to reveal a financial conflict of interest. I was a co-investigator on a

$100,000 research grant from Servier Pharmaceuticals while I was at Cornell University.

If I could have the slides, please? As an overview, pulmonary hypertension is a lethal side effect which may have been underestimated. The neurotoxicity as indicated by over 80 reports needs to be investigated further in humans. Third point, serotonergic mechanism of action is not unique. And the agents already approved act by increasing serotonic availability and have some efficacy in the area of weight loss in, most importantly, the risk-benefit analysis for lifelong use.

Pulmonary hypertension is a lethal side effect of all amphetamine analogs. Dexfenfluramine-induced pulmonary hypertension has a 37 percent mortality. Pulmonary hypertension is very difficult to diagnose. It's invasive to diagnose and especially likely to be under-recognized in the obese. Dyspnea, heart failure, and sudden death resulting from pulmonary hypertension may be incorrectly attributed to the obesity itself.

Clinically pulmonary hypertension predominates in young women, the very group most likely to use anoretics. Thus, it is quite possible that pulmonary hypertension currently within our

population may be largely iatrogenic due to currently available anorectic agents.

In France, where dexfenfluramine is approved for short-term use, at least 20 percent of the pulmonary hypertension cases could be attributed to dexfenfluramine. Animal studies indicate that dexfenfluramine is a pulmonary arterial vasoconstrictor.

If dexfenfluramine is approved by this Committee, it is certain that at least the minor epidemic of pulmonary hypertension will likely result. A possible remedy would be a prospective evaluation of the evolution of pulmonary vascular pressures during a long-term trial of dexfenfluramine.

Brain damage, again, dexfenfluramine is a standard neurotoxin used in basic science studies. All of the known serotonin-releasing agents are neurotoxic, in contrast, the uptake blockers. The consequences for humans may be unknown. However, the rebound depression resulting after dexfenfluramine withdrawal may reflect serotonic neurotoxicity.

The limitations of the current data, though, are that there is no clinical test for serotonin depletion available and no data on lifelong use. The remedy would have to require, first, a

validation of a clinical test for serotonergic function in humans followed by a prospective evaluation long term.

Other hazards documented -- and you can pull this up in 15 seconds on MEDLINE -- are internuclear ophthalmoplegia, cerebral and retinal infarcts consistent with neurotoxicity, acute pancreatitis, acute angle glaucoma. Psychotic reactions have been documented in a number of studies. And in animal studies there are chromosomal aberrations, DNA damage, reactive and toxic intermediance formed by P450.

I'd like to suggest that double-blind trial of dexfenfluramine against fluoxetine or another safe and established compound, especially if the subgroup analyses are planned, this would be required to establish unique efficacy.

We've talked about the risk-benefit analysis. The meta analysis shows a three-kilogram loss on the average. This Committee has heard about the Nurse's Health study, but the previous study of 1.8 million persons in Norway, world's largest epidemiological study, actually showed similar results in young women up through about age 45.

Mortality is doubled or increased half

again when you compare obese women to lean women. However, at older ages, this difference disappears. If you consider the 50 percent point, which is the median life expectancy, there is no difference.

If we plot median life expectancy versus BMI, the slope of this line -- that's my single point -- is very low. So a three-kilogram or even a six-kilogram weight loss has only a month or two effect on a median life expectancy.

CHAIRMAN BONE: Thank you very much.

DR. ERNSBERGER: Thank you very much.

CHAIRMAN BONE: The next speaker will be Dr. James O'Callaghan, a toxicologist with U.S. Environmental Protection Agency.

DR. O'CALLAGHAN: Good afternoon, ladies and gentlemen, members of the Advisory Committee and FDA staff. I have no interest, financial interest, with the sponsor. And I'm not an official representative of either the FDA or the EPA.

When I'm not temporarily laid off due to a government shutdown, I'm employed as a senior research toxicologist with the Neurotoxicology Division of the U.S. EPA National Environmental and Health Effects Research Lab.

The Neurotoxicology Division is the older

of two federally mandated programs conceived to deal with the problem of assessing and characterizing the potential neurotoxic effects of chemical exposures. The other federal program charged with dealing with this issue is the Division of Neurotoxicology of the FDA's National Center for Toxicological Research in Jefferson, Arkansas.

Okay. Now you know who I am and where I work, but you probably don't know why I'm here. I'm here to give a brief account of research performed in my laboratory at the EPA that has to do with the issue of dexfenfluramine neurotoxicity.

To begin with, let me inform you that a major component of my research responsibilities at the EPA concerns the development and validation of approaches for assessing the potential neurotoxic effects of broad classes of chemicals and chemical mixtures. EPA is a regulatory agency, and we need to have tests with which we can assess the potential adverse health effects, including neurotoxicity, that are associated with exposures to chemicals in the environment.

What have I done that relates to the issue at hand, neurotoxicity assessment? What I have done is develop an assay for a protein in a specific brain

cell. The protein is called GFAP, and the brain cell is called an astrocyte.

Okay. Why is this important? It's important because astrocytes become larger and sometimes they divide in response to all types of brain injury, disease states like Alzheimer's, traumatic injury to the brain, ischemia, and exposure to chemical toxic agents.

This cellular response often is referred to as active gliosis. And the hallmark of this generalized reaction to brian injury is an accumulation within this cell type, the astrocyte, of the protein I mentioned earlier, GFAP. Thus, by assaying GFAP, you should be able to detect and quantify all types of neurotoxic injuries.

Stated in another way, if GFAP goes up in a sample of brain prepared from an animal previously exposed to a chemical or drug, then this chemical or drug should be presumed to be neurotoxic.

Okay. How do I know that my assay for GFAP can be used to detect and quantify all types of chemical insults to the nervous system? At the outset of this research program, I certain did not. Therefore, I spent the last decade using a broad variety of chemicals known to damage the central

nervous system simply as positive controls, known neurotoxicants, to validate the utility of the GFAP assay and the assessment of neurotoxicity.

Many of these validation experiments were done with collaborators in academia and industry, including firms that are subject to regulations by EPA and in other agencies of the federal government, certainly including the FDA, both at the NCPR and here at the Center for Drug Evaluation and Research.

The chemicals used as positive controls could include agents that range all across the board, from those that produce obvious necrosis based on classical histological assessments to those that produce damage to very discrete brain regions to those that affected very small elements of neurons within given brain regions, such as nerve terminals and nerve axons.

Using this validation scheme, we found no false negatives. Moreover, evidence of neuronal damage could be quantified at compound dosages well below those needed for neurotoxicity detection using traditional neuroanatomical techniques.

Very importantly, where pharmacological doses of therapeutic agents were used as negative controls, there were no false positives. On the basis

of these findings, the GFAP assay was incorporated as a recommended component of the U.S. EPA neurotoxicity testing guidelines.

Okay. Now that you know what I've done, how did I get EPA involved in work on substituted amphetamines?

CHAIRMAN BONE: Excuse me.

DR. O'CALLAGHAN: Yes. Okay. In a series of experiments conducted on GFAP with dexfenfluramine and other substituted amphetamines, all the substituted amphetamines made GFAP go up except dexfenfluramine, which had no effect.

So I bring these data to the attention of the Committee in order to inform them of the --

CHAIRMAN BONE: Thank you, Doctor.

DR. O'CALLAGHAN: -- existence of published findings that do not equate changes in markers of specific neurotransmitter systems with neurotoxic effects. And I'll --

CHAIRMAN BONE: Thank you, Dr. O'Callaghan.

DR. O'CALLAGHAN: Thank you.

CHAIRMAN BONE: The next speaker is Joe McVoy from the Association for Health Enrichment of Large People.

DR. McVOY: Thank you.

I feel like a Federal Express ad up here. I might add that I'm a private practice clinician who specializes in obesity and eating disorders and do represent the Association for the Health Enrichment of Large People, which is opposed to the approval of dexfenfluramine for clinical use at this time.

Our objections are based on the same risk-benefit ratio discussed at your previous meeting because we feel that efficacy was not fully reviewed and was overstated. In the last meeting, outcome results were discussed that did appear to validate efficacy for the medication over placebo.

The problem presented by these studies is that they examine, we feel, too short a treatment period and lack long-term follow-up. Further, other dexfenfluramine studies have not been presented to the Committee that tend to reflect a less impressive outcome.

I feel the most significant advance in obesity clinical research has been the emergence of long-term studies. Such studies have already transformed the way we see treatment through behavior modification and very low-calorie dieting.

Previously they were subjected to one to

12-month studies and showed great efficacy until they were evaluated on a longer-term period. And, as you know, consequently because of these longer studies, these treatments and the enthusiasm for them have waned.

The studies for dexfenfluramine previously presented ranged from one month to a year with three months being the most representative. One could consequently retain a healthy skepticism about the results until adequate long-term treatment trials are performed and reported. I will briefly present three studies to illustrate this.

Slide, please. Slide, the slide. Oh, I'm talking too fast. I can't use my eyes.

The researchers at the University of Amsterdam established the same conditions of scientific observations as the index studies, but their studies did not reveal a significant difference between placebo and dexfenfluramine in weight loss. And health risk indicators were ameliorated close to the same extent for both groups.

The study also found that discontinuation of the active treatment resulted in more weight gain for the treatment group, 3.24 kilograms, than the placebo group of .84 kilograms. Researchers'

conclusions were that dexfenfluramine may not be a breakthrough in treatment strategies. In fact, one of the index studies done at the University of Tubejin found similar results to the Netherlands study, finding significant rebound phenomena as well as marginal differences between placebo and treatment.

At the end of the one-year treatment phase, the treatment group had lost 11.2 percent of their weight; whereas, the placebo group had lost 9.1 percent of their weight.

Treatment was followed by a two-year posttreatment phase. Here researchers found the treatment group rebounded beyond their pretreatment weight by 1.5 kilograms while the placebo group maintained a 2.1-kilogram weight loss.

This has important significance given the fact that usually at least one-half of all participants in long-term fenfluramine/dexfenfluramine studies drop out from treatment. And based on this we could expect that long-term treatment for at least half of the patients would actually result in weight gain, rather than weight loss, because of the rebound effect which they would experience.

These researchers stated that even long-term treatment with group therapy, nutritional

education, and dexfenfluramine medication resulted in weight regain and impairment of cardiovascular factors three years later.

Unfortunately, I have no clinical trials of sufficient length to evaluate the degree of waning of outcome beyond one year for dexfenfluramine. A compatible study that many of you know about is that of Weintraub's fenfluramine studies with Ionimin and Pondimin, which was done in 1992. Admittedly, we do not have comparison trials of these two similar medications to help us extrapolate between them, but despite these limitations, I feel it's important to look at his outcome.

As you know, the Weintraub study was extensive and provided a degree of treatment which he himself acknowledges is beyond the practical scope of a clinical program, offering intense involvement with dieticians, counselors, and exercise for over three and a half years.

Initial results were impressive of 14.3 pounds, but you'll see at the end of the study it had reduced to 5.9 kilograms. And the difference between placebo and active group, who are upside down, had also narrowed.

Based on these findings, I feel that it

paints a different picture than presented before and argue for extended clinical trials of three years or more before approval by this Committee.

Thank you.

CHAIRMAN BONE: Thank you, Dr. McVoy.

The next speaker will be Dr. Judith Stern speaking for the American Obesity Association.

DR. STERN: As Vice President of the American Obesity Association and, as such, our organization has accepted unrestricted donations from the following companies, Best Foods, Hoffmann-LaRoche, Interneuron, Knoll, Servier, I am also Vice president of the American Society of Clinical Nutrition, professor of nutrition and internal medicine at the University of California at Davis, and a member of the Institute of Medicine National Academy of Sciences.

Today I represent the American Obesity Association, whose mission is to promote education, research, and community action that can improve the quality of life for people with obesity. We want health care professionals to have more options available to treat the obese patient whose obesity places her or him at increased risk for disease and death.

Obesity has been recognized as a chronic

disease by NIH since 1985. Our government has provided us with irrefutable evidence that obesity has reached epidemic proportions in the United States and that it shows no signs of abating.

There's increased recognition that small amounts of weight loss that are maintained decrease many of the risk factors associated with obesity. And it's obvious that this will reduce costs of health care, costs associated co-morbid conditions, and result in significant improvements of health.

AOA urges this Advisory Committee and the FDA to treat obesity as it would any epidemic that prematurely kills about 300,000 Americans annually. We strongly recommend that the development and approval of drugs to treat this disease be given special priority.

This Committee's actions are being closely watched by all of us who view the increasing prevalence of obesity in our children and adults and the lack of action on the part of our government officials with growing frustration.

The Institute of Medicine has sounded the alarm, but the intractability of the disease of obesity should not be an excuse for inaction. The Institute of Medicine and the National Institutes of

Health both agree that there is not convincing evidence that weight cycling causes additional risk to health to recommend against appropriate weight loss efforts in overweight people. Furthermore, the evidence from the few existing long-term drug trials gives hope that when they're used, anti-obesity drugs help with the maintenance of weight loss.

AOA endorses the consensus statement issued by NAASO that it is essential to develop effective drug therapies. Extensive data have been presented that dexfenfluramine in combination with dieting, exercise, and behavior modification doubles the percent of people who lose 10 percent of their initial body weight.

There is an exceedingly small risk for developing primary pulmonary hypertension. Although in very high doses in experimental evidence, there is some evidence that it's neurotoxic, it's 20-fold to 30-fold higher than the doses people take.

I just want to read from Dr. O'Callaghan's statement. I was unaware of his data. But he does not find neurotoxicity with large doses of dexfenfluramine in comparison to methamphetamine. And, basically, his subsequent studies have demonstrated that elevation in body temperature with

methamphetamine play a role in substituted amphetamine toxicity. Because dexfenfluramine has a tendency to lower core temperature, he reasoned that not only might this compound not be neurotoxic, it might be neuroprotective.

I want to conclude my statement with saying that AOA urges this Committee to carefully consider the comments of one of their own members, Dr. Nemat Borhani, that was made in response to a preliminary vote last September when the preliminary vote was to reject approval of the drug, and I quote, "I cannot live with my conscience tonight. We're dealing with a very severe epidemic of obesity with no medical treatment."

Thank you.

CHAIRMAN BONE: Thank you, Dr. Stern. Thank you for mentioning the interests of the organization that you're representing today, but would you care to further discuss any other interests as an investigator or consultant?

DR. STERN: I'm supported by the NIH and hope to continue to be so.

CHAIRMAN BONE: I see. Thank you. We all hope for that.

(Laughter.)

CHAIRMAN BONE: Following Dr. Stern, the next speaker is Dr. Arthur Frank, Medical Director of the George Washington University Obesity Management Program. Dr. Frank?

DR. FRANK: My name is Arthur Frank. I'm an internist. And I'm the Medical Director of the George Washington University Obesity Management Program in Washington, D.C.

I have worked for about 19 years with about 6,000 obese patients. As a physician, I realize obviously it's an extraordinarily difficult disease to treat. It's extraordinarily difficult, frustrating, and it's been a Herculean task. But I recognize also that this disease is not caused by willful misconduct and the traditional view of blaming the victim demonstrates a substantial misunderstanding of the scientific basis of weight regulation.

Obesity is not, as our culture ordinarily perceives, a trivial disorder. The discrimination in employment, education, and income is substantial. And its impact on health, comfort, and social function destroys the lives of good people who devote enormous effort to the mostly unsuccessful management of their disease. In one study, 44 of 49 morbidly obese people said they would rather be blind than obese. All said

they would rather be deaf. We need help in the treatment.

Those of us who are treating obese patients realize that traditional treatment programs do little which can be helpful. Obese people are not lazy and indifferent to the problem. Their efforts, however intense, are typically not enough to control this disease. Behavior therapy alone won't solve the problem any more than it would solve the problem of hypertension or diabetes.

Can medications help? Yes, but they do not solve the problem. They will not be useful in an indifferent or passive patient. They will not make a person stop eating. They will not deprive a patient of his puritan obligation to continue to struggle with the disease.

But for help in using medications, particularly in individualized programs, is real. The effects are subtle. I've had 3 and a half years of experience in treating about 300 patients with DL-fenfluramine and/or phentermine. This is roughly about 20 percent of the patients I treat.

These medications can be helpful. They will help a determined patient to eat less and to eat more carefully. They do not cause inappropriate or

addictive behavior or tolerance. They do help to medicalize the disease of obesity and diminish the destructive attitudes with which our culture has dealt with obesity for decades. They do help people sustain the effort.

And side effects are infrequent. And powerful, significant side effects are rare. I've seen no cases of any neurotoxicity, none with pulmonary hypertension, no new case of eating disorders, and none of which there has been an intensification of the disease. I've hospitalized no patients for complications of these medications and have discontinued its use in only two patients because of uncomfortable side effects.

Is the risk greater with D-fenfluramine than it would be with DL-fenfluramine? Is the risk of dexfenfluramine greater than the risk caused by other medications, say the analgesic nephropathy from acetaminophen, the sexual dysfunction of the anti-hypertensives, the peptic ulcers of anti-inflammatories? Is it less risky to be on a chronically unsuccessful diet with all of the devastating emotional consequences than on a more stable long-term program using medications, which is appropriate for the management of this disease? How

severe must a disease be before we are willing to accept some risk?

With the use of these medications, we must address important issues about the individualization of continuing treatment. How can we establish systems to assure that patients are properly monitored or that subsets of the obese populations are suitable candidates for the use of anti-obesity medications?

Do patients need continuous therapy or can we use intermittent long-term therapy? The medications we have now are effective, but we need all the help we can get.

We need better, more potent medications with more targeted impact. We need to expand our therapeutic options. We need a more enlightened understanding of the metabolic basis of obesity.

What we do not need is more confusion surrounding obesity therapy, more therapeutic preaching, more quick fixes, more blaming the victim, and the dispensing of more therapeutic pablum. What we do not need is a double standard for obesity medications, which makes it impossible to treat this disease with the sophistication its complexity requires.

Thank you.

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

The next speaker is Dr. Ron Innerfield from the Epidemiology and Clinical Trials Branch of the National Diabetes Center.

DR. INNERFIELD: Thank you.

My name is Ron Innerfield. I'm with the National Diabetes Center. I'm a former medical officer with the Division of Metabolism and Endocrine Drugs at the Food and Drug Administration. I have no known conflict of interest. I thank Ms. Karl for letting me speak for the National Diabetes Center.

I want to say in general that there is inadequate NDA safety demonstration of drugs with applications in chronic diseases. Unfortunately, the epidemiologic surveillance system of approved drugs at the Center for Drug Evaluation and Research at the FDA is hopelessly inadequate. And, really, the surveillance system needs to be its own center.

First of all, medicine is primium no nocari. First of all, do no harm. The first Food and Drug, Cosmetic Act in 1938 required safety alone for interstate marketing of drugs. The amended Food and Drug Act in 1962 added efficacy. Now drugs have to demonstrate both safety and, additionally, efficacy.

This is a boule and anding operation, not a ratio or a subtraction, risk-benefit or otherwise. Any subset allowed by the 1962 Act must be less than or equal to that allowed by the 1938 law; i.e., safe.

Finally, short-term efficacy studies simply do not prcvide an adequate safety database. Consider, for example, metformin. The same Committee met on March 18th, 1994 to evaluate data from 2 29-week trials. You concluded that the safety database was inadequate and decided unanimously that were metformin to be approved, a registry be established of all patients to be given this prescription.

What you did not know at that time was that a two to three-year open enrollment study of patients who had completed 29 weeks of double-blind therapy increased the total duration of exposure to 1,136 patient years. And there were a total of seven deaths seen during heat exposure, all seven of which occurred in patients who had been randomized to metformin, all seven of which had occurred in the population with sulpharunea failure and six out of seven of which were on combination metformin plus sulpharunea therapy at the time of death.

The probability of falsely ascribing these

deaths to the effects of metformin randomization are less than 100. This information is not in the prescribing information. And you, this Advisory Committee, need tho be aware of it.

Twenty-nine excess purely hypoglycemic events per 100,000 patients treated a year with metformin and gliburide compared to those treated with gliburide alone in controlled trials, the p-value for this is less than .001. The prescribing information says there is no excess hypoglycemia with metformin.

There were 4,800 excess cardiovascular events per 100,000 patients treated per year in controlled trials, p-value of less than .05. This information was compiled as a result of your request to assess EKG changes seen during double-blind therapy. It, too, is not in the prescribing information.

There was also one case of lactic acidosis among these seven deaths. You may remember that I calculated the total mortality benefit of tight control in Type II diabetes to be 53 lives per 100,000 patients a year. The excess mortality from metformin, even in this small database, was 616 per 100,000 patients per year.

As the primary safety reviewer for

metformin and the only primary cluneal reviewer whose reviews were not written by the sponsor, I recommended strongly against approval.

I'm sad to report to you that neither your unanimous recommendations for a registry post-approval nor my humble one for non-approval was followed by Food and Drug Administration. Metformin is effective in lowering blood sugars, but it may not be safe.

Dexfenfluramine causes pulmonary hypertension, which is both lethal and debilitating. Its long-term benefits have yet to be established. It is both unsafe and ineffective. It should simply not be approved.

The recent User Fee Act may have placed the FDA in certain compromising positions with the pharmaceutical industry. There really is not enough time for adequate safety reviews. Dwight Eisenhower warned against the military industrial complex. I suggest beware of the regulatory industrial complex.

Finally, we need to demand convincing long-term safety information for chronically administered pharmaceuticals. If this requires longer marketing protection and exclusivity, then I say so be it. But until then I urge you do not recommend approval for any drug which has not proven itself safe

in the requisite population at risk unless and until thorough and adequate surveillance is assured.

CHAIRMAN BONE: Thank you, Dr. Innerfield.

DR. INNERFIELD: Primium no nocari.

CHAIRMAN BONE: Thank you.

Dr. Marcus?

DR. MARCUS: May I ask the speaker, please, to identify what or who the National Diabetes Center is?

DR. INNERFIELD: Yes. The National Diabetes Center is an organization which has been around for two to three years. And it is devoted to the protection of the lives and livelihood of diabetic patients, not only in Washington, D.C. --

DR. MARCUS: Are you affiliated with the American Diabetes Association?

DR. INNERFIELD: Yes, sir, I am.

DR. MARCUS: No. Is the organization a wing or --

DR. INNERFIELD: No, sir, it is not.

CHAIRMAN BONE: Thank you.

The next speaker is Dr. Eric Rose, who is the Chairman of the Department of Surgery at Columbia University. Dr. Rose?

DR. ROSE: I'm Eric Rose, Chairman of the

Department of Surgery at Columbia University in New York. I have no known conflict. I'm also the surgeon in chief at the Columbia Presbyterian Medical Center. I appreciate the opportunity to represent only myself before your panel to bring a surgical perspective to the anti-obesity drug upon which you're deliberating today.

Surgeons deal with obesity in three contexts. First, we operate on hundreds of thousands of patients each year, usually to only palliate health problems very often due to obesity. These operations include coronary bypass surgery, gall bladder and common bile duct surgery, hernia repairs, knee and hip replacements, peripheral arterial bypass procedures, and limb amputations.

Second, we see a markedly increased incidence of morbidity, which complicates surgery in obese patients. These complications result in higher operative mortality and higher incidence of pneumonia, wound infection, wound dehiscence, myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism.

Thirdly, we have employed complicated and often dangerous procedures to affect weight loss, including such things as jaw wiring, intestinal bypass

procedures, and stomach stapling procedures.

Obesity is a very common chronic disease. Indeed, some might conclude that surgeons have a vested interest in the perpetuation of this illness, rather than the development of effective drugs for the treatment of obesity, including drugs like dexfenfluramine. Our primary obligations, however, are to our patients and dictate our encouragement of new, though potentially competitive, drug therapies.

We can all agree that effective oral medication would be far preferable to gastric staples. Critics point to two down-side risks for dexfenfluramine: first, a possible increased incidence of primary pulmonary hypertension, a disease with an annual incidence of only one case per million population, which I might add we at Columbia Presbyterian treat extensively with lung transplantation. This incidence might hypothetically increase to two to three per million in patients taking the drug. This hypothetical increased risk is still only a small fraction of the risk, for example, of acquiring a driver's license.

Second, toxicological studies in animals of extremely high doses of the drug when given raise again the very hypothetical specter of neurologic

toxicity, which in my opinion is overwhelmingly refuted by the lack of a definable clinical correlate when millions of patients, tens of millions of patients, throughout the world receive this drug in appropriate doses for more than a decade.

In closing, let me say that you are charged today to make a judgment weighing benefits versus risk for an important new therapy for a common and debilitating illness. This is just the type of decision-making process that we surgeons go through on a daily basis with our individual patients. Understood in this context, the decision to approve dexfenfluramine is more than justifiable. Yet, the epidemic makes it imperative.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Rose.

The next and final speaker in the open public comment session will be Dr. Barbara Moore, Executive Director of Shape Up, America!

DR. MOORE: Mr. Chairman, I'm making my remarks on behalf of Dr. C. Everett Koop, who is the Chairman of Shape Up, America! And his remarks are as follows.

Since I provided testimony to this Committee nearly one year ago, I am concerned and

frustrated that there is still no evidence that the regulatory environment is more conducive to the development of pharmacological interventions targeting obesity which with a death toll of 300,000 per year will soon be the number one preventable cause of death in the United States.

There should be no doubt that obesity is a disease. There should be no doubt that the growth in prevalence of obesity should be faced exactly as what it is, an epidemic. It is obvious that obesity represents the consequences of a mismatch between energy intake and energy expenditure.

Because hard physical labor is no longer required of us, men and women living in industrialized societies must reduce their intake of food in order to match their sedentary lifestyles. The energy expenditure of the average American laborer is half of that demanded at the turn of the century, when the labor force was predominantly agricultural.

I ask the Committee to consider the fact that the ability to decrease calorie intake to match a drastically reduced energy expenditure is a formidable challenge to many of us, but not to all of us.

This difference between individuals is

crucial. The fact that some people remain in energy balance without difficulty; whereas, a growing number of others do not, is not surprising.

The development of physiological mechanisms that support a robust appetite and efficiency energy storage were undoubtedly favored, as we have for centuries needed to engage in heavy labor in order to live. Now we do not. This is a mixed blessing for 53 million Americans, who struggle to reestablish a balance between their daily appetites and their daily expenditure of energy.

Our society is rapidly evolving toward an ever smaller energy expenditure. Our appetites are not keeping pace. This Committee would be remiss if it failed to appreciate the significance of the discovery from Friedman, et al. of a protein that plays a critical role in the physiological control of appetite in the genetically obese ob/ob mouse. It is absurd to think that such controls of appetite exist only in the rodent. There is assuredly a parallel system in the human. And it will only be a matter of time before such systems are fully elucidated in the human.

In the meanwhile, must we wait until every last detail is delineated before therapeutic

interventions are approved? Using this approach, we still would not have drugs to treat hypertension?

Obesity is a disease. It is rooted in part in a derangement in the control of appetite. There are pharmacological interventions currently in use in other industrialized nations with a proven efficacy and safety record. The FDA should have only the most compelling reasons to deny the use of such interventions to the American people who need them.

The proportions of the obesity epidemic are enormous. It has already claimed one out of every three adults in the United States. It is seizing increasing numbers of children and young people, for whom the consequences will be most dire in terms of health care costs and human suffering. Already the Institute of Medicine has estimated the costs of obesity to exceed $100 billion annually.

The government should respond to this as a crisis. It should mobilize itself to address the problem on every front: in the home, in the community, in schools, and in the workplace. The FDA is in a position to influence the battle in every doctor's office across the United States.

As research continues to elucidate the physiological control of food intake and energy

storage, every effort to develop increasingly targeted interventions should be supported.

To our shame, we continue to do almost nothing about this major health threat. The government, the medical community, the health insurance companies, no one has done much to encourage Americans to prevent the obesity that is costing us and killing us. Furthermore, we put unnecessarily costly barriers in front of organizations that are willing to take action.

The pharmaceutical industry awaits a signal that --

CHAIRMAN BONE: Thank you.

DR. MOORE: -- the enormous costs associated with the development of appropriate targeted pharmacological interventions will be worth their while.

CHAIRMAN BONE: Thank you, Dr. Moore.

It will just be a moment while we're connecting up with Dr. Illingworth. He does have a copy of the slides. This is not a break. This is not a break. We would also like to welcome Dr. New. Dr. Illingworth, can you hear us now?

DR. ILLINGWORTH: Yes.

CHAIRMAN BONE: Thank you very much. What

arrangement do we have for signaling if Dr. Illingworth has a question during the question periods? Dr. Illingworth, when we get to appropriate question times, the only way we'll know that you have a question is for you to say that you have a question.

DR. ILLINGWORTH: Okay.

CHAIRMAN BONE: All right?

DR. ILLINGWORTH: Yes.

CHAIRMAN BONE: Welcome, Roger. Thank you.

We are starting up again. The next part of the afternoon will be the sponsor's presentation. The introduction and overview for the sponsor will be presented by Dr. Glenn Cooper.

SPONSOR PRESENTATION

INTERNEURON PHARMACEUTICALS INCORPORATED PRESENT NDA 20-344, DEXFENFLURAMINE HYDROCHLORIDE (REDUX)

INTRODUCTION AND OVERVIEW:

DR. COOPER: Mr. Chairman, members of the Committee, Dr. Bilstad, Dr. Sobel, members of their staffs, we are here once again to talk about dexfenfluramine for the therapy of obesity.

As Dr. Bone and Dr. Bilstad have noted, at the September 28th panel meeting, dexfenfluramine was neither approved nor turned down. With your

permission, I'd like to give you my view of what happened at that meeting.

Going into the September 28th meeting, we felt there were four important issues that the Committee needed to consider: first, the efficacy of the drug; second, the possible association with an extremely rare but serious disease, primary pulmonary hypertension; third, the risk-benefit ratio; that is, the benefits of treating obesity with long-term pharmacotherapy versus the potential risk of this rare cardiopulmonary disorder as this is really the only serious adverse event that has appeared as an epidemiological signal in over 10 years of worldwide marketing; and, finally, the relevance of long-term serotonin reduction in animals treated with large doses of fenfluramine or dexfenfluramine and whether there was a potential for neurotoxic effects in clinical usage.

I believe the FDA and the Committee were satisfied with the efficacy of the drug, the Committee voting seven to one that efficacy was sufficient for approval. And I believe the FDA and the Committee were comfortable that the benefits of the drug in treating obesity far outweighed the very small possible risks of pulmonary hypertension. But I also

believe the Committee was concerned about the issue of neurotoxicity. So we're going to be spending the lion's share of time today on that issue.

For the benefit of those Committee members who did not attend the last meeting, let me first give you an overview of the issues where there was common ground and consensus.

On the question of efficacy, there was, as I mentioned, a near unanimous view that the drug had meaningful efficacy in the long-term therapy of obesity. For the Committee members again who did not attend the last session, I'm going to briefly show you a summary of the efficacy data that persuaded your fellow panel members, then move on to other unresolved areas.

As a one-slide summary of the mechanism of action, dexrenfluramine increases serotonergic neurotransmission and is not a sympathomimetic agent. Let me stress once again that dexfenfluramine is not an amphetamine or an amphetamine-like drug. it is a serotonic reuptake inhibitor similar to Prozac and other marketed agents but also releases serotonin into the synapse and is a serotonin receptor agonist.

The drug enhances satiety and reduces daily caloric intake by about 500 kilocalories per

day. The drug also has no abuse potential. For those Committee members who did not attend the Drug Abuse Advisory Committee meeting on September 29th, that committee voted to remove fenfluramine and dexfenfluramine from the schedules of the Controlled Substances Act.

At the previous meeting on guidelines for obesity drug approval, this Committee decided that there were three valid methods for analyzing weight loss data. The relative merit of one method versus another was not established. So we decided to analyze our data each way.

The three methods were: first, an analysis of differences between means of placebo versus drug-treated patients against a background of equivalent diet therapy in both groups; second, responder analyses; and, third, categorical analyses.

Of the 19 placebo-controlled trials in the NDA involving over 4,500 patients, we highlighted 4 long-term studies for presentation, although 18 of the 19 studies were positive.

The first study, IP003, which I will not go into, we established in a three-month dose response trial of the optimum dose, which balanced significant weight loss with optimal tolerability. That dose was

15 milligrams b.i.d. or approximately 0.3 milligrams per kilogram.

The other 3 studies shown here were all 6 and 12-month studies. In the 12-month study, all 3 analyses methods were prospectively defined in the protocol.

In this slide you can see the mean weight loss and drug versus placebo-treated patients. For this analysis, the Committee has focused in on a five percent difference between drug and placebo as a meaningful spread, although I must tell you that this remains a highly controversial decision within the academic obesity research community given the enormously variable response to diet in these types of trials.

Nevertheless, in the six-month study, UK18, there was over a 6 percent difference favoring drug at the endpoint in these patients who had already lost 11 kilograms in an 8-week drug run-in with an 8-week very low-calorie diet run-in period prior to randomization.

In the six-month Noble study, there was about a four and a half percent difference. In the large 12 month index study involving over 1,000 patients, there was about a 4 percent difference at

endpoint if you look at mean data and over a 5 percent difference when FDA statisticians looked at median differences. When you look at the responders and categorical analyses, the magnitude of efficacy becomes even clearer.

I personally believe that the responder analysis is the most important tool for clinicians to answer the question, "What is the likelihood of my patient achieving a meaningful clinical result?" I think there is nearly universal agreement based on the epidemiology of obesity that losing more than 5 percent or losing more than 10 percent of initial body weight are important benchmarks that correlate to morbidity and mortality reduction. Let me highlight the data on a 10 percent or greater reduction.

In the index study, 40 percent of patients achieved a 10 percent or more reduction, compared to just 21 percent in the placebo group. That's a 95 percent improvement in the response rate for drug-treated patients.

In the Noble study, there was a threefold difference, 21 percent versus 7 percent, although the sample size here prevented significance. In UK18 study, 18 percent of dexfenfluramine-treated patients were responders versus zero for placebo. And let me

remind you that these were patients that had already lost over 10 kilograms immediately prior to study entry.

For brevity's sake, I will just show the categorical analysis for the index study. This kind of analysis looks at the percentage of patients who fall into various predetermined weight gain or weight loss categories.

About twice the percentage of placebo-treated patients had no weight loss or weight gain compared to dexfenfluramine. At the other end of the spectrum, about twice the percentage of dexfenfluramine-treated patients achieved a 10 percent or more weight loss compared to placebo. And overall the difference between groups was highly significant at the p less than .001 level.

So I think it was fairly clear to everyone that an obese patient's dexfenfluramine plus diet therapy produces clinically meaningful weight loss compared to diet therapy alone and that significantly larger proportions of patients lose clinically meaningful amounts of weight when compared to placebo.

Now, what about the issue of whether losing weight helps people? That question is central to the risk-benefit analysis for any obesity drug.

It's axiomatic to practicing physicians that their obese patients should be encouraged to lose weight.

When I was an internal medicine resident, I trained at the Joslin Clinic. And although I did not become a diabetologist, as many of you are, I earned my merit badge in diabetes care.

Many Type II diabetics are overweight or obese. And weight loss, of course, is the primary therapy that is always recommended but almost never successful, necessitating poly pharmacotherapy for diabetics' hyperglycemia and often their hypertension, hyperlipidemia, and osteoarthritis.

After chronic lack of success in the arena of weight reduction, most physicians have become therapeutic nihilists. It's well-documented in the literature that diets do not work in the long run for over 90 percent of the patients and very few physicians are going to prescribe amphetamines. So there have been very few effective long-term solutions save gastric bypass surgery for the morbidly obese.

The reason we're here today is that dexfenfluramine changes the paradigm as a non-amphetamine serotonergic agent effective in long-term weight loss and weight maintenance.

Up until recently, three's been a relative

paucity of epidemiological data on the health risks of obesity and, even more importantly, a paucity of data on the benefits of weight loss as risk factor interventions.

At the last meeting, Dr. Joanne Manson from the Brigham and Women's Hospital presented some of her new research and research of some of her colleagues. Dr. Manson is here today to answer questions, but in the interest of time, I'll just show you a couple of key studies.

This slide presents the best estimates available, which we believe to be conservative of the number of deaths per year that could be attributed to obesity. We use two methodologies to extrapolate mortality data, examining cause-specific deaths seen on the left and all-cause mortality seen on the right.

Both methodologies have yielded a similar result, approximately 300,000 excess deaths per year attributable to obesity, making obesity the second leading cause of preventable death, behind cigarette smoking.

We're in the midst of a bona fide public health epidemic in this country. Thirty percent of the adult population is now obese. And the prevalence is steadily increasing.

This slide shows the striking correlation between body mass index and all-cause mortality in non-smoking women. The findings are from the nurses' health study, which is a prospective study of more than 115,000 U.S. women age 30 to 55 at entry recently published in the New England Journal of Medicine.

In this study, after accounting for bias from cigarette smoking and underlying disease, Dr. Manson's colleagues found that women who had a BMI of 27 to 28.9 had a 60 percent excess risk of premature mortality compared to lean women. Those women with BMIs of 29 to 31.9 had a 110 percent increase in risk. And those with a BMI greater than or equal to 32 had a 120 percent increase in risk.

Overall, the researchers found a strong positive association between BMI and the risk of mortality. And the excess was substantial, beginning with BMIs of 27 to 28.9. In this study population, about 23 percent of all deaths were directly attributable to obesity.

An incredibly strong association exists between body mass index and non-insulin-dependent diabetes mellitus. Colditz, et al., found a very striking increase in risk of NIDDM among women according to their BMI. Those women who had a BMI of

27 to 28.9 had nearly 20 times or a 2,000 percent increase in the risk of developing NIDDM as lean women. And once BMI is 31 or higher, women had a greater than 40-fold risk of developing diabetes.

A critically important question that everyone ought to be interested in is whether intentional weight loss can lower mortality risk. One very important study that was recently published by Williamson and colleagues at the Center for Disease Control studied intentional weight loss in an American Cancer Society cohort of 28,000 obese non-smoking women between the ages of 40 and 64 with no preexisting illnesses.

They found that an intentional weight loss of 9.1 kilograms or more within the previous year was associated with a statistically significant 25 percent reduction in all-cause cardiovascular and cancer immortality. That's a very powerful result. Nine kilograms of weight loss can produce a 25 percent mortality reduction within one year.

Williamson and colleagues also looked at a subgroup of over 15,000 women who also had BMIs of 27 and higher with co-morbid conditions this time, including coronary heart disease, hypertension, stroke, and diabetes.

They found that an intentional weight loss of any amount, even a very modest weight loss, was associated with a 20 percent reduction in all-cause mortality, a 30 to 40 percent reduction in diabetes-associated mortality, and a 40 to 50 percent reduction in mortality from obesity-related cancer.

I think we have all known intuitively that obesity is harmful and that weight loss can benefit our patients. We now have powerful epidemiological evidence to support these beliefs.

Against this background, the case for pharmacotherapy of selected obese patients with dexfenfluramine is overwhelming, just as the case is overwhelming for the pharmacotherapy of hypertension, diabetes, and hyperlipidemia in selected patients.

Another issue that we touched upon during our presentation last time was the direct influence of dexfenfluramine on co-morbidities. Although the primary criteria for the approvability of an obesity drug has been determined by this Committee to be weight loss, co-morbidity data is also of interest and importance.

Late in the day on September 28th, it became clear to us that the Committee wanted more time to examine the available co-morbidity data. There are

persuasive data available in the NDA on the effect of dexfenfluramine on obese hypertensive, obese diabetic, and obese dyslipidemic patients. That data will be presented to you this morning by Dr. Arthur Rubenstein, Chairman of the Department of Medicine at the University of Chicago.

Although it seems self-evident that successful long-term therapy of obesity will lead to reductions in morbidity and mortality, it's important in the regulatory sense to create a quantitative ledger of potential morbidity and mortality associated with the disease and compare it with the ledger of morbidity and mortality associated with the therapy.

At the last meeting Dr. Gerald Faich, one of the country's leading experts in pharmacoepidemiology, did just that and determined in his risk-benefit analysis using a set of conservative assumptions that dexfenfluramine therapy will save hundreds of lives each year in this country and will have a significantly favorable impact on morbidity in many more. Because it's an important exercise, he's going to revisit that analysis for you later this afternoon.

However, there are a few elements of the overall risk-benefit assessment I'd like to mention at

this point. I want to make a couple of comments about pulmonary hypertension, which, again, although extremely rare, is the most serious adverse event that merits discussion on the risk side of the ledger.

Then I want to briefly discuss two issues: the responders' analysis and a tightened "Indications and Usage" section for the package insert. Both of these topics directly influence the risk-benefit assessment in a positive way.

Then I want to brief you on how European regulatory authorities have assimilated this information on risk-benefit, which culminated in new prescribing instructions for dexfenfluramine just three weeks ago in France.

After 10 years of marketing experience throughout the member states of the European Community and a total of 65 countries around the world, a single safety issue, primary pulmonary hypertension, has emerged as an epidemiological signal meriting further evaluation. A total of 101 cases have been reported in associated with dexfenfluramine in the last 10 years.

We believe European physicians have had a heightened awareness of pulmonary hypertension since there was an epidemic several years ago of pulmonary

hypertension associated with the amphetamine anorectic agent Aminorex. This heightened awareness appears to have led to hair-trigger reporting.

A careful analysis of these 101 cases by an outside expert, Dr. Taylor Thompson of the Pulmonary Unit of the Massachusetts General Hospital, who is here today, reveals that almost half of them are either not actual cases of pulmonary hypertension, but other misdiagnosed cardiopulmonary disorders or patients whose symptoms of dyspnea clearly predated administration of dexfenfluramine. In fact, there were 53 valid cases of primary pulmonary hypertension postdating dexfenfluramine exposure against a backdrop of 10 million patients exposed. Still, for rare disease, this incidence merited investigation, investigation that European regulatory authorities required.

The study performed was a careful international case control study, the IPPHS study that was presented last time by the principal investigator, Dr. Lucien Appenheim. Dr. Faich will briefly review the findings of that study for you during his presentation.

I believe it was the consensus of the Committee that the relative and absolute risks of

primary pulmonary hypertension were very small. I also believe the Committee and the sponsor concurred with Dr. Appenheim's conclusion that, and I quote, "The exact role of the anorexigens in the risk of PPH cannot, however, be definitively established due to lack of knowledge of the pathogenic mechanisms, the lack of specificity of the effect within the class of anorexigens, the non-exclusion of all potential confounders, and the low, absolute risk."

I want to spend a few moments on an element of the risk-benefit analysis that received almost no discussion at the last meeting, namely response predictors for dexfenfluramine-treated patients. I want to revisit the subject because it represents a ground-breaking approach to pharmacotherapy in general and to dexfenfluramine use in particular.

For most drug therapies, markers do not exist to enable a clinician to predict therapeutic success up front. Clinicians generally must rely on trial and error to assess whether a particular therapy is going to work in a particular patient.

By evaluating a host of factors, we were able to identify a single variable that turned out to be a highly significant predictor of therapeutic

success, which FDA defined to be a 10 percent weight loss by one year.

We found that if a patient treated with dexfenfluramine lost four pounds in the first four weeks of treatment, they were highly likely to lose 10 percent of their initial body weight by 12 months.

We found in practical terms that 22 percent of patients randomized to receive dexfenfluramine did not lose 4 pounds in the first month of treatment. And 91 percent of these patients also did not lose 10 percent of their body weight by the end of one year. This was compared to 78 percent who successfully lost four pounds in the first month of treatment. And 60 percent of these went on to lose at least 10 percent of their body weight by month 12.

Therefore, we believe that a simple four-week trial of dexfenfluramine therapy is predictive of which patients are likely to achieve a 10 percent weight loss with continued treatment and, equally important, can identify those patients unlikely to achieve a 10 percent weight loss. This responders' analysis will help the clinician target patients likely to benefit and further tilt the risk-benefit analysis in favor of drug therapy.

We believe it is important enough to be

included in the package insert. And let me read the proposed language in the package insert to you, quote, "Analysis of numerous variables revealed that patients who lose at least four pounds in the first four weeks of treatment with dexfenfluramine have a statistically significant change of losing at least 10 percent of their initial body weight by the end of one year of treatment. If a patient has not lost at least four pounds in the first week of treatment, the physician should consider discontinuation of dexfenfluramine."

At this point I'd like to address another labeling issue involving the indications for dexfenfluramine use. The academically accepted definition of obesity is a BMI of 27 or greater. And that was the inclusion criteria in our clinical trial database, although 80 percent of our patients had BMIs of greater than 30 in the database.

At the last meeting, several Committee members expressed the opinion that they would prefer a more stringent criteria for drug therapy of a BMI of 30 or greater in the absence of co-morbidities and a BMI of 27 or greater when co-morbidities are present.

Since we're committed to the use of dexfenfluramine in patients who are at greatest risk and share your desire to make sure that the drug is

not casually used for cosmetic overweight conditions, we will propose the following language for the "Indications and Uses" section of the package insert, quote, "Dexfenfluramine is indicated for the management of obesity in patients on a reduced-calorie diet. Dexfenfluramine is recommended for obese patients with initial body mass index of 30 or 27 if there is a risk of presence of other factors; for example, hypertension, diabetes, hyperlipidemia. Below is a chart of body mass index based on various heights and weights." And we would append an easy-to-use-and-interpret nomogram for the purpose of calculating BMI.

I believe it's important for you to be current on the regulatory status of dexfenfluramine. The international pulmonary hypertension trial showed a small but statistically significant association between the independent variables of anorectic drug use, obesity, and systemic hypertension, and the development of pulmonary hypertension.

When this data became available in May, the French and other regulatory authorities examined the risk-benefit of all anorectic drugs, including fenfluramine and dexfenfluramine, which have been on the market there for many years. Historically all

anorectic drugs had been restricted to short-term or three-month labeling in Europe.

Last month the French regulatory authority reaffirmed the three-month restriction on all amphetamine and amphetamine-like drugs. At the same time the French regulatory authority also determined that the benefits of long-term treatment with dexfenfluramine significantly outweighed the risks. Accordingly, they have actually liberalized the use of dexfenfluramine.

For the first time, French specialists and internists may now initiate dexfenfluramine therapy for long-term use. Initial prescription can be for up to one year provided that there has been a response to the drug. Patients may then be continued indefinitely beyond one year based on the ongoing assessment of their specialist or general practitioner.

Prescribing guidelines in other member states of the European Union are pending, but we believe that the outcome with respect to long-term use will be similar to the French action.

It's important to note that, although the French and other European regulatory authorities are well-aware of the controversy about the neurotoxicity question involving the fenfluramines, it was not

considered a significant issue and did not even enter into the debate in Europe about the potential risks versus the potential benefits of these agents.

That leads us to this Committee's principal remaining concern: the issue of neurochemical changes in animals associated with fenfluramine and dexfenfluramine therapy and whether there was a risk of neurotoxicity in patients.

Once again, I believe this was the pivotal issue leaving some Committee members to withhold their endorsement of the drug. On September 28th we did not present all of our data on the neurochemical effects question because our interaction with FDA in preparation for that meeting indicated that this would not be a major issue for the Committee's consideration.

The FDA background package to the Committee was consistent with FDA's oral representations to us. I want to read to you the only conclusions on neurotoxicity provided to the Committee and the sponsor in FDA's background to the September 28th meeting.

These statements refer to clinical studies performed by the sponsor to address this issue, quote, "The F19 MRS technique used in the study as a research

tool and its clinical applicability has not been validated. The results, however, offer support for the concept of non-accumulation of drug with duration of use and of concentrations well below those that produce neurotoxicity in experimental animals. Although the number of subjects was small, the small standard deviation offers a degree of comfort concerning the safety of this drug."

There is another quote, "PET is an experimental tool in these studies. The data support the thesis of lack of effect of dexfenfluramine on serotonergic receptors at doses used for production of weight loss." And we, the sponsors, essentially agree with this assessment of the margin of safety of the drug.

You will notice that the critics of these drugs who presented to the Committee last time called the issue neurotoxicity while we use the term "neurochemical changes." I want to make it clear that we are not being coy in our choice of language. Based on the scientific data, we do not believe fenfluramine and dexfenfluramine are neurotoxic.

We do agree with these individuals that high doses in animals can cause significant and in some cases prolonged reduction in brain serotonin

content. Understand, please, that other serotonergic drugs, such as Prozac, Paxil, and Zoloft, have a similar effect on brain serotonin levels. But that is not neurotoxicity.

And showing histologic evidence for neuronal damage, like neuronal swelling and neurofibrillatory tangles using high doses of the street drug MDMA or Ecstacy and relating that to dexfenfluramine because of some chemical similarities between the molecules that was done by outside speakers during the last meeting is just not scientifically valid.

And I think we saw an example of the confusion and obfuscation of this issue when one of the speakers in the open public hearing believed erroneously that the slides that showed neurofibrillatory tangles were, in fact, dexfenfluramine or fenfluramine-treated animals. In fact, those were with MDMA or the street drug Ecstacy, which has no similarity to this drug.

I think it is unlikely that this Committee will come to a definitive scientific conclusion on the technical aspects of whether serotonin depletion represents a pharmacological action of the drug, as we contend, or neuronal damage, as the critics contend.

This has been a 25-year debate among neurotoxicologists. And it's probably not going to be settled today. We've provided our point by point scientific rebuttal to their position in your new background package. Professor John Blundell, professor of psychobiology at Leeds University, will have a few things to say about that during his presentation.

What I want to focus on this afternoon is the complete lack of clinical significance of these high-dose animal toxicology studies. This is an area where I believe you can achieve a significant level of comfort in your decision-making.

You're all well-aware that giving large multiples of clinically useful drugs, even over-the-counter drugs, can cause harmful effects, even death. The drug's critics typically use an unusual high-dose pulse regimen of fenfluramine or dexfenfluramine to obtain the long serotonin depletion in animals, typically 10 milligrams per kilogram per day parenterally for 4 days. That is 30 times the clinically recommended human anorectic dose for dexfenfluramine, or about 900 milligrams per day in an obese patient.

Why do they use doses that large? Because

they do not see the long-term changes they want to see with lower doses or, more importantly, with continuous administration of the drug. The fact that you cannot replicate their findings with continuous administration calls to question the clinical relevance of their studies using an artificial pulse regimen.

Consider the effects of giving approximately 30 times the usual daily dose of a few common medications. Two hundred forty acetaminophens or Tylenols will produce liver failure and death. Nine thousand milligrams of Imipramine, actually considerably less will cause seizures, cardiorespiratory collapse, and death. Seven thousand, five hundred milligrams of Diabenase will cause hypoglycemic coma and death.

While clinical overdose experience is limited, 900 milligrams of dexfenfluramine will transiently sicken a patient with mydriasis, agitation, or somnolence, but full recovery has been the rule.

Dexfenfluramine's critics have presented their case for neurotoxicity based on techniques that rely on serotonic content as a putative surrogate marker for neurotoxicity.

I want to point out to you that there are a number of classical techniques that do not rely on serotonin content that have been used to assess potential neurotoxicity of compounds in general.

In well-controlled studies using these techniques, including studies done by neurotoxicologists at the EPA, dexfenfluramine did not produce argyrophilia, gliosis, or reduce retrograde transport at doses well above those that produce acute reductions in serotonin content.

In contrast, known neurotoxins consistently produce these effects. Thus, by techniques independent of serotonin content, dexfenfluramine does not produce any effects at margins in excess of 16 to 25-fold higher than relevant human doses.

If you choose to take the most conservative position that prolonged serotonin depletion represents a hypothetical concern, then there is a large margin of safety between clinically recommended doses and the doses that produce prolonged serotonin depletion in animals.

We have done numerous dose-response studies designed in conjunction with the FDA dosing rats from four days to two years with dexfenfluramine,

then measuring brain serotonin content. Everyone I believe accepts that serotonin depletion seen acutely represents the pharmacology of the drug, not toxicology.

There's a certain amount of interpretation in deciding what is a no-effect dose for serotonin depletion. Conservative view would be that eight milligrams per kilogram is the no-effect dose since after the first week of treatment there is no serotonin depletion at any time point. A more liberal view is that 16 milligrams per kilogram is the no-effect dose since there is a full normalization of serotonin content by 26 weeks.

We know from these studies that eight milligrams per kilogram produce steady state dexfenfluramine brain levels in rats of about 35 micromolar. We further know from the clinical data we presented last time that steady state brain dexfenfluramine concentrations in obese patients taken 15 milligrams b.i.d., the usual clinical dose, or about 4 micromolar, although it's probably based on validation studies in monkeys that human levels were actually overestimated by as much as a factor of two.

So taking the most conservative view, there is at least a 10 to 20-fold margin of safety

between clinically achievable brain levels in patients and the no-effect level in animals for serotonin depletion. That translates into a daily dose of dexfenfluramine of 300 to 600 milligrams per day just to get up to the no-effect level.

Then there are those who might turn around and say, "Well, fine, but this drug is going to be used chronically. What about the neurochemical effects of very long-term exposure?" Well, here's the data that addresses that concern.

In this lifelong carcinogenicity study, mice were treated with doses up to 27 milligrams per kilogram per day of dexfenfluramine. At the time of sacrifice, at two years, brain serotonin content index fenfluramine levels were measured. As you can see, animals dosed at the 27 milligrams per kilogram level had very high brain levels of 51 micromolar, over 10 times the concentration seen with human clinical doses, without any evidence of depletion of serotonin content or loss of paroxetine binding, an independent measure of serotonergic neuroterminal viability.

These data are not consistent with persistent or delayed neuronal damage. Long-term; in fact, lifelong, administration of high doses was simply not a problem.

Professor Blundell is going to show you this afternoon some preclinical data we didn't get a chance to show you last time on the lack of functional impairment in animals that received very high doses of fenfluramine or dexfenfluramine at the level the drug's critics claim to be neurotoxic. This data involves behavior such as locomotor activity, cognition, aggression, and social behavior.

This data was presented at the Drug Abuse Advisory Committee on September 29th. And we think it is further powerful evidence of the total lack of functional significance of the critics' observations.

Ultimately, the burden of proof of a drug's safety lies in the clinic. More often than not, you, as an Advisory Committee, must make decisions on the approvability of a drug based on the clinical trial database only, often only a few thousand patients. In this case you have the comfort of one of the largest post-marketing experiences in regulatory history.

Over 10 million patients have been exposed to dexfenfluramine in the 10 years it has been marketed outside the U.S. in 65 countries. Over 30 million patients have been exposed to fenfluramine in the 25 years it has been on the market, including

millions of Americans since the drug was approved in the U.S. in 1973.

I think it's important to make it clear that fenfluramine, the original racemic drug, contains equal parts of dexfenfluramine and Levofenfluramine.

The usually daily dose of fenfluramine is 60 milligrams per day, although the package insert permits doses up to 120 milligrams per day. So patients who take fenfluramine are receiving at least 30 milligrams of dexfenfluramine per day, our recommended dose, in addition to an unwanted pharmacological agent, the L isomer, a dopamine antagonist, which has no weight loss properties. That is why the safety exposure data for fenfluramine is relevant to dexfenfluramine.

When that many obese patients, especially patients with concomitant diseases and medications, are exposed to a drug, it's typical for the drug company and regulatory authorities to receive numerous reports of adverse events which may or may not have a causal relationship.

Last time during FDA's presentations, you were shown this slide of serious and non-serious events reported since 1984 with dexfenfluramine. What was basically said was look at all of these CNS events

we see here. Perhaps this is evidence for neurotoxicity.

Deriving specific conclusions from raw spontaneous adverse reaction data is a hazardous exercise since you cannot extrapolate incidence data or causality from spontaneous reports, it's necessary to consider the context of the data, including the total number of patients exposed over the time period.

In the case of dexfenfluramine, we have over 10 million patient exposures during this 10-year period. About 1,000 serious and non-serious CNS events in the context of 10 million patients exposed to a drug that has a CNS mechanism of action can, in fact, lead one to the conclusion that CNS adverse events are fairly uncommon.

I'd like you to consider the spontaneous post-marketing safety data for another CNS agent, Prozac, a drug so utilized it took only three years of U.S. and international use for 10 million patients to be exposed. I've chosen this cutoff point to be comparable to dexfenfluramine's worldwide exposure.

There were 6,000 serious and non-serious CNS adverse events reported with Prozac among the first 10 million patients, about a 6-fold or higher relative reporting rate for dexfenfluramine.

To highlight just a couple of statistics, there were over 1,000 cases of sleep disturbance compared to 200 for dexfenfluramine. At the last meeting, concerns were raised about the 39 cases of amnesia for dexfenfluramine in this drug's database. Prozac produced about 180 cases of amnesia, 27 of them serious. Nevertheless, there is certainly no evidence whatsoever that Prozac is neurotoxic. I could have shown you similar data for other marketed serotonergic agents, such as Paxil, Zoloft, or Buspar.

The conclusions to be drawn here are threefold. One, the interpretation of post-marketing safety data must be approached cautiously. Two, CNS-active serotonergic drugs, like dexfenfluramine, Prozac, and others, by virtue of their pharmacology are not devoid of CNS side effects. And, three, CNS side effects are not prima facie evidence for neurotoxicity.

It's important for you to know that European regulatory authorities have also been interested in the neurotoxicity issue. This is difficult to read, but I will read it to you. Since fenfluramine and dexfenfluramine are on the market and patients are taking these drugs every day, the medicines commissioned in the U.K., the drug

regulatory body there commissioned a European review to examine whether fenfluramine or dexfenfluramine had adverse neurological effects.

Let me read you the letter our European partner, Servier, received two months ago from the medicine's control agency, quote, "We have now completed our assessment of the report prepared by Professor C. K. Atterwill and have reviewed the spontaneous reports of neurological adverse drug reactions associated with dexfenfluramine and fenfluramine received to date. We conclude that no action is required in relation to this aspect of the drug's safety profile at present." I urge you to seriously take this regulatory opinion into consideration in your decision-making today.

One of the most important things you'll see this afternoon is clinical data on the lack of neuropsychological effects of dexfenfluramine in patients. The clinical relevance of high-dose animal toxicology studies pales in comparison with sensitive neuropsychological testing in double-blind placebo-controlled clinical trials.

Dr. Rich Gammans, Interneuron's Vice President of Clinical Development and an expert on the development of serotonergic drugs, is going to present

important data we did not show you last time on neurocognitive and neuropsychological testing involving cognition, depression, mood, and sleep in several hundred patients who received dexfenfluramine in short-term and long-term placebo-controlled trials.

Data from 16 of the 17 relevant controlled trials were contained in the original NDA submitted over 2 years ago. There's one additional recently completed and analyzed long-term trial by Dr. Noble in San Francisco that we just completed and submitted a couple of weeks ago.

This study is important because it was prospectively designed to look at neurocognitive effects in a placebo-controlled trial in obese patients. Additionally, the study involved both long-term treatment of six months and a long-term post-treatment follow-up of 12 months.

Although we were able to present a small portion of this data on September 29th at the Drug Abuse Advisory Committee, some of you have expressed the opinion that if this kind of data had been made available on September 28th, it would have been valuable and persuasive.

Following the September 28th meeting, we collated all of our available data on

neuropsychological assessments into a dossier which is similar to the documentation given to you in your backgrounder from the company.

We shared this dossier with a panel of distinguished neuroscientists who specialize in the field of neurobehavioral testing. None of these individuals have previously consulted with Interneuron, Servier, or Wyeth-Ayerst on dexfenfluramine.

I would like to read to you summary verbatims from their expert reports provided to us. And I believe all of these reports have been provided to the Committee.

Dr. Paul Spiers from M.I.T. writes, "Dexfenfluramine does not appear to pose any risk of neuropsychiatric or neurocognitive adverse effects."

Professor Marcel Mesulam from Northwestern University and Medical School says, in sum, "I am impressed by the number of patients who have taken this substance without obvious adverse effects on the parameters that you list."

Professor Malcolm Lader from the University of London has written, "I see no evidence for any adverse effects on brain function as monitored by neurologic, psychiatric, behavioral, and cognitive

examinations."

Professor John Mann from Columbia University has written, "The data available for the assessment of the safety of fenfluramine with regard to neurotoxicity are considerable. And the evidence available indicates that this drug is safe. Studies using more sophisticated neuropsychological testing and functional brain imaging techniques, such as PET, can further establish the safety of the drug."

Professor John Rush from Southwestern Medical Center writes, "I could find no evidence of long-term neurotoxicity or neurofunctional impairment, either on or off the drug, in humans in therapeutic doses."

Professor Emil Coccaro from the Medical College of Pennsylvania writes, "In conclusion, I believe that dexfenfluramine in the recommended doses is safe for use in human subjects. There is no evidence of long-term neurotoxicity or impairment in behavioral or cognitive parameters in human subjects. Finally, given the worldwide exposure to dexfenfluramine, I believe that its safety profile is perhaps better established than most other psychoactive agents that are approved by the FDA for use in human subjects."

These assessments from experts in the field give us confidence in the conclusion that clinically recommended doses of dexfenfluramine do not produce neurotoxicity.

You will also note that FDA obtained their own consultation of this data package from a distinguished neuroscientist at the National Institute of Mental Health, Dr. Judith Rapoport, who wrote, and I'm quoting from Tab 3 of FDA's backgrounder to this meeting, quote, "I have reviewed the enclosed clinical amendments and agree that there is no evidence of significant toxicity from dexfenfluramine. We have completed a study of DL-fenfluramine in children with similar findings."

That leads us to the area of Phase IV studies. At the last meeting, the Committee was interested in post-marketing Phase IV studies to look further at neuropsychological effects. While we believe the available clinical data eliminate concerns about neurotoxicity, Interneuron and our marketing partners, Wyeth-Ayerst, are nevertheless committed to doing these studies if the Committee recommends them after you have seen our data today.

Let me summarize now and give the floor over to our other speakers. By the end of this

afternoon, we hope you will agree with us on the following points concerning the most extensively studied weight loss agent in history: one, that long-term efficacy has been well-established; two, that the drug has a positive effect on co-morbid conditions, such as non-insulin-dependent diabetes mellitus and hypertension; three, that the common adverse events are mild and self-limiting; four, that serious toxicities are very rare; five, that neurochemical changes caused by high doses in animals have no clinical relevance; and, six, that the risk-benefit ratio is highly favorable.

The rest of our program for the afternoon is as follows. Dr. Rubenstein will present the co-morbidity data. Dr. Blundell will talk about preclinical neurochemistry and behavioral studies. Dr. Gammans will discuss the neuropsychological effects of dexfenfluramine in controlled clinical trials. Dr. Faich will present the risk-benefit analysis. And Dr. Marc Deitch, Vice President for Medical Affairs of Wyeth-Ayerst, will discuss Phase IV plans.

Dr. Rubenstein will now come up for his presentation. Dr. Rubenstein needs to depart shortly after his presentation. So, with the agreement of the

Chair, we'll take questions for Dr. Rubenstein on co-morbidities immediately after his presentation. And I'd ask that if FDA has any comments about the co-morbidity data, it would be helpful to make them at this time so Dr. Rubenstein can properly respond.

Thank you.

DR. RUBENSTEIN: Thank you. Dr. Bone, members of the Committee, I appreciate your forbearance in allowing me to talk today and depart not too long. I wish it hadn't been like that, but I appreciate your consideration.

EFFECTS ON CO-MORBIDITIES:

DR. RUBENSTEIN: The issues which I will address this afternoon are listed in my first slide. I'm going to discuss the data that's available on obese hypertensive patients, obese diabetic patients, and obese dyslipidemic patients. These are patients who are obese with these co-morbid conditions.

The potential importance of the use of dexfenfluramine in the management of obese non-insulin-dependent diabetics is based on a number of premises, the most important of which is that weight reduction will improve the degree of diabetic control. There are many studies in the literature which support this conclusion, and I have chosen but

one for purposes of illustration this afternoon.

In 1986 Henry and others in Diabetes Journal studied a number of obese non-insulin-dependent diabetic patients before and after they had lost a mean of 16.8 kilograms over a period of 60 to 380 days.

This slide, taken from the article, shows a very significant reduction in the fasting and post-glucose, plasma glucose levels after weight reduction, before and after. The panel on your right indicates that there was a small improvement in the insulin secretory capacity.

It is interesting to note that these subjects remained obese, despite their significant weight loss. And, yet, the improvement in the blood sugar levels was substantial, the point being that you don't have to go back to normal weight to show an improvement in blood sugar in obese non-insulin-dependent diabetics.

The second premise that I would like to draw to your attention is the relationship of overall blood glucose control and diabetic complications. The conclusions of the diabetes control and complications trial, a prospective, controlled intervention trial in Type I diabetic patients, were that there was a direct

relationship between the blood glucose level and the risk of complications in diabetes.

Although not conclusively proven as yet, most authorities believe that the effects of better control of blood glucose will also apply to patients with non-insulin-dependent diabetes as well. The eye, kidney, and nerve abnormalities appear quite similar in IDDM and NIDDM. And it is likely that the same or similar underlying mechanisms of disease apply.

A recently publication by Perlenski and others in the New England Journal is interesting in this regard and came to somewhat different conclusions in regard to the relationship of the overall blood glucose level in diabetic nephropathy, again in patients with IDDM. As can be seen in this figure, their findings indicate the possibility of a threshold for glucose level, as marked by the hemoglobin A1 percentage, below which nephropathy was much less likely to occur.

The value corresponded to an average blood sugar of about 200 milligrams percent. The implications of these results are that modest reductions in blood glucose levels may have important effects in minimizing the development of diabetic complications. These are important ongoing areas of

research, but I think the findings have revolutionized ideas in terms of how aggressively we should treat diabetic patients.

I will now review the results in which dexfenfluramine has been used to enhance weight loss in non-insulin-dependent diabetic patients. Dr. Lutwak's analysis of several of these manuscripts was made available to me. Basically, I do not have a substantial disagreement with these conclusions.

The studies were generally of short duration, about 12 weeks, and enrolled a relatively small number of subjects. In some studies there were differences between the dexfenfluramine group and the placebo subjects. Nevertheless, I do believe that it is quite reasonable to draw several important conclusions from these publications.

Stewart, et al., studied 40 patients with NIDDM over a 12-year period. These results are summarized in this slide. During treatment, the dexfenfluramine group showed -- you can see them listed here -- a greater weight loss than placebo, a greater decrease in hemoglobin A1C, a greater decrease in fasting blood sugar, a greater decrease in triglycerides, and no change in their cholesterol or blood levels. All of the first few that I mentioned

were statistically significant.

In 1992 Wiley and others in a publication in Diabetic Medicine enrolled 34 patients in a 12-week study. Their findings are summarized in this slide. They showed that there was a significant decrease in weight loss, a significant decrease in fructosamine, in hemoglobin A1C, and in systolic and diastolic blood pressure. And all of these changes were greater than in the placebo group.

An additional study by this group, by Wiley and others, in Diabetic Medicine in 1994 investigated 20 obese non-insulin-dependent diabetic patients poorly controlled on metformin and insulin. The group given dexfenfluramine had a significant decrease in the hemoglobin A1C from 8.5 to 7.1, a change in 1.4 percent, while those in the placebo group did not change.

The decrease in their hemoglobin A1C was associated with weight loss, although as a total group, the changes in weight and BMI were not statistically significant. So the point in this group was that the change correlated with the group who lost weight.

The results in the hemoglobin A1C are summarized in this slide. These are the three studies

I mentioned to you, two by Wiley at different times and one by Stewart.

As you can see, these are changes in hemoglobin A1C. In each, the group on dexfenfluramine dropped their A1C significantly more than the control group. And these changes were quite significant and of a clinical significant nature.

Now, the recent publication by Manning and others in Diabetic Medicine in 1995 is of particular interest in my opinion. They compared four weight reduction strategies in the diabetic population who previously had shown little motivation to lose weight. There was a large study, and 159 patients were randomly assigned either to regular clinic visits; a behavioral therapy group; dexfenfluramine, 30 milligrams a day, but only for an initial 3 months of this 1-year study; or a clinic and home visit group.

At three months the best weight loss occurred in the dexfenfluramine group, which is not shown on this slide. At 12 months the weight loss in the 4 groups was similar but contrasted with a 1.2-kilogram weight loss in the controls.

Most interesting, the decline in hemoglobin A1C at three months, which is shown on this slide, was 0.57 percent in the dexfenfluramine-treated

group vs. lower amounts in the other groups. That's shown here in blue in the clinic group, the behavioral treated group, and the home and clinic visit group. In comparison, the dexfenfluramine group was greater than all of these.

At one year there wasn't a difference, but the investigators chose, as I stress, to discontinue the drug at three months as part of their protocol.

I will now briefly mention several studies that measured blood lipids and blood pressure before and after the administration of dexfenfluramine. The index study, which is well-known to you in your packets, is most important in this regard.

In a 6-month and 12-month post hoc subset analysis for patients with moderately elevated cholesterol levels, that is about 6.1 millimoles per liter, shown here at the beginning of the study. There was a greater force in the dexfenfluramine-treated group at both 6 months and 12 months. At the beginning there was no difference, and these are the changes at 6 months and 12 months in the dexfenfluramine group compared to the placebo randomized control.

In those studies or in this index investigation with a baseline sitting or supine

diastolic blood pressure of greater than 90 millimeters of mercury, there was a fall in the blood pressure during the treatment with the drug, which was maximum at one month and then continued unchanged thereafter for the 12-month, as noted in the slide, with significantly different degrees of fall compared to the placebo-treated group at each of the times over the 12-month period.

Now, in a three-month study by Kolanowski and others published in the European Journal of Clinical Pharmacology involving obese hypertensive patients, the dexfenfluramine-treated group lost more weight than the placebo group. And both their diastolic and systolic blood pressures fell greater than the placebo group at one month.

The reason I picked out this study to show you is that the norepinephrine levels measured in a variety of ways were lower in the dexfenfluramine-treated group than in the controls. This represents a marked difference from amphetamine-like drugs, which dexfenfluramine, of course, should not be confused with.

What conclusions are reasonable to draw from these post hoc subset analyses in the long-term index study cases and the short-term studies, some of

which I've reviewed, but there are more, in fact, in the literature?

These are the conclusions that I think are really reasonable. There is no evidence that dexfenfluramine treatment adversely affects diabetic control, lipid concentrations, or blood pressure. This would be an important negative effect of the drug. And I looked hard in all the published literature for that. And I came to the conclusion that there was absolutely nothing in this regard of concern.

The data are suggestive of favorable effects on diabetic control, lipid concentrations, and blood pressure. And I outlined to you the reasons that I drew that conclusion.

Some of the studies are short-term, but all the responses were in the correct or in an appropriate direction. And it would be reasonable later to study these things longer, but I think the favorable effects are seen clearly in the studies that have been published.

And then dexfenfluramine is an effective weight-losing agent in patients. And this does not defend those with co-morbid conditions. Thank you.

What I would like to do, with the

permission of Dr. Bone, is ask any questions for me at this time, which I would appreciate.

CHAIRMAN BONE: Yes. Are there questions from members of the Committee for Dr. Rubenstein? Dr. Marcus has a question.

DR. MARCUS: I'm curious as to whether the lipid-lowering effect follows, as you would predict, from the weight loss or is there any reason to believe that there might be an independent lipid-lowering action of this drug?

DR. RUBENSTEIN: There are a number of very short-term studies on weight-maintaining diets that show some reduction in lipids. Most of them are very short, over a period of a month or some even shorter. So the fact is there is suggestive evidence.

There is also some suggestive evidence in animals of increased fatty acid turnover and oxidation that may lead to this. I think in longer-term studies, those data, at least in my analysis, are not available.

CHAIRMAN BONE: Other questions or comments from members of the Committee? I have one, Dr. Rubenstein, and I'd like to be very specific here.

DR. RUBENSTEIN: Sure.

CHAIRMAN BONE: Did you find in long-term

studies direct evidence of a reduction in co-morbidity or co-morbid conditions for sequelae as a result of drug treatment?

DR. RUBENSTEIN: Well, in the one-year index study, there was a significant fall in the blood cholesterol and blood pressure. And it seems to me that those two are very, very important morbid conditions that are well-established to cause morbidity and mortality. So those --

CHAIRMAN BONE: Are those specifically in hypertensive or hyperlipidemic patients?

DR. RUBENSTEIN: Yes. In those two specifically, that's how the analyses were done.

CHAIRMAN BONE: Okay.

DR. RUBENSTEIN: Those were important, if I could just comment, because there was the question, I think, whether in those people there was an increased risk of giving a drug like this. And, yet, the data turned out that there was an improvement in these parameters over one year.

CHAIRMAN BONE: Thank you.

Dr. Critchlow?

DR. CRITCHLOW: Yes. Can I interpret, then, from the answers to the previous two questions that if you compare the responders to the

non-responders, is there a greater reduction in the co-morbid conditions in the responders than the non-responders?

DR. RUBENSTEIN: I think I would need some help in absolutely answering that question. You're talking about in the index. These were all analyzed together. And I think I'd need some help from the company whether I'm giving the right answer to that specific question. Can somebody help me?

DR. SANDAGE: I'm not sure I understand the question of the responders, Dr. Critchlow.

DR. CRITCHLOW: My interpretation from the data presented to us was that there was a relatively modest change in, for lack of a better term, the co-morbid, the cholesterol or whatever, when looking at the drug versus placebo.

My question is: If you compare those that responded with a greater than 10 percent weight loss versus not, was there an equally comparable reduction or a greater reduction in, for example, cholesterol or blood pressure among those that responded? Is there a greater difference between drug and placebo in that group versus --

DR. SANDAGE: I understand now. We didn't do an analysis looking at those patients, 40 percent

that lost more than 10 percent. The way that we did the analysis was identify patients at baseline as having either elevated cholesterol or elevated blood pressure. We didn't look at the subset, 40 percent, that actually had --

CHAIRMAN BONE: Dr. Rubenstein, again, what was the actual magnitude of the difference in blood pressure change between the placebo and the treatment groups?

DR. RUBENSTEIN: On that group there?

CHAIRMAN BONE: Yes, in the index study.

DR. RUBENSTEIN: Bobby can help me. I think it was of the order of 10 -- we can put it up -- 10 millimeters of mercury.

CHAIRMAN BONE: Difference between groups?

DR. RUBENSTEIN: Second to last slide. We can look. Next one. Next one. Here and here you can see it's --

CHAIRMAN BONE: About four millimeters? Is that about right?

DR. RUBENSTEIN: About five.

CHAIRMAN BONE: Four to five millimeters? Is that correct? Four to five millimeters. And the difference in the -- that's only total cholesterol that was measured. Is that right?

DR. RUBENSTEIN: Yes.

CHAIRMAN BONE: And what was the magnitude of that difference?

DR. RUBENSTEIN: Then we go back to that slide, one back.

CHAIRMAN BONE: And that was about half a millimole, which would be about 20 milligrams per deciliter?

DR. RUBENSTEIN: That's correct.

CHAIRMAN BONE: And that was not fractionated?

DR. RUBENSTEIN: No.

CHAIRMAN BONE: So we don't know how much of that was LDL and how much was HDL?

DR. RUBENSTEIN: No. It wasn't included in the study.

CHAIRMAN BONE: Thank you.

Are there other questions? Dr. Sherwin?

DR. SHERWIN: Arthur, two questions. One relates to impression of response in people with diabetes in terms of weight loss now. Is the weight loss response the same or less in people with diabetes compared to people without diabetes? Is there any sense of that from the pieces of data you have?

DR. RUBENSTEIN: Well, I don't know of a

specific study in that. The data that I'm aware of in diabetes is that less than 15 percent of people at most respond adequately to diet in terms of weight loss. And usually it's between 5 and 10 percent.

Whether in non-diabetic individuals those percentages are different, the best I can tell from the literature is not so different. But I've never seen a comparison along the lines you're asking.

DR. SHERWIN: Equivalent to drug? You're talking about to drug?

DR. RUBENSTEIN: No. I'm talking about --

DR. SHERWIN: No. I'm talking about to drug. In other words, --

DR. RUBENSTEIN: You're asking me if --

DR. SHERWIN: -- my impression was that weight loss response tended to be a little less perhaps in the diabetic patients compared to the non-diabetics. But I don't know if my impression is valid or not valid.

DR. COOPER: I think the sample sizes are, as you can see, relatively small in tnese studies, but overall there was really no significant difference in the magnitude of weight loss seen in the diabetic sub-population than with the non-diabetic sub-population.

DR. RUBENSTEIN: Certainly at three months in those studies that were done, it did not look different to me.

DR. SHERWIN: Okay. The other question relates to the fact that this drug affects serotonin and CNS. Has anybody looked at steroid production in these people since manipulation of serotonin might impact on steroid production and excretion and that could ultimately impact on morbidities?

DR. RUBENSTEIN: I didn't see that in all the papers I reviewed. So I'd be happy if anyone in the company has that data.

CHAIRMAN BONE: Dr. Cara?

DR. CARA: Dr. Rubenstein, I'm having some trouble with the notion of short term versus long term. And the problem I have having is that to a large extent several studies that have been done short term show a significant benefit; whereas, long term there is a tendency for those kinds of effects to ultimately wash out.

And if you look at the slide that you showed regarding glycohemoglobin levels in patients with diabetes treated with dexfenfluramine, that certainly is suggested by your rebound effect. Is that at 12 months? Could you show that slide?

DR. RUBENSTEIN: The Manning data? The Manning data? What Manning did was he treated a number of groups. He used dexfenfluramine for three months and then stopped using it --

DR. CARA: Right, right.

DR. RUBENSTEIN: -- and then just continued that group. At 12 months there was no difference. At three months there was a big difference.

DR. CARA: Right. But if you look at the other therapies, there was also an effect initially that tended to wash out by 12 months of therapy.

I guess the question that I had since we're considering long-term therapy is whether or not you have any personal experience in terms of long-term therapy with dexfenfluramine. And if you have anything to share in that regard, I would appreciate it.

DR. RUBENSTEIN: No, I don't have any personally. I reviewed the literature that was available. As best as I can tell, this drug has not been studied for a 12-month period in terms of diabetic control. It has been in terms of lipid values and blood pressure. And the studies I reviewed are three-month studies that are in the literature in

terms of diabetic control.

There is no reason for me to -- and this is a personal opinion -- think that if weight reduction continued, that there wouldn't be a continued enhancement in the drop in the hemoglobin A1C.

The question comes again to the improvement of insulin sensitivity for weight loss and whether one can hope that such a thing would continue. I think there is not data that says it one way or the other, in direct answer to your question.

CHAIRMAN BONE: Thank you.

Other questions from the Committee members, any comments immediately, or the FDA?

DR. LUTWAK: I tend to agree with Dr. Rubenstein's final conclusions, last slide.

CHAIRMAN BONE: Thank you. All right.

DR. RUBENSTEIN: Thank you. I appreciate that.

CHAIRMAN BONE: We've completed the first part of the company's presentation. We've used actually an hour and five minutes of the original hour that was planned for the company's presentation. So we're going to have to be very concise from here on out in order to cover the topics and complete in a

timely way.

We had originally planned to have a break at this time, at 3:30. I think the alternatives are either to complete the company's presentation, then have the break, and then go ahead with the FDA.

Wait. Excuse me. One other question. Did Dr. Illingworth have any questions for Dr. Rubenstein?

DR. ILLINGWORTH: No. Basically, I have the hard copy of the graphs in front of me. So I was following those here.

CHAIRMAN BONE: Good. Thank you.

DR. ILLINGWORTH: No. I think the information is clear to me. I think we just need more long-term safety data and current long-term efficacy data to see what happened to the one and two years.

I'm impressed by the 3-month data, but that's 3 months, not 12 months or 2 years.

CHAIRMAN BONE: Thank you. Okay.

I think we'll go ahead and finish the company's presentation and take the break immediately afterwards.

DR. BLUNDELL: Can I just check that you can hear me because I usually have a rather soft voice? Can you hear me at the back? Yes? Okay.

Thank you.

NEURO ISSUE:

PRECLINICAL DATA:

DR. BLUNDELL: Dr. Bone, members of the Committee, I'm here this afternoon to review information on long-term neurochemical change in animals.

By way of background, I can mention that I'm from the University of Leeds in United Kingdom. I do have a longstanding interest in anti-obesity drugs and have conducted research under grants awarded by a number of companies in the field, including Lilly, Connaught, Servier, and Astra. I've also acted as consultant for each of these companies as well as for Procter and Gamble, Unilever, and others. And I'm also carrying out research for the U.S. government and for research councils in the United Kingdom.

Much of my work has concerned the relationship between nutrition and 5-HT; that is, serotonin. And I followed this issue of neurochemical changes for a number of years. And I believe that what I will say will not stop investigators discussing this issue, but I hope to clarify some of the issues so that we can feel that we understand what is important and what is not important.

I should mention that I was present as an observer at the meeting on September 28 of this Advisory Committee. And I do confess to being somewhat perplexed at the end of that afternoon because I felt that a true picture about this drug had not emerged. This afternoon I believe this will be corrected.

When I reviewed the transcript of the September 28th meeting, I discovered the reason for part of my confusion. Much of the case built up against dexfenfluramine by the outside guest speakers on this topic was based on the argument that dexfenfluramine is typical of the class of serotonergic neurotoxicants, including PCA, MDA, and MDMA, parachloroamphetamine, methylene dioxyamphetamine, and methylene dioxymethamphetamine.

The outside guest speakers presented evidence for PCA and MDA and argued that this would naturally also be true for dexfenfluramine. In fact, much of the material presented by one of the outside guest speakers was not about dexfenfluramine at all, but the impression given was that it all referred to dexfenfluramine.

This slide shows just some of the examples of this form of argument taken from the transcript.

First, we have not studied this with fenfluramine, but we think that it is likely to be very similar.

Second, while we have not done exhaustive studies on fenfluramine, the effects of fenfluramine are essentially identical to those of PCA. And we have observed this with PCA and MDA and almost complete loss of retrograde axonal transport in the raphe neurons, a very damaging finding. We have not studied this with fenfluramine. And I could also have added the effect on neurological tangles that was shown for MDA, but not observed with dexfenfluramine.

I got the impression from this information on PCA and MDA that it also applied to dexfenfluramine. And, apparently, Mrs. Mackaphee was also misled because she left the meeting believing that comments about the swollen tangles applied to dexfenfluramine. It did not. It was demonstrated for MDA. And this is on Page 202 of your transcript. This is one of the reasons why I felt that a true picture had not emerged last meeting.

Indeed, when we examine markers for specific neurotoxic effects, silver staining, increased GFAP, retrograde transport, it becomes clear that there are big differences among these serctonergic compounds and dexfenfluramine and also

between dexfenfluramine and the 5HT neurotoxin 5, 7 - DHT.

Now, this slide summarizes much of the work in the scientific literature that shows when you examine these other compounds using generally well-accepted measures of neurotoxicity, you see that they get positive results; whereas, dexfenfluramine does not.

I did consider showing you summary charts of these data and photographs of rat brains to more fully visualize this, but the time is too short. I want to just note two of these findings.

First, the FDA asked the sponsor to conduct this retrograde transport study with dexfenfluramine in order to assess the functional integrity of the axons. The FDA assisted in the design of the study, including the recommendation for positive control, PCA, to be added.

The FDA expressed confidence at the time that if this study came out negative, the matter of possible neurotoxicity may be settled. The sponsor did the study. The results were negative.

Second, particular consideration should be given to GFAP because this indicator of neurotoxicity was developed in part by the EPA and is recommended by

the EPA in their neurotoxicity testing guidelines.

Furthermore, work done by the EPA's own scientific staff, which we actually heard already this afternoon, has failed to demonstrate any action of dexfenfluramine on GFAP. Therefore, all of these compounds which do influence brain serotonin also produce changes in the widely agreed markers of neurotoxicity. Dexfenfluramine does not.

Indeed we almost certainly know the reasons for the differences in neurotoxicity between dexfenfluramine and these other compounds. The neurotoxic effects of these other drugs likely depend on the involvement of dopamine.

Even further evidence against the idea that all of these compounds can be uncritically lumped together comes from looking at how these drugs are used in humans.

For example, MDA and MDMA are the so-called designer or street drugs which are known as Adam or Ecstacy. They produce a characteristic mental activation, psychological effects, accompanied by hyperthermia. These are drugs of abuse. Dexfenfluramine produces none of these effects. And it produces hypothermia. And it is not a drug of abuse.

Let's go now to the reduction in brain serotonin levels, which is important in interpretations about neurotoxicity. How should this reduction in brain serotonin be interpreted?

The way in which the studies on animals are being carried out is critical. First, the most severe reductions of brain serotonin have been shown with a particular dosing regime which is not related to the clinical manner of drug delivery.

This peculiar regime involves twice daily dosing for four days only and no more. This pulse dosing is quite unlike the clinical use of a drug which involves continually daily administration.

Second, the change in the food consumption, which naturally accompanied administration of dexfenfluramine, -- indeed they are its main effect -- have never been taken into consideration when evaluating the effects of dexfenfluramine on brain serotonin.

Now, in this slide we see the effects on brain serotonin when a drug was administered in a gradually increasing regime from one to 10 milligrams over 28 days. We see that after the drug has been discontinued at this point here, there is a fall in brain serotonin consistent with the pharmacological

action of the drug. But this decrease rapidly, though, turns to baseline values and stays there.

In passing, I can note that the first regime would produce much greater decrease in brain serotonin. And it would stay down.

The other major feature of these studies concerns the effects of food reduction itself. And this slide also shows the effect on brain serotonin of a group of animals pair fed to the drug-treated rats.

Now, the pair fed rats received the same amount of food consumed by the drug-treated animals on a day to day basis. What would be surprising to many people is the observation that food restriction itself caused a decrease in brain serotonin, which, however, did return to baseline values and at this point here was not significantly different from the drug-treated rats.

Now, at this particular point there was no difference in the brain levels of serotonin in those animals which had received the drug and those which had never received the drug but had experienced a similar reduction in food intake.

And it's interesting to note that 5HT serotonin reduction is apparent for some time after food restriction had ceased and then comes back to

baseline. This is an important finding that has never been taken into account by any investigators who looked at the effects of dexfenfluramine on brain serotonin.

Now, scientists who work in regulatory physiology -- I include myself here -- will, of course, be familiar with pair feeding and the need to include it as a control procedure. Apparently it is not recognized by many in the field of animal neuroanatomy.

Indeed, if we examine the scientific literature, we can find that it is rather well-established that food consumption is related to serotonin activity in the brain.

For example, 20 years ago Gerald Curzon at the Institute of Neurology in London showed that food deprivation in rats increases serotonin release and lowers serotonin levels in the brain.

Second, and more recently, Neil Rowland showed that lean mice had significant lower brain cortex serotonin levels than obese animals eating more energy. And I don't think that we would wish to argue that these lean mice are showing signs of neurotoxicity.

In addition, two weeks of food deprivation

in rats reduces paroxetine binding by 32 percent. Now, this is particularly interesting because paroxetine binding is the technique used to measure the serotonin transporter, sometimes called the serotonin uptake mechanism.

Paroxetine binding has been used as an indicator of neurotoxicity. But, just as reductions in brain serotonin alone are not an indicator of neurotoxicity, it's obvious that neither is paroxetine binding alone an indicator of neurotoxicity.

And, finally, here there are now a number of studies showing that dieting in humans lowers plasma tryptophan and upregulates serotonin 5HT-2C receptors in the brain.

Taken together, these data indicate that brain serotonin levels and other serotonin markers are influenced by change in food consumption. This appears to be a natural adaptation of the brain to changes in supply and nutrients required for serotonin synthesis.

As far as I am aware, these effects have never been taken into account by any investigators in interpreting the effects of dexfenfluramine on brain serotonergic markers.

I want now to turn to those specific

studies undertaken in response to recommendations by the FDA. As you know, for a number of years, the sponsors have been working in collaboration with the FDA on a number of investigations that could answer the question of whether dexfenfluramine is associated with neurotoxicity.

The first recommendation shown here was for a study of dexfenfluramine on retrograde transport. In an earlier slide, I referred to the results of this study, which showed that dexfenfluramine had no effect on retrograde transport, while the positive control recommended by the FDA, namely PCA, did show adverse effects.

The second recommendation was for a study designed to determine using a battery of FDA-suggested tests whether there are any long-term adverse effects.

The third recommendation was for the calculation of the brain concentration of the drug in humans using the most sensitive and advanced technique available.

And the fourth recommendation was to calculate exposure margins using the human brain correlations. And it's these last three studies that I want to turn to.

The long-term study involved the

administration of a number of doses of dexfenfluramine from 2 milligrams up to 16 milligrams per kilogram, again including pair fed controls. And the animals are being followed for one year after 21 days of dosing.

At the present time the six-month results are available. And these interim results are consistent with the absence of neurotoxicity. Now, this study has yielded a large amount of data, more than can be presented here. I've got time to discuss only two aspects.

This slide shows measures of serotonin cell bodies. And in the table we can see that exposure to dexfenfluramine, even at high doses, 16 milligrams per kilogram per day, shows no change in neuronal cell number when compared with saline-treated controls, either at one week or 6 months after treatment had ended. And none of these values here is statistically significant from the control value. And this shows that there is no delayed effect of dexfenfluramine on serotonin neurons long after the end of dosing.

Now, this study was also designed to measure the effect of these doses of dexfenfluramine on brain serotonin levels. As Dr. Cooper has already

mentioned, even by 13 weeks after treatment, the 8-milligram per kilogram dose, showed no change in brain serotonin compared with the pair fed control. Therefore, this is a dose that can be used as the no-effect level for calculating exposure margins for serotonin reduction. I'll come back to this in a moment.

First I want to describe the study that was set up in response to the third FDA recommendation. That is to measure the concentration of dexfenfluramine and dexnorfenfluramine, its metabolite, in the human brain.

Eleven obese patients were given the drug, 30 milligrams per day, the usual therapeutic dose, for 90 days. The technique used to measure brain levels was a magnetic resonance spectroscopy, MRS, also known as NMR.

We can see four features of the study in this slide. First, brain concentrations reach a peak value after 10 days, consistent with the known half-life of the drug. Second, thereafter, a steady state was maintained for 90 days, indicating no accumulation of the drug in the human brain. Third, there was very low variability between the patients. And, fourth, these levels are well below those which

cause serotonin changes in animals.

However, the MRS provides only an estimate of the level of drug in the brain. In order to validate this assay method, MRS, it will be necessary to kill the patients and directly measure the drug in the brain and compare it with the MRS values.

This clearly cannot be done. Therefore, validation was carried out using three rhesus monkeys in order to compare the MRS values and the actual measured values following postmortem analysis.

It was found that the MRS overestimated the brain levels. Therefore, a correction factor was calculated taking into account the overestimation. And this is shown here in the lower line. And it accounts for the overestimation of brain levels by the MRS technique. These values, therefore, give the upper and lower limits of brain levels of dexfenfluramine plus dexnorfenfluramine.

Now, with this information on brain levels in humans, it is possible to go on to calculate exposure margins. The exposure margin is the difference between the brain level, which would normally be attained in humans, and the highest brain concentration in animals, which produces no effect on the particular biomarker of interest. This is the

no-effect level, or NOEL.

We see here the NOELs for various biomarkers listed. The values indicate the number of times that the brain levels in animals are greater than the brain level in humans, yet still produce no effect. The higher and low values here represent the calculations based on the upper and lower limits seen in the MRS study.

Now, overall these data mean that no effect can be detected in animals, brain drug levels between 10 and 48 times the brain levels attained in humans.

Up to now I've been considering neurochemical or morphological markers, but personally I would argue that equally important are those changes which may occur in behavioral functions.

Now, we do know that in research funded by NIDA, a strenuous effort was made to demonstrate functional impairment in rats following the unusual high-dose regime to which I referred previously. Results from those experiments are shown in this slide.

As you can see, no persistent changes were observed for exploratory behavior, motor coordination, stamina, defensive behavior, one and two-way

conditioned avoidance responding, spatial memory for doses between 5 and 10 milligrams per kilogram per day. These changes are observed at eight weeks following treatment.

Now, these measures are ways of measuring the capacity of the animals to respond appropriately or intelligently when the environment is deliberately made unfamiliar, challenging, hostile, dangerous, or difficult to remember. They are, in fact, practical tests of the capacity to perform. And the drug produces no impairment of these capacities.

In addition, in two studies involving primates, no persistent effects of fenfluramine were seen following dosing of up to 10 milligrams per kilogram per day for up to 70 days.

Now, in summary, I feel that a number of conclusions can reasonably be drawn from this presentation. And I've actually tried to be brief to make up some time.

First, dexfenfluramine is different from PCA, MDA, and MDMA as assessed by accepted specific indices in neurotoxicity.

Second, reduction in serotonergic markers alone is not indicative of neurotoxicity. And we know that it can occur with changes in food consumption.

Third, there is no evidence of cell loss or neuronal regeneration, even at high doses.

Fourth, the exposure margin is large based on brain levels in animals which are unobtainable by the patient at normal therapeutic doses. And there are no persistent adverse functional behavioral effects in animals.

Now, having been asked to review and present this information, it is probably the case that there are a number of interesting data of the investigators still to be had regarding the outcomes of specific studies and specific conditions. But it strikes me, no matter how you interpret the outcome of animal studies, there is a large enough exposure of margin and enough information available in humans to be able to evaluate the drug on the basis of human data.

I will now ask Dr. Gammans to describe the assessment of behavioral and cognitive effects in humans.

DR. GAMMANS: Thank you, Professor Blundell and members of the Committee.

CLINICAL NEUROPSYCHOLOGY:

DR. GAMMANS: Up until now the focus of our discussions on serotonergic neurotoxicity have

been the interpretation of findings in animals and their implications for human use. And, as you have heard, this debate has continued with respect to fenfluramine for at least 20 years.

I'm sorry. I guess I should stop and reintroduce myself. I thought Professor Blundell had done that. Dr. Richard Gammans, Vice President of Clinical Research at Interneuron. I assumed you knew that part.

As I said, this debate has continued with respect to fenfluramine among preclinical neuroscientists for nearly 20 years. And it is notable that despite the controversy about the interpretations of the preclinical findings, there have been no indications of adverse neurobehavioral effects of dexfenfluramine in man.

I will now summarize the findings from a medical and safety review of the clinical, behavioral, and cognitive testing data collected during therapeutic trials with dexfenfluramine.

The conclusions from this review, I believe, are clear. There are no indications that there are important clinical adverse neurobehavioral effects of dexfenfluramine in man when used as indicated to treat obesity.

Next, please. Most of the data were collected in 16 trials concluded in NDA 2344, which was submitted in May of 1993. And, in addition, one new study of six months' treatment duration with 12-month placebo follow-up phase was ongoing at the time of the submission has been completed and was included in the review.

The psychometric data from this study, some of which was mentioned briefly at the last meeting, have now been completely analyzed and recently submitted to FDA. And I will refer to this study as the Noble long-term study. Ratings were prospectively defined in these studies as safety or efficacy outcome measures.

We have summarized all of the neuropsychological testing data in response to the Committee's request during our September 28th meeting. That summary was included in your yellow briefing document.

As part of the review of the neuropsychological data, a panel of reviewers who are experts in neuropsychopharmacology who were not involved in the original NDA submission were engaged. Dr. Cooper quoted some of their comments earlier. They, like the FDA's reviewer, have independently

concluded that the data that I will summarize for you today indicates no evidence of adverse neuropsychological effects in man.

They include prominent neuropsychopharmacologists, neurologists, and clinical neuropsychologists, experts in the areas of interest for the review. Three of them, Drs. Robinson, Shouldson, and Coccaro, have served in roles like yours and are current or past members of an FDA advisory committee within the Neuropharmacologic Drug Products Division. Professor Lader has served a similar role in the U.K.'s Committee on Safe Use of Medicine. Drs. Robinson, Coccaro, and Spiers are here today if you have questions of them.

The focus of our review was clinical signs of altered serotonergic function. The reason for this focus is the assertion that dexfenfluramine and fenfluramine are specifically toxic to the serotonergic neuronal plexus of the CNS. And, therefore, the review and my presentation are organized around symptom complexes that it is postulated would have been affected by a change in serotonergic function.

Appetite, mood, or emotion, and suicide are strongly linked to altered serotonergic function

and are a focus of the review. Appetite is reduced while on dexfenfluramine.

If serotonergic function were decreased, cravings, particularly carbohydrate cravings, post-treatment would be predicted. However, the strongest link, as has been mentioned previously, between serotonergic function is to that of depression and to suicidal behaviors.

If dexfenfluramine decreased serotonergic function, we would expect to see evidence of substantial numbers of depressed patients or an increase in reports of suicidal behaviors. Other behaviors and symptom complexes are also affected by serotonergic drugs. These would include effects on sleep, on cognitive function, or peripheral effects.

Initially I'll review the clinical findings that pertain to each of the symptom complexes. Because of the large amount of data, I have selected studies with the longest duration of treatment or follow-up for presentation. Following that, I will present the psychometric findings from the Noble long-term study that were briefly mentioned previously.

The data are extensive that are included in this review. Over 1,300 dexfenfluramine-treated

patients and 1,000 placebo-treated patients were evaluated across the 17 trials, which included 9 weight loss studies, 4 clinical pharmacology studies, and 3 studies of therapeutic effects and other disorders plus the Noble long-term study. In each case, the rating instruments were included prospectively as defined safety or efficacy outcome measures for the effects of dexfenfluramine on behavioral or psychological function.

To supplement these findings, the conclusions from the psychometric tests were compared to adverse experience reports and the post-marketing safety database to assure agreement between the two types of assessments. And, finally, 55 published reports, human data on dexfenfluramine or fenfluramine with psychological testing were identified and reviewed.

In addition to data from the area of obesity, there are a number of studies of the therapeutic use of fenfluramine in some troubling neurobehavioral disorders of children, including autism, Prader-Willi syndrome, and attention deficit disorder. The study mentioned by Dr. Rapoport is among these.

These reports show limited benefit of

dexfenfluramine in comparison to the comparative treatments, such as methyl phenadate, but are in concert with all the publications in showing no neurobehavioral adverse effects.

Substantial data are available for each symptom complex in terms of the numbers of patients treated, the dose and duration of treatment, and the rating instruments to be employed.

Ten of the studies that I mentioned listed here involve dexfenfluramine treatment durations of three months or longer, a treatment duration that is adequate to test tne assertions that have been made.

The treatment group sizes are in the general range that are common among psychopharmacology studies and are sufficient size to draw valid conclusions from the findings. A detailed list of the trials and the tests included was provided to you as Table 1, Page 49 of the yellow briefing document.

Summarized here are the numbers of patients with formal ratings in the clinical trials on each of the symptom complexes to be reviewed. For suicidal thoughts, the numbers referred to the numbers of patients who were rated on the Hamilton depression rating scale as to the intensity of suicidal ideations.

Validated and well-recognized instruments were used throughout. I will not summarize the details of these testing instruments, but I would be very happy to answer questions regarding any of the tests at your discretion.

The instruments for rating mood include scales that rate all the symptoms of depressive disorders and the full spectrum of mood states as rated by the instrument called a profile of mood states, or POMS. Sleep ratings included tests of sleepiness and questionnaires on other sleep parameters.

Tests of cognition are shown here. The mini mental state exam is a brief clinical evaluation often used as a screening instrument for clinical trials. The remainder of these tests are measures of specific functions related to cognition and are included, along with some of the tests on the previous slide, in neurobehavioral testing batteries developed by agencies such as the World Health Organization or divisions of the Public Health Service, to examine neurotoxic effects of chemicals.

Now I'd like to begin the review of the data for each of the symptom complexes beginning with appetite. The effect of dexfenfluramine on appetite

is well-established as presented in our last meeting and is the basis for its therapeutic effects.

As I mentioned, for our purposes in this review, the post-treatment effects are those that are of interest. Decreased serotonergic function should produce overeating or food cravings, especially carbohydrate cravings.

Post-treatment appetite ratings are available in three placebo-controlled studies. Two of the studies were of three months' duration and had a one-month follow-up period. The third study is the Noble long-term study that included a 12-month placebo substitution follow-up.

Dexfenfluramine and placebo-treated patients did not differ with respect to food preferences or appetite ratings during these follow-up periods. And, thus, there are no abnormal clinical findings that would suggest adverse neurobehavioral effects of dexfenfluramine on appetite.

Depressive disorders are closely linked to serotonergic function. Increased incidence of major depression would be expected with decreased serotonergic function. These data are from two large weight loss studies of three months' duration that included a one-month post-treatment follow-up period.

The Hamilton depression rating scale was included prospectively as a divine safety outcome measure. The scores on this rating are low, well within the normal range, and do not differ between dexfenfluramine and placebo treatment either during the treatment phase or in the post-treatment follow-up phases at any of the doses tested.

A bipatient review of this same Hamilton depression rating data revealed no evidence that dexfenfluramine patients had treatment emergence symptoms suggestive of a major depressive episode. The point of reference for you, Hamilton depression rating scale score of 18 would be a typical minimum entry criteria for an antidepressant drug trial. And patients with major depression would average values between 25 and 30 on this rating instrument.

Shown here are corresponding data from a three-month study that employed the Beck depression inventory to rate depressive symptoms. As with the previous studies, these scores are low, well within the normal range, and do not differ between dexfenfluramine and placebo treatment. As for the Hamilton depression rating scale, scores of 18 or greater would be anticipated for patients with major depression.

Depression and other mood states were evaluated in an additional four studies that used a different rating scale, the profile of mood states, or POMS.

Shown here are the data from one of those, the UK18. You may recall that UK18 evaluated six months of dexfenfluramine treatment versus placebo in the maintenance of weight loss achieved by a very low-calorie diet regimen. POMS ratings were obtained monthly.

Shown here are the scores for all the profile of mood states factors at the endpoint or the last observation carried forward data set. Dexfenfluramine-treated patients scored somewhat lower; that is, a favorable effect, on the depression factor and on the confusion factor. And a trend toward significance on the tension anxiety factor.

Similar results were obtained at all the ratings that had been collected throughout the study. These findings from UK18 are representative of the four studies that employed the profile of mood states ratings. I will review the profile of mood states score for the Noble long-term study at the end. Collectively the data on mood states, particularly on depressive syndromes, indicate a lack of adverse

clinical effects of dexfenfluramine on mood or emotion.

An issue closely related to the evaluation of mood states and depression is that of suicidal behavior and other losses of impulse control, which I'd now like to discuss. Decreased serotonergic functions and serotonergic Type II receptor numbers have been strongly associated with suicidal behaviors.

We evaluated the effects of dexfenfluramine on measures related to suicide in three ways. First, the intensity of suicidal thoughts is rated on the Hamilton depression rating scale, Item Number 3, and was not increased either during dexfenfluramine treatment or after abrupt discontinuation.

Secondly, serotonin Type II receptor numbers were measured in two clinical studies, positron emission, tomography clinical studies. No effect of dexfenfluramine treatment on receptor number was observed following a three-month treatment duration.

Perhaps the most meaningful data when it is available are the suicide report rates from post-marketing experience. And these data are shown here along with what I feel may be the most suitable

comparative data that derive from the nurses' health study, a cohort of women of similar age to the population treated with dexfenfluramine.

The data expressed here are derived from the same source as those in your briefing document, but are expressed in slightly different terms for this comparison. And, as you can see, the suicide rate is extremely low and gives no indication that dexfenfluramine is associated with increased risk for suicidal acts.

Suicidal behaviors are perhaps the most worrisome outcomes associated with a loss of impulse control. But we were, however, able to look at two additional measures of impulsivity. First we looked at the anger and hostility factor in the four studies that employed profile of mood states. The items in the anger and hostility factor include measures of both anger and of progressive impulses. No dexfenfluramine/placebo difference on anger and hostility was observed in any of the four studies.

Secondly, we evaluated impulsive response rates on the digit symbol substitution, letter cancellation, and continuous performance tests. Again, no treatment or a favorable effect were noted. And, thus, there are no abnormal clinical findings on

any of these outcome measures related to impulse control.

Next I'd like to review briefly effects on sleep. The fact that dexfenfluramine produced mild sleepiness was observed early in clinical trials. And, for this reason, sleep effects were systematically evaluated in the development program. Sleep ratings were included in 10 of the control trials.

As you recall from our last meeting, dexfenfluramine produces mild sleepiness in about four percent of patients across these trials. And these ratings confirm that dexfenfluramine produced sleepiness, but only in the early months of treatment. Sleepiness appears to resolve with continued treatment. And, importantly, no effect on sleep is observed for up to 12 months after treatment.

No difference in the insomnia report rate is observed between dexfenfluramine and placebo-treated patients. And, thus, the data suggest some mild sleepiness in association with dexfenfluramine early in treatment, but there are no other adverse clinical findings on sleep.

At our last meeting, some Committee members expressed concern about the number of reports

of memory disturbance and about the incidence of thinking abnormal. In the COSTART system, which is a standard FDA dictionary for coding adverse experience reports, any forgetfulness that is reported is coded as amnesia.

Thinking abnormal in the case of the dexfenfluramine database is primarily decreased concentration. And confusion is a complaint that is closely associated with these adverse experiences. I'd like to place these reports in some context.

Shown here on this slide are the rates in excess of the corresponding placebo rate for confusion, amnesia, and for thinking abnormal for several marketed serotonergic drugs at the recommended therapeutic doses. You'll note that the rates for these adverse experiences attributed to dexfenfluramine are low and in some instances are lower than these other drugs.

Now, the conclusion for this exercise is simply that reports of these adverse experiences which would resolve upon discontinuation of the drug, as is the case with dexfenfluramine, are not construed as neurotoxicity. Rather, they reflect the pharmacologic profile of the drug.

Clinical reports, both in practice and in

trials, are so benign relative to other CNS drugs that dexfenfluramine's effects on cognitive function have really attracted little attention by researchers in this area. However, in the interest of completeness, I will review the available psychometric data.

Shown on this slide are the profile of mood states confusion factor scores at the end of dexfenfluramine or placebo treatment across the four studies that employ this measure.

I'm showing you these data, in part, because the symptoms rated within this score of the seven COSTART with code 3 as confusion, 2 as amnesia, and 2 as thinking abnormal. There are no dexfenfluramine/placebo differences or a favorable effect on the confusion factor scores in these four independent studies of three to six months' treatment duration. There are no adverse clinical findings on the POMS confusion factor score.

Shown here are the endpoint scores for four sensitive tests of cognitive function from a study of dexfenfluramine for the prevention of weight gain in obese patients who quit smoking.

The letter cancellation test, digit symbol substitution test, continuous performance test, and simple auditory reaction time test measure specific

functions related to cognition. And at the end of five weeks of treatment, there are no dexfenfluramine/placebo differences among patients on these indices of cognitive function. Again, there are no adverse clinical findings.

Thus, we have used a variety of measures that are capable of detecting subtle decreases in specific functions related to cognition. And we have been unable to detect dexfenfluramine/placebo differences using these tests. The available psychometric data offer no evidence of the adverse clinical effects on cognitive function.

Now I'd briefly turn to the issue of peripheral nervous system's effects. Paresthesias have been reported with most serotonergic drugs. And structured neurologic examinations were performed in 470 of the dexfenfluramine and 254 of the placebo-treated patients.

No evidence that dexfenfluramine was associated with paresthesia was noted in these exams. And these findings are consistent with the adverse effects reported in the adverse experience database in which no difference between dexfenfluramine and placebo-treated patients in the incidence of paresthesias was observed.

Now I'll turn to a report of the findings of a study prospectively designed to examine the effects of dexfenfluramine on mood and on cognition in obese patients for an extended period after dexfenfluramine. The study was conducted by Dr. Rudolph Noble in the United States. And I've referred to it as the Noble long-term study to distinguish it from the earlier study.

Patients who were 25 to 75 percent over ideal weight were randomized to receive dexfenfluramine 15 milligrams b.i.d. and placebo and were treated double blind on this treatment for 6 months. At the end of six months, patients all received placebo, but the investigator remained blind as to the original treatment assignment throughout this placebo substitution period. And patients were unaware that placebo had been substituted.

The duration of this follow-up period was a total of 12 months. So the total study duration is 18 months.

Tests included those I've mentioned previously the profile of mood states for mood, mini mental state exam for cognitive function, the Center for Epidemiologic Studies, a division of NIMH, depression questionnaire for depressive symptoms

specifically, and the Stanford sleepiness scale, the results for which I've discussed earlier. These scales were administered baseline and 3 and 6 months during treatment and at the points 9, 13, and 18 months, corresponding to 3, 7, and 12 months after the discontinuation of dexfenfluramine.

The profile of mood states factor scores at the end of the 18 months for completers of both phases of the study are shown here. There are no significant differences between dexfenfluramine and placebo at this or at any time point during the study using either the observed cases or the completer data sets, as I've shown you here. These data indicate no effects of dexfenfluramine on mood states and are consistent with a lack of lasting or delayed adverse clinical effects.

Depressive symptoms were measured with the CES depression questionnaire. Data for the completers at each time point are shown in this slide. There are no dexfenfluramine and placebo differences on the CESD scores, either during treatment or in the 12-month post-treatment evaluation period. For your reference, scores on the CES questionnaire 20-item version would average about 35 in patients with major depression diagnosed by interview.

Cognitive function was measured with the mini mental state exam. And shown here are the scores, again, for the completers at all visits. Scores for all patients were well above 25, well within the normal range, and did not differ for dexfenfluramine or placebo-treated patients, either during treatment or in the 12-month follow-up period for either the observed cases or completer data.

The conclusions from this study are that dexfenfluramine did not adversely affect mood, depressive symptoms, or cognitive function on treatment. And there were no changes on any parameter in the post-treatment follow-up evaluations.

Weight loss, a secondary outcome to this study, was similar to that seen with other dexfenfluramine weight loss studies. And medication compliance estimates were in excess of 90 percent during the 6-month treatment phase.

In summary of this review, an extensive medical and safety review of the available clinical neuropsychological testing data was undertaken specifically to look for clinical signs of decreased serotonergic function in man. Dexfenfluramine reduces appetite on treatment, but no post-treatment effects could be discerned.

The main outcomes postulated to be a consequence of decreased serotonergic function are a marked increase in the incidence of depressive syndromes or an increase in the incidence of suicidal behavioral reports.

There is extensive and persuasive evidence that neither of these effects are associated with dexfenfluramine treatment. And, similarly, dexfenfluramine treatment does not have remarkable effects on sleep control, cognition, or appear to produce seizures.

From this review, we find no evidence of adverse clinical neurobehavioral effects using a variety of sensitive and well-recognized clinical instruments in 17 studies that involved over 1,300 dexfenfluramine-treated patients. These clinical findings give no indication of serotonergic neurotoxicity in man.

Thank you for your attention. I believe I'll turn to Gerry Faich at this point. Dr. Gerry Faich will discuss refinements of risk-benefit analysis.

CHAIRMAN BONE: I think the sponsor suggested we have questions at this point. I think what we'll do in recognition of the fact that we're

far over the originally allotted time -- the sponsor has indicated that the last three presentations will be abbreviated. I just think it would be, in keeping with the original understanding with the sponsor to allow questions about the preceding presentation from the Committee if there are any at this time. Dr. Gammans?

DR. GAMMANS: Yes, sir?

CHAIRMAN BONE: Do I understand from your presentation that the only measure that you specifically looked at in the one-year study was sleep?

DR. GAMMANS: In the index study, that's right.

CHAIRMAN BONE: Yes. That's the one you --

DR. GAMMANS: Yes.

CHAIRMAN BONE: So that's the only one.

Are there others? Dr. Critchlow?

DR. CRITCHLOW: I have a quick question for Dr. Blundell.

CHAIRMAN BONE: Dr. Blundell?

DR. CRITCHLOW: Okay. This may be self-evident, but it's not to me. On your slide for the generally accepted indices of neurotoxicity when

you compared the dexfenfluramine to PCA, MDA, and et cetera, what would that data look like when looking at fenfluramine?

DR. BLUNDELL: Yes. They would be rather similar because fenfluramine has not been shown to have any effects on those specific neurotoxic indicators.

CHAIRMAN BONE: Dr. Blundell, Dr. New had a question.

DR. NEW: Professor Blundell, I have before me a paper by Molliver and Molliver which is on the anatomic evidence for neurotoxic effects of fenfluramine on the serotonergic projections in the rat. And what I see -- I'm not a neuroanatomist -- is that there seems to be depletion. Is that owed, according to you, to the fact that these rats were losing weight?

DR. BLUNDELL: That's one possibility because that has never been taken into account. And depletion does certainly occur in response to the drug. We know it also occurs in response to decreasing the food consumption.

DR. NEW: Do you think there could have been significant weight loss in two weeks?

DR. BLUNDELL: Well, there would certainly

be significant loss of food intake with that particular regime. And that would mean that there was no precursor going into the neurons while the transmitter was being released. I wonder if one of the neurotoxicologists wants to respond to this.

DR. NEW: Do you know this? Have you seen this paper?

DR. BLUNDELL: I've seen similar papers.

DR. NEW: Yes.

DR. BLUNDELL: Perhaps I could just mention that it's certainly true that, as they say, a picture is worth 1,000 words. But those pictures can sometimes be misleading. We saw some of them on the last occasion.

The issue here really is that the inferences are made about loss of structure from the absence of chemicals. These chemicals can be the transmitter itself and sometimes the trans-water and sometimes the enzyme for synthesis.

The question is: If you don't see the chemicals, is it because the structure is not there or the structure is there but there are no chemicals in it for you to see? And this is an issue which I think will remain a debate among scientists for a long time to come.

DR. CAMPBELL: As I understand that paper, the drug which was used was DL-fenfluramine at the dosage of about 14 milligrams per kilogram per day, which amounts to approximately 100 times the human exposure margin. So we're talking about very, very high levels.

What he's actually showing there is the lack of immunofluorescence, which is shown in the lack of 5HT content. He's not actually showing that there were no neurons there. This is an important factor because they do have a certain sensitivity limit.

And there have been investigators, Professor Lawrence, who have shown, for example, in monoaminoxidase inhibitors, which are necessary to actually show the levels of 5HT within those neurons, that you do have a sensitivity problem. So the fact that you can't see them doesn't mean to say they're not there.

This is the reason why the FDA had importantly asked that we look at the functional transport of those neurons. And when we do that, when you inject one part of the brain and you look at the transport of the retrograde to be labeled down to the neuron, you find that, in fact, the neurons can do that.

This simply means that, although you can't see them, the 5HT is not there. They're still functionally able to act as neurons. And, therefore, when you see these pictures, you must realize that, in fact, what we're looking at is depletion of 5HT within those neurons.

DR. NEW: And what are those neurons using for neurotransmitters at that point when they're depleted of 5HT?

DR. CAMPBELL: Well, they don't have to actually have the chemical there to actually function.

DR. NEW: I see.

DR. CAMPBELL: The fact that the 5HT is not there doesn't necessarily mean that they're not functionally active.

DR. NEW: Thank you.

CHAIRMAN BONE: Pursuant to that, are you talking, is this the Brain Research paper, Dr. New, that you're referring to?

DR. NEW: The paper I'm referring to is in Brain Research 1990. It's by Derek Molliver and --

CHAIRMAN BONE: Yes. In that same paper, they did describe swelling and other morphologic changes, which don't seem to be explainable by the absence of serotonin

DR. CAMPBELL: Yes. I mean, this is difficult quite to understand. There have been suggestions that when you release 5HT by the action of fenfluramine of the compounds, you can get accumulation around the external amount and size of the axles. And this can account for these sort of swellings.

But these swellings, although they're there, seen there within, say, up to two weeks, they do disappear afterwards. Therefore, this is not a long-term effect. This, therefore, is not really suggestive of any neurotoxicity.

CHAIRMAN BONE: But we did actually see one paper that suggested that there wasn't a higher concentration, I take it?

DR. CAMPBELL: This is micro dialysis by Sobel, which was looking at the synapses around there. I think we can carry on discussing this backwards and forwards. We're reaching the level of what we don't know. The things that we do know are what's been shown in terms of accepted neurotoxicity markers. And they're not changed.

CHAIRMAN BONE: Other questions from the Committee? Dr. Sherwin? And then Dr. Borhani.

DR. SHERWIN: In the clinical papers

because I think we want to get to the -- I don't think we're going to resole the animal data here today. There was an interesting report. And I don't know what you think of it.

There was apparently a couple of patients who developed micro infarcts in the brain and micro infarcts in the retina during clinical treatment with fenfluramine. And I just want to know what you think of that. And maybe you can tell me your sense of what that means.

DR. GAMMANS: Well, Dr. Campbell can answer that, I think would be better, because those are really --

DR. SHERWIN: Right. That's who I was referring the question to.

DR. CAMPBELL: Yes. These were two interesting observations which were found by the FDA. If you look at them very carefully, they were two young women who had developed some time after taking fenfluramine what appeared to be these small infarcts.

One woman took the drug for three weeks and then one week and then developed the problem, I think it was, something like nine months afterwards. And she was also taking oral contraceptives and other drugs, which are as likely as not to also produce

these micro infarcts.

The other lady took it on two occasions. She also had migraine and was taking migraine therapy. And it's well-known that you get vasoconstriction of pablums with this.

So these are two isolated cases. And, to be quite honest, I don't think one can make a lot from this.

DR. GAMMANS: But perhaps Dr. Campbell can correct me, but I recall that there are 14 or 16 reports of this in the literature. It happens that two of them were the ones we're talking about. The remainder had not taken dexfenfluramine, to our knowledge. That's my recollection of distributions.

CHAIRMAN BONE: Dr. Borhani?

DR. BORHANI: Yes. Thank you, Mr. Chairman.

I have a question to Professor Blundell or anybody else who wants to answer. Of all the things I have read about this going back to the clinical implication of the animal data, the asscciation with the long-term more than 12 to 13 weeks brain 5HT depletion, the clinical margin of safety at the maximum dose recommended for this drug is around 15 micromolar, if I understand it correctly.

DR. GAMMANS: Fifteen-fold, I think.

DR. BORHANI: No.

DR. GAMMANS: A multiple of 15.

DR. BORHANI: Can I have Dr. Blundell explain that and tell me? You mentioned margin of safety but didn't really explain it. And I'm confused. What is what he called margin of safety clinically at the maximum dose the patients would use if this drug is approved?

DR. COOPER: Well, let me try and give a simple answer for that. And perhaps Professor Blundell can refine it.

The margin of safety for this drug is absolutely enormous. If you look at defined classical markers for neurotoxicity, those kind of markers that everyone in the room would agree with, then the margin of safety to no-effect levels is on the order of 16 to 25-fold. That's to no-effect levels. We can't see an effect with doses in excess of 16 to 25-fold.

If you choose to look at prolonged serotonin depletion as being evidence for concern. And you've heard a lot of data that we believe strongly refutes that this is a toxicological response, as opposed to a pharmacological response. Then the margin of exposure is 10 to 20-fold or doses

on the order of 300 to 600 milligrams of this drug per day just to get to the no-effect dose.

And I think there's an overwhelming need to get back to the clinical data here, as I've heard one Committee member mention, because that really is the bottom line here.

Not only do we have the data that you saw Dr. Gammans present on 17 studies that have looked for neurocognitive, neuropsychological deficits and have failed to find at clinically relevant doses, but there is an enormous exposure history here of 10 million patients who have taken this drug, 30 million patients who have taken fenfluramine. And there has not been a single epidemiological signal that has emerged from that huge database to indicate, quote, unquote, "neurotoxicity."

Does that satisfy your need, Dr. Borhani?

DR. BORHANI: Well, yes, but I just wanted to know if that number 15, "micro M." in these books that I have read over and over again -- do you agree with it? Because that's what FDA in their review keeps saying. The margin of safety, the conclusion or finding is, quote, "15 micro M." What does that mean to me as a clinician? That's what I want to know.

DR. COOPER: Let me try and help with

that. We believe that humans based on the MRS data that we have conducted in clinical trials, collected in clinical trials, that the human brain concentrations with dexfenfluramine range from two to four micromolar, that those levels are achieved within a week or so of initiation of therapy at 30 milligrams a day, which is the clinically relevant dose, and stay plateaued at that level indefinitely. The steady state is reached. And there is no evidence of accumulation.

We have seen some assertions that levels of approximately 55 or 60 micromolar might be associated with prolonged serotonin depletion. And I think you just look at the ratio between the levels that are putative to cause problems in animals and the levels that are actually achieved in humans. And then you can get those margin of exposure ratios that we were referring to.

DR. BORHANI: Thank you.

CHAIRMAN BONE: Further questions or comments? Dr. Bilstad?

DR. BILSTAD: This is a question either for Professor Blundell or for Dr. Cooper. I believe, Professor Blundell, you made the statement that in the long-term ongoing rat study, that the no-effect dose

level for serotonin depletion is the eight milligram per kilo dose?

DR. COOPER: Perhaps I'll tackle that. I think one can choose the eight-milligram per kilogram dose as being the most conservative dosage that produces no effect since there's no serotonin depletion at any time point beyond one week.

If one picks an eight-milligram per kilogram dose in animals, then that leads to a margin of exposure of 10 to 20-fold. The 16-milligram per kilogram dosage form is also a very valid no-effect level to choose since, although there initially is serotonin depletion, there is full recovery by 6 months. If one uses that dosage, then one gets a margin of exposures from 20 to 40-fold.

DR. BILSTAD: So you're basing that on the 6-month data and not the 13-week data?

DR. COOPER: Well, I think you can take the 8-milligram per kilogram as indicative of no effect at all at a 13-week time point and get a 10 to 20-fold margin of safety or choose the 16-milligram per kilogram data at a 6-month time point and get to the 20 to 40 margin of exposure level.

DR. BILSTAD: I think that there is some margin of safety, although my understanding of the

data at 13 weeks is that, in fact, if you look at the regional serotonin depletion, there was a statistically significant difference in the hippocampus and the striatum at the 8-milligram per kilo dose. So you're beginning to see some effect on 5HT depletion at that point. That's the only point that I'm making.

DR. COOPER: Yes. I think, again, we can specifically debate that point if you like about the regional variabilities -- and I think there is some variability in the data -- or we can, again, try and take this out of the realm of trying to discuss neurotoxicity esoteria and look at the clinical situation, which I think is overwhelmingly more relevant to the situation.

DR. CAMPBELL: Just to refresh my memory, I just got the data out to make sure that I'm saying the right thing. I think you're right to a certain part, and that is when you compare it with the controls.

But I think, as Professor Blundell showed, the pair feeding also has a reduction in 5HT. And when you compare it with the pair feeding animals, there is no significant reduction with the 8 milligrams at the 13 weeks. And, therefore, that's

the reason we say that there is no significant difference and this is our lower.

CHAIRMAN BONE: Well, thank you.

Are there any other questions from the Committee? Yes, Dr. Zawadzki?

DR. ZAWADZKI: This is a question for Dr. Cooper, a general question about recommended dosage from your point of view. Since there have been few long-term studies and since there is a significant rebound effect, what do you recommend as usage of this drug?

DR. COOPER: Well, I would take exception with the notion that there's a significant rebound effect. I think what one sees when one withdraws an anorectic agent is that patients regain weight.

I think people generally come back to their baseline and not necessarily above that baseline if they haven't made any other changes in their overall diet and lifestyle habits.

So we know that drugs work as long as they are taken when an antihypertensive is withdrawn or a cholesterol-lowering agent is withdrawn. Generally the beneficial physiological, pharmacological response also wanes. And the same is true I think for dexfenfluramine.

Given the fact that obesity is a disease of chronicity, certainly we think that long-term therapy is appropriate. Our clinical trials were up to one year in duration. And certainly there is an experiential database with the fenfluramine used for three or four years in controlled clinical trials.

I think Dr. Bone is indicating that he'd like me to wind down.

CHAIRMAN BONE: Yes. Thank you.

Are there further questions concerning neurotoxicity from the Committee?

(No response.)

CHAIRMAN BONE: If not, we will have the concluding segment of the sponsor's presentation.

DR. COOPER: We are cognizant of time. And we will endeavor to go very quickly through this last section.

RISK/BENEFIT:

DR. FAICH: I'm Gerry Faich. And I'm going to talk about risk-benefits. I'm mindful both of the time and the fact that much of what I'm going to say has been previously presented. As a consequence of that, I'll turn my slide show into a moving picture show, if you will.

I am going to talk about risk-benefits.

And I'm mostly going to concentrate on the risk side of this. We're going to talk about primary pulmonary hypertension. Benefits are defined in this presentation as obesity-related mortality change, but I'd also like to include some comments about morbidity. And I'll base much of this on the nurse health study and index, again doing this rapidly.

I would point out that the international primary pulmonary hypertension study that you've heard about came about because of a cluster of cases of dexfenfluramine-associated primary pulmonary hypertension and because there had been an epidemic related to an amphetamine-like compound in the '60s.

To summarize the case control study, this was an effort to collect all cases of primary pulmonary hypertension in five countries over two years. So it was intended to be a population-based study. And only 95 cases were found. That is a way of saying this is indeed a rare disease.

Of those 95 cases, 21 of them had been exposed to anorexigens. So we're talking about 21. That's all anorexigen exposures in five countries over two years. Controls were 355 controls. 6.5 percent of them were exposed to anorexigens.

From that data and its analysis, the

conclusions were that anorexigens, obesity, and systemic hypertension were all independent risk factors for this very rare disease with the odds ratio shown here. And, in particular, for all anorexigens with exposures over 3 months, the odds ratio was 10.6, which is a relatively high odds ratio.

So the association appears to be real given the magnitude of that odds ratio, but it's an odds ratio. Converting an odds ratio to absolute risk is multiplying that to odds ratio times the background rate. Multiples of a very rare event are still quite rare. And that's the point.

The real conclusions from the IPPHS were that obesity itself doubles the risk of PPH, that dexfenfluramine and fenfluramine exposures of less than three months had little or no risk; that is, the lower bound was near one; and, as I've just said, anorectic agents used for more than three months result in an increased but very rare risk. Translating an odds ratio of 10.6 into absolute risk turns out to be 1.9 excess cases per 100,000 exposures, indeed a very rare risk.

I would contend that that rare risk is indeed a worst case scenario for several reasons. The couple of biases that are built into this study would

serve to inflate that estimate. Those include referral and diagnostic biases, recall biases, and confounding by indication itself.

And I would just caution -- and I won't go into detail in this because of time -- that small numbers make subset analyses asking the question, for example: What about exposures of more than a year for one specific anorexigen in obese individuals gets you down to very small numbers and into very thin statistical ice?

Indeed there were fewer than seven cases where both of these had more than three months' exposure. And of those, not all of them had dexfenfluramine exposure. So, again, I would say -- and I accept the 10.6 number -- other sub-analyses are hazardous.

The other thing I would like to point out is that the international primary pulmonary hypertension used as its measure of obesity the maximum BMI that individuals had in their lifetime. That is, it didn't collect serial weights on either cases or controls. And the consequence of that is the study is unable to examine magnitude of weight loss and its relationship to likelihood of developing primary pulmonary hypertension or issues of weight

fluctuation.

The reason I make this point is it is entirely conceivable that part of the association found is related to weight loss itself and that in this instance the anorexigens are innocent bystanders or at least in part.

I would also point out that what the IPPHS found was 20 cases in toto of anorexigen-exposed PPH. That contrasts to 400 to 1,000 cases found in the earlier Aminorex epidemic, which occurred quite abruptly and dramatically 6 months after marketing of Aminorex, where the rate was over 2,000 per million. Remember, we're talking here about 20 per million. And the odds ratios were 1,000.

What I'm trying to say here is that the international primary pulmonary hypertension study was done to ask the question: Are we looking at an epidemic of primary pulmonary hypertension of the like here? And the answer absolutely is no.

Let me now move on very quickly -- that's the risk side of the equation -- and talk about the benefit side of the equation primarily. And I do this, and I'd like to emphasize this, as a conceptual framework to understand what the rare risk is of primary pulmonary hypertension against the potential

benefits in terms of survival enhancement for treating obesity. I do this not because the sponsor is seeking a labeling claim for prolonged survival, but, rather, to put this risk into a context and also to emphasize the problem of obesity in and of itself.

You've seen these data before. This is Manson's data. It simply shows that as BMI goes from 26 to 32, the risk of death doubles, pure and simple. And this is multivariate analysis controlling for age, smoking, exercise, diet, and the like. And it simply says that obesity is a killer of a disease if you subset this and look at some smaller intervals.

As obesity goes, as weight goes from 27 to 32, -- and that's a gain of about 12 kilos or 14 kilos -- the increased risk of death, all-cause death, is 80 percent. That translates in absolute numbers to in excess of 86 lives per 100,000 patient years. Even when you look at 30 to 32, a very small increment, there's a 10 percent increase in death. And that translates to 11 lives per 100,000 person years.

I would remind you and what I'm going to put in this model in a moment is that in the index study if you look at weight loss greater than 15 percent, there were 29 percent of the responders who achieved that.

If you look at 10 to 14 percent, 23 percent, 5 to 5.9 percent, 20 percent, I'm going to use 20, 20, 20. And I'll use the lower bounds, 15, 10, and 5, in this model. So, again, the point is that this is a conservative model.

The model basically says if we treat 100,000 women who start out with a mean BMI of 32, ranging, meaning, from 30 to 34, with a woman who is about 190 pounds on average and stands 5-5, we're going to use index data to estimate her rate of BMI change or her changes in BMI. We use nurse health study to interpret what that means in terms of lives saved. And we'll use IPPHS to estimate risk.

Again, I apologize. I'm going fast. Most of you have seen or many of you have seen this before.

This is what that looks like. We can anticipate, then, of these 100,000 women 20,000 will lose 15 percent of their body weight. That is, they'll reach a BMI of 27. That means 17 deaths will be avoided or 17 lives will be saved per year.

Similarly, for loss of 10 percent of body weight, there's a savings of 8.6 lives; for loss of 5 percent of body weight, 2.2 lives, a total of 28 lives saved per 100,000 women per year.

Recall in this situation the expected

number of PPH cases that would occur here are 1.9 cases and about one death. Now, that's not the whole story. And I think this is the key slide in this presentation. Recall in these 100,000 women half will have become discontinuers, which actually halves the risk from 1.9 to 1.

If you adjust for the bias that I pointed out before, I believe the real risk in this case is about half of that, which is down here. In addition to the lives saved, we can estimate there will be 44 myocardial infarctions and strokes prevented.

So if you add up the morbid and the mortal events, you're talking about 72 events avoided. And that would suggest that the risk to benefit ratio is 144. There's nothing sacred about that number. What I'm really trying to show here is that the benefit to risk ratio is huge here.

We've talked about this before as well. What I've just told you is that while the Manson data and other data show that as weight goes up, mortality goes up, the question is: Is it reasonable to believe as weight goes down, mortality will go down as well? And there are at least four reasons to think that that's true.

There are improvements in glycemia lipids

and hypertension and certainly quality of life promptly after loss of weight. That's apparent from clinical studies as well as clinical experience.

The Williamson data suggest a 20 percent reduction in all-cause mortality, particularly for those with co-morbidities after loss, after intentional loss, of in the case of individuals with co-morbidity anyway and others a weight loss of 20 pounds.

The Colditz study shows a 50 percent reduction in NIDDM with a loss of only 5 kilos. And then the Swedish data show some relatively high cure rates for glycemia and hypertension in individuals with morbid obesity treated with GI surgery.

Now, just two additional comments about what I have just shown you. And, again, I'm going rather quickly. Dr. Stadel correctly has said what I have just presented is influenced by the placebo effect that if I'm using index trial data, half of the benefit is due to diet, exercise, and placebo.

I do not deny that. I would simply point out that these don't occur without the absence of the structure provided by a trial. And that is a way of saying placebo effect is not going to happen in clinical practice ir the absence of a drug that is

linked to diet and exercise.

The other question is: Is risk not higher than this, not 1.9, but 2.7, because of the adding up of independent risk looking at the risk from both anorexigen exposure combined with obesity?

And my answer to that is that, again, the IPPH data get thin when you do this sort of subset analysis. But, even if you do it, you need to be mindful that exposure itself will be truncated in trials because of dropout rates. And if you put this into the equation, you still have a very large risk to benefit, benefit to risk ratio.

My conclusions, then, are that the IPPH study results may have been affected by publicity and referral channels and referral pattern and recall bias that obesity itself is an independent risk factor for primary pulmonary hypertension, that the risk of dexfenfluramine-associated PPH is very small. Dexfenfluramine I believe is effective and will prevent excess obesity-related deaths. And the benefit to risk ratio is very large.

So that's a 5-minute compression of a 15-minute talk. Thank you.

CHAIRMAN BONE: Actually, that was a 13-minute talk.

(Laughter.)

CHAIRMAN BONE: The next comments will come from I believe Dr. Deitch.

DR. DEITCH: How about three minutes in two?

PHASE IV STUDY COMMITMENT:

DR. DEITCH: Dr. Bone, members of the Committee, my role today is to discuss very briefly considerations for Phase IV post-marketing studies. First, if your answer to Question Number 2, "Should the approval of dexfenfluramine be contingent on a commitment from the sponsor to conduct post-marketing studies?" is affirmative, let me say that Interneuron and its marketing partner, Wyeth-Ayerst, are committed to carrying out any required Phase IV investigations in a timely and expeditious manner.

In fact, Wyeth-Ayerst and Interneuron have met with the division on two separate occasions since the September 28th, 1995 meeting of this Committee. And we have discussed Phase IV considerations in clinical trial design issues with the division.

Dr. Stadel will elaborate further on these discussions and provide you with perspectives, his perspectives, during the division's presentation later this afternoon or should I say later this evening.

Prior to the meeting of this Committee on September 28th, 1995, Interneuron had concluded that effects on co-morbidities such as glycemic control or blood pressure control were to be a consideration for post-approval studies. During the meeting of September 28th, this Committee expressed a desire to see clinical data such as cognitive and behavioral assessments and other neuropsychological tests. This was in response to having heard and seen presentations alleging neurotoxicity in animal models.

Today you have seen and heard clinical data which indicate clearly that no evidence of neuropsychological function has been seen during clinical trials of dexfenfluramine nor has any emerged after therapy or have any signals emerged or been detected during post-marketing surveillance of more than 10 million patients exposed to dexfenfluramine and 30 million patients exposed to fenfluramine.

However, as I stated at the outset, if it is the advice of this Committee that we conduct post-marketing studies, any required Phase IV investigations will be designed in consultation with FDA and the division and performed in a timely and expeditious manner.

Thank you. I turn the program back over

to Dr. Cooper.

CONCLUSIONS:

DR. COOPER: Okay. Let me just conclude this very, very briefly. Recent scientific discoveries have destroyed the archaic notion that obesity is simply a disease of willpower. It's increasingly clear that obesity is a complex, multifactorial condition with a strong genetic component and that appropriately safe and effective pharmacotherapy is indicated for patients who have failed diet and lifestyle changes.

In the future, genetic therapies may become available that correct specific inborn errors of metabolism and alter the energy balance, but this is the present. And dexfenfluramine is far and away the best available therapy for helping patients maintain a reduced level of caloric consumption.

I can understand the concerns that you may have about approving a drug for any condition as prevalent as obesity. I understand there will always be a desire to see some additional data before a drug is approved. But I submit to you that the FDA is unlikely to ever see a more thoroughly studied and utilized anti-obesity agent prior to approval nor one which so solidly establishes both safety and efficacy.

Let me for the last time describe the magnitude of this database. Over 4,500 patients were studied in the NDA. And significant efficacy has been unequivocally established for this single isomer, which has a defined and specific pharmacologic mode of action.

There have been over 10 years of clinical usage in 65 countries, including virtually all the member states of the European Community. Post-marketing safety data is available on over 10 million patients treated to date with dexfenfluramine, and another 30 million have been exposed to fenfluramine.

One relies on post-marketing surveillance to find rare adverse events or patterns of events. And here the system worked like it was supposed to work. A single epidemiological signal, pulmonary hypertension, emerged from the database. And a two-year prospective observational study was conducted to address it.

And while this case control study has not established a causal linkage between this extremely rare disorder and anorectic drug use, at least we have enough information to properly inform physicians and patients about a possible rare association and let

that enter into prescribing decisions.

On the issue of neurotoxicity, 17 double-blind controlled clinical trials, 10 of them at greater than 3 months in duration, looked at neuropsych and neurocognitive parameters of dexfenfluramine treatment.

In one study, the 18-month Noble study was specifically designed for that purpose. None of them showed any evidence for clinical neurotoxicity. And an independent panel of the country's leading clinical neuroscientists, including FDA's own consultant, agree that this drug shows no signs of causing neurological damage.

Finally, your careful consideration coincides with the conclusion of a prolonged European regulatory review of the risk-benefit analysis for all anorectic weight loss drugs in general and dexfenfluramine, in particular.

The European authorities have not considered the animal data on long-term serotonin depletion to be a significant issue. They are well-aware of the assertions about toxicity, but it has never entered into their risk-benefit deliberations.

In the U.K., after thorough deliberation,

the study has specifically dismissed the issue. However, European authorities have been interested in pulmonary hypertension as an issue. They have decided to continue the three-month prescribing restrictions on all weight loss agents with the sole exception of dexfenfluramine and fenfluramine, which may now be prescribed for long-term, potentially indefinite use given appropriate patient selection and monitoring.

Let me emphasize the importance of their decision. They felt the benefits of long-term treatment with dexfenfluramine far outweighed the small hypothetical risks of pulmonary hypertension. And they loosened, rather than tightened, prescribing limitations on the duration of use.

Let me give you my last word on the neurotoxicity question. We have cooperated with two divisions of the FDA, the Neuropharmacology Division, where the IND initially resided, and the Endocrinologic and Metabolism Division on the evaluation of the significance of the neurochemical changes, the high-dose animal toxicology studies.

Virtually every study that has been requested we have performed. We have involved some of the most prominent neuroscientists in the world in the design, implementation, and interpretation of these

studies.

And we have convinced, first, ourselves and, second, the overwhelming majority of the academic, scientific, and medical community that dexfenfluramine is not a neurotoxin.

We have given you ample evidence today that the clinical margin of safety for dexfenfluramine is huge. Even if one chooses to view animal findings as a cause for concern, patients will not be taking 900 milligrams of this drug daily. They will be taking 30 milligrams of the drug daily.

At clinical doses, there is no actual, hypothetical, or possible risk of harm. Nevertheless, additional post-marketing studies can and will be done if after your deliberations you have any lingering concerns about the neurological effects of the drug.

Currently there are no approved drugs in the United States for the long-term therapy of obesity, a disorder which requires long-term therapy. Some older drugs, most of them amphetamine-like agents, are being used alone or in combination. And some are routinely used off-label for long-term use, despite minimal clinical testing.

Dexfenfluramine is the first drug to emerge from years of extensive rigorous mono testing

and represents the first safe and effective monotherapy for the long-term therapy of obesity.

Physicians in 65 countries around the world are able to prescribe dexfenfluramine because regulatory authorities around the world have approved the drug and have continued to endorse the safety and efficacy. We believe that physicians in the United States should have the same option as their international colleagues to improve the health and well-being of their obese patients.

And I thank you very much for your attention.

CHAIRMAN BONE: Are there questions from the Committee members for any of the last group of three speakers? Dr. Kreisberg?

DR. KREISBERG: My question is to Dr. Faich. And I want him to sort of check my calculations here. The sponsor has convinced me that the drug is safe. Now my question is: Is it effective?

And from the data that's been presented plus your interpretation of epidemiologic data, it appears to me that on average the drug makes the difference of one body mass index unit between a patient who doesn't take it and a patient who does

take it. Is that correct?

DR. FAICH: No. Let's see. How did you get there? Let me --

DR. KREISBERG: You showed that going from a body mass index of 32 to 29 was related to a 10 percent loss in weight. Therefore, if that's correct and if the difference between the placebo group and the treatment group is the difference between a sustained five percent weight loss and a sustained eight or nine percent weight loss, then the difference between the treatment group and the placebo group is one body mass unit, one body mass index unit.

DR. FAICH: Let me back you up and tell you what I think I showed. The first thing, the numbers you're referring to were the Manson data that speaks to as you move from 32 to 27, let's say, that results in an 80 percent reduction in mortality. That was one figure.

Then, as you move down, if this is where you got that, as you move from 30 to 32 -- maybe we can put up that slide.

DR. KREISBERG: No. Your slide was the one that had to do with a 15 percent reduction, lives saved; 10 percent reduction, lives saved.

DR. FAICH: Let me put the slide up.

CHAIRMAN BONE: Four percent of 27 is about one.

DR. FAICH: Okay. Now, is this where you started from?

DR. KREISBERG: No, it's not.

DR. FAICH: Then go forward. Next one.

DR. KREISBERG: There it is.

DR. FAICH: Okay.

DR. KREISBERG: It's at 10 percent. You started a body mass index of 32 hypothetically.

DR. FAICH: Correct.

DR. KREISBERG: You come down to 29. That represents a 10 percent weight loss. And that's the effective presumably of diet plus drug.

DR. FAICH: Right.

DR. KREISBERG: That's what we're talking about here. But diet alone would give you a degree of weight loss that was about three to four percent less. So we're really talking about a difference between diet versus diet plus drug of about one body mass index unit. Is that correct?

DR. FAICH: Well, it's correct, but let me stipulate something. What this analysis does is it does not take into account -- this is not a responder analysis per se. That is, what you're looking at is

20 percent on average, on average, across all of the patients if you go back to the index data, that the average patient lost 10 percent of his weight, that is. So all of the patients would be on that one line.

CHAIRMAN BONE: But this did not subtract placebo.

DR. FAICH: It did not subtract placebo. But, again, I would point out that you're not going to have placebo effect without structured diet, without structured exercise, or the like.

The other thing I would point out is that, even here, what you're saying is, "Well, you've got to look at the spectrum." And so what you're looking at is 14 down at the bottom, 14 lives saved, taking away the placebo effect.

DR. SANDAGE: We've actually analyzed for BMI change. And the percent change is about the same. So in the index trial, you get just over one BMI unit change between the treatment groups.

In other studies; for example, the UK18, it goes up to three BMI units between the placebo groups. So the studies range from one to three BMI units.

CHAIRMAN BONE: But in the long-term study, Dr. Kreisberg's original calculation is

correct.

DR. SANDAGE: Just a little over one BMI.

CHAIRMAN BONE: Dr. Cara and Dr. Marcus.

DR. CARA: This again is a question to Dr. Faich. If you could stay at the microphone, please? I would argue that the data that you have presented, or at least the figures that you have presented since it's really not based on data, is really the best case scenario. And my rationale for that is the fact that there is really no one-year study. You are assuming that the effects are going to persist for a year, but, in fact, that has not been looked at.

The other issue is that we know based on experience that any effect if you're going to have an effect, if there's any effect there, will be achieved sometime between the first three to six months of therapy and weight loss.

Based on that, then I would argue that your case scenario, the case scenario that you present, is really the best case scenario. Would you comment on that?

DR. FAICH: Yes. Again, looking at index, what index actually did is most people achieved their 10 percent weight loss within the first three months and then maintained it if you remember the shape of

that curve. So what we have is nine months of observation showing maintenance of a 10 percent on average weight loss.

So we have a nine-month study, if not a year study. You're right. I made the assumption that that would persist for a year.

DR. CARA: But it's six months of treatment.

DR. FAICH: No. It's a year of treatment.

CHAIRMAN BONE: They were on drug for 12 months in that study, in that particular study.

DR. CARA: Just in that one study.

CHAIRMAN BONE: That's right.

DR. COOPER: That was a large study, 1,000 patients.

DR. FAICH: The other thing is what I did in this model is this is a one-year model. The fact is I would contend that it's quite likely that every year that weight is maintained at that level, you, in fact, achieve an equal benefit because the calculation here is lives per hundred thousand patient years. So, that is, with each additional year of weight loss, if weight loss is maintained, you continued to accrue benefit.

CHAIRMAN BONE: Any further questions from

the Committee for any of the last three speakers from the company? Dr. Borhani? I'm sorry. It was Dr. Marcus' turn, Dr. Borhani, then Dr. --

DR. MARCUS: I just have one further thing to deal with Dr. Faith on this issue. I actually like this type of analysis. It does tend to put things in perspective. But there's an issue here that concerns me a little bit.

You used the ground rules based on the nurses' , retired nurses' , study, which, of course, sets a certain age limitation on it. And we're talking about a medication that may be used by women for 30 years before they ever get to that age.

I recognize what you've done is a first pass. I would like to see you expand this type of analysis to assume that some substantial portion of patients who get this medication may be on it for 30 years before they get to the area of accelerated coronary heart disease, for one thing, and also build into it the implications to those women if 30 percent of them, which is the average nationwide, decided to take a hormone replacement therapy at age 50 and also to see what the implications with respect to endometrial and breast cancer would be. I'd like to see you expand this model to much more --

DR. FAICH: Let me comment on that.

CHAIRMAN BONE: Not tonight, please.

DR. FAICH: Yes. Not tonight. One quick question. And that is that the nurses at the point of entry to the study ranged in age from 30 to 55. We followed them for 16 years. This is a age-adjusted number that went into the calculation here. So it actually takes that into account.

The reality is using nurse health study as the basis for figuring out benefit is quite conservative because they're likely to have a lower mortality rate than other populations, not least because they're health care providers, because they modify their smoking behavior, because they're mindful of this.

And Joanna is sitting next to me. I'd ask her, Joanna Manson, to add. But the point is that using that as a base population is a conservative estimate of the benefits.

CHAIRMAN BONE: Next question was from Dr. Borhani and then Dr. Colley.

DR. BORHANI: Yes. I'm a little bit disturbed, Mr. Chairman. And I hope that I can express why I am disturbed. I think the presentation of the model based on the results of observational

studies and other studies to predict what will be 5 years, 10 years down the road is a good exercise in scientific, academic discussion.

I believe to relate and equate mortality and morbidity and morbid events that would result, quote, unquote, because people receive a drug that the whole sole purpose of the drug is claimed to be losing weight is at best premature and at worst very disturbing.

I would like to remind everybody yesterday in American Heart Association after all of these years that we have been using cholesterol-lowering drugs and arguing among ourselves in academic circles whether cholesterol should be lowered or not to save life, for the first time there were data.

The New York Times covered it this morning. I saw it. And I heard the results, and I saw the data, as did many, many thousands of people through television.

For the first time we showed that lowering cholesterol will save people from having acute myocardial infarction. We extrapolated for the last 30 years on that. But now for the first time we have the data.

Hypertension. We approve drugs. People

use them to treat hypertension. And that's where I had my training for the past 30 years and experience. Until HDFP and MRC data came out to demonstrate that if you bring hypertension down, you will save life, everybody else was speculating.

If we can demonstrate that this drug is efficacious in reducing body weight, as FDA regulations have stipulated, five percent compared to placebo, that's all we need.

The rest of this discussion is beautiful, academic speculation. And I'd love to participate if you want me to. But it has nothing to do with the job before us in this Committee.

So I would like to make sure that the FDA officials correct me if I'm wrong. I think I'm wasting my time here listening to an academic debate which is the classroom debate. It has nothing to do with approving or not approving a drug.

I don't expect anybody to give me convincing data that this drug has saved life or saved diabetic patients from dying or saved coronary heart disease patients. I don't expect them. That takes 10, 15, 20 years from now. If they want to do it, that's fine. That's a different study.

I want to know if this drug used properly

causes weight loss, 5 percent compared to placebo, period. That's where I am. Now, if I'm wrong, please correct me.

(Laughter.)

CHAIRMAN BONE: I think the next question was from Dr. Colley.

DR. COLLEY: Forgive me if I slip back into an academic discussion for a minute, but I do have a discussion for Dr. Faich. In trying to put this in perspective for the patient who may ultimately use this drug, I'm thinking of your comment that placebo effect wouldn't be as dramatic outside the rigid confines of a study.

And certainly there will be patients who use this drug and look at it as a cure in and of itself or something to help in and of itself and may not have exercise or dietary changes to augment the effect of the drug. And I wonder how much the potential benefit in morbidity might be blunted in using in a situation where there aren't any other lifestyle or exercise modifications.

Do you have data in patients using the drug alone without any other modification that --

DR. FAICH: Right. I think the best data for that is the FM study, which I actually had on one

of my slides, which was a less structured loosely single-arm uncontrolled trial that went on in Europe, largely in France.

And, Bob, you can correct me if I have this wrong, but it showed that 52 percent of patients lost 10 percent or more of their body weight. And that was in a study with very little structure around it in terms of protocol-driven diet and exercise.

So at least I find encouragement in that, number one. Two is I think the issue of patients blunting the effect, much of this is going to be motivational on the patients' part to begin with. We know that. And I think the claim here is that this is an adjunct to other means of losing weight.

Bobby, would you care to expand on that?

DR. SANDAGE: Yes. In analyzing the data, I agree completely. We did a couple of studies where there was no diet prescribed. Patients lost a little bit of weight, not nearly as much as you see when you add it as an adjunct to diet. This drug should not be used unless it's added to a behavioral modification, diet program that's appropriate. It performs much better.

But in those two studies that there was no diet prescribed, patients were just told to take the

drug, -- and it was actually feeding studies -- the two placebo groups gained weight. And the dexfenfluramine lost weight. It just wasn't very much weight loss.

CHAIRMAN BONE: Are there further questions from the Committee members regarding the last three presentations?

(No response.)

CHAIRMAN BONE: If not, we will take a break here for a moment.

Now, first of all, I hope that the sponsor appreciates the extraordinary patience of the Committee in going far beyond the amount of time that it was expected to be allotted for the presentations and the questions. And I'm sure we've had the most thorough possible exposition of the points that the sponsor wished to make.

I have 10 minutes after 5:00. We will reconvene sharply at 20 minutes after.

(Whereupon, the foregoing matter went off the record at 5:08 p.m. and went back on the record at 5:20 p.m.)

CHAIRMAN BONE: The only way we can do our job well is if everybody will resume their positions. Thank you. I believe the Committee is back in place.

The audience will please resume their seats and be quiet.

The FDA presentations will be given by Dr. Leo Lutwak and Dr. Bruce Stadel. The fact that we had a longer presentation from the sponsor than was originally contemplated does not diminish our need, I think, in any way for the information from the agency.

So I'm looking forward and I'm sure the Committee members are looking forward to the presentations by Dr. Lutwak and Dr. Stadel. And I will say after these presentations, we will proceed to the discussions and questions directly without a further break.

The first presentation will be the medical review by Dr. Leo Lutwak of the Division of Metabolism and Endocrine Drug Products.

DR. LUTWAK: Thank you, Dr. Bone. And good evening, ladies and gentlemen. May I have that first overhead, please?

FDA PRESENTATION

MEDICAL REVIEW

DR. LUTWAK: As has been repeated time and again this afternoon, the questions before us are the relative safety and efficacy of dexfenfluramine for the indication of weight loss as an aid to diet and

changes in behavior and other factors associated with eating behavior. And, as in every other instance of drugs evaluated by the agency, we're concerned with the relative balance between safety and efficacy.

The safety factors have been discussed in a great deal of detail today by the sponsor. And we have discussed them with this Advisory Committee many times in the past. The principal one that most of our attention has been taken with today is the neurotoxicity factors, cognitive and behavioral changes, and possible organic changes, as suggested by the animal studies, and the primary pulmonary hypertension.

The benefits, the efficacy factors are as recommended by this Committee in the past, demonstration of a significant amount of weight loss. And the concept of significance has been discussed several times before; and, secondarily, decreased co-morbidity, as was discussed earlier today by Dr. Rubenstein.

May I have the next overhead, please? Let me go very rapidly over the neurotoxicity and the other safety factors since safety is of primary importance in our considerations here. I am not going to touch on any of the animal studies. I don't

pretend to be a neurophysiologist, and I'm looking at this primarily as a clinician.

The Noble cognitive study, the 6-month study followed by a 12-month follow-up, which we, fortunately, had an opportunity to review about 2 weeks ago, was a 6-month double-blind study followed by a 12-month observational phase in a placebo-controlled 12-month follow-up.

There were 28 subjects per group that were valuable. At 6 months this had changed to 24 subjects in the drug group and 21 in the placebo group. Since we did not have the data in the submission to us of the initial weight, we really could not evaluate actual amount of weight loss and the significance of this because there appeared to be weight loss in all of these subjects. And there were no significant differences in any of the cognitive functions that were measured in this particular population from a well-established investigator with a large private practice of obese patients.

In addition, as an addendum to this submission, there were four previously conducted controlled studies that we evaluated and there were comments concerning observations from mixed design studies that were submitted along with this.

From all of these studies, we found a reassuring lack of evidence of neurotoxicity in the populations studied over the intervals studied and using the tests that have been fairly well-established by the earliest speakers today.

May I have the next? Just briefly looking at the well-controlled studies that were submitted, there were four well-controlled studies in addition to the six-month Noble study. These were randomized. All four of these were randomized. They had variable numbers of subjects who were valuable. The duration was as short as 5 weeks in one study and as long as 26 weeks in the United Kingdom studies.

And various tests that were conducted of mood and cognitive function all failed to show any significant effects, either positive or negative, of dexfenfluramine. And, to my way of thinking, this lays the concept of neurotoxicity on the far, far burner, probably no significance at present.

May I have the next slide? The other significant risk that has been raised again and again is risk of primary pulmonary hypertension. As Dr. Faich has summarized so nicely, this is a relatively rare occurrence.

I think the relationship of this to the

use of dexfenfluramine appears to be fairly clear-cut, but it's an extraordinarily rare phenomenon. And it may take many more tens of thousands of subjects before we have any real indication of its actual clinical significance. For the time being, this, too, is something of -- it's rather reassuring to state that this is probably not of significance.

So we have to look now at the other side of the balance: What are the benefits that have been demonstrated? The indication that's being requested is an indication for long-term use. And long term in terms of what everyone has been discussing today is a year or longer.

There has been the one study referred to time and again today and in our last meeting, the index study, of 48 weeks' duration. The index study was, quote, placebo-controlled.

We have to remember that both the dexfen subjects and the placebo patients were on diet and modified activity. And I think most clinicians will agree that for weight loss to be effective and to be maintained, it has to be associated with control of diet and control of activity.

What was seen is there was little difference in percent of weight loss from baseline at

48 weeks, whether we looked at completers only or at the last observation carried forward population, which was considerably greater, of course, approaching the thousands altogether.

There was approximately 10 percent weight loss on the drug plus exercise and diet modification. And there was approximately five to seven percent weight loss with diet, exercise, and other behavior factors alone, for a difference of approximately three percent, which does not quite meet the criteria that this Committee set up, but we are cognizant of the fact that these criteria are set up at some time after submission of this original NDA and that we have looked at the categorical analysis. And on the basis of categorical analysis, we see that about one and a half times as many patients on drug lost significant amounts of weight as compared to those just on the diet and exercise regimen.

So, from this, we can conclude that dexfenfluramine appears to have a moderate effect in promoting weight loss over the period of a year, which is greater than that without dexfenfluramine.

May I have the next overhead, please? Now, the issue of co-morbidity, while not critical, I suppose, to total evaluation of the drug, has been

raised by this Committee at the last meeting and at various other meetings. And so we have asked to review the data on co-morbidity.

One of the co-morbidity factors that has been brought under consideration has been effects on lipid metabolism. The other is effect on glucose metabolism. And the third is on hypertension.

As I replied to Dr. Bone's question at the end of Dr. Rubenstein's presentation, I'm generally in agreement with Dr. Rubenstein in that co-morbidities are important to consider, that dexfenfluramine does produce weight loss.

There is a leap of faith, however, that I still have some difficulty with. I feel there is absolutely no question that co-morbidity factors such as dyslipidemia, abnormal glucose tolerance, hypertension are increased in obese patients.

I think the data are beginning to become available that weight loss may have a very beneficial effect on these co-morbidities. The leap of faith that I still have some difficulty with is that weight loss by any means is equivalent.

We know that weight loss by surgical means, where drastic amounts of weight are removed from the patient, such as in Scandinavia studies,

there are beneficial effects on the metabolism, there are beneficial effects on carbohydrate metabolism.

We know as endocrinologists that modification of diet, introduction of exercise improves diabetes very dramatically and often within a few weeks. What we are looking for are the data to show that weight loss by drug A or drug B or drug C produces the same effect as the weight loss that we introduce by dietary modification alone.

Now, what has been submitted with this for our consideration with dexfenfluramine are five studies in which lipid metabolism was measured. I've summarized them on this slide.

First study, 12 patients on drug, 14 on placebo, 21, 20, 20, 17, 25, and 25, and 9 and 11. In these five studies, where lipids were measured, we found a decrease noted in cholesterol and triglycerides in the first study. But this study had some problems for our statistician in terms of randomization.

There are many, many more males in the placebo group than in the drug group. There was much higher caloric -- actually, it was measured in joules, a much higher energy intake in the placebo group than in the drug group. And the alcohol intake was

dramatically higher in the placebo group than in the drug group. And so I have some difficulty accepting any of the results from that particular study.

The other studies, the Cameron study demonstrated a decrease in triglycerides. The Stewart study, which was conducted on the identical protocols, showed no effect on triglycerides. The Holdaway study showed a decrease in total cholesterol only. And the U. Wiley showed no effects on lipids. I have difficulty drawing any conclusions about effect of dexfenfluramine on lipid metabolism. These were all three-month studies.

May I have the next slide, please, or the next overhead? I just wanted to show this one distinct difference in the Bremer study since I have discarded that one from my considerations.

The dark bars are the subjects on placebo. The almost clear ones are the subjects on dexfenfluramine. And, as you can see from those bars, the total energy intake was much higher in the placebo group. And the alcohol intake was dramatically higher.

I think you can skip the next one. In the interest of time, I'm not going to go through the individual studies. Let's go to the one that has the

words across it. I should have numbered them.

Now, in terms of glucose metabolism, again, we have six studies here in which glucose metabolism was evaluated. Again, these were all three-month studies. The numbers of subjects actually on drug and on placebo are listed there.

The first two studies, the Bremer and the Cameron study, showed no effects on any glucose parameters. The Stewart study showed a decrease in glycolated hemoglobin, although the Cameron study on the same protocol did not show any significant effect. The Holdaway study, which was designed to demonstrate effects on glucose metabolism specifically, showed a decrease in fasting plasma insulin in the drug group. And the U. Wiley study showed also a decrease in glycosated or glycolated hemoglobin.

Again, the net effect of this group of studies suggests that while there may be some effects on glucose metabolism, none of them are dramatic and none of them are clear-cut. And there may be some other explanations for them.

The next one with words. I have the individual studies plotted out there. If questions arise, we can go back to those. But in the interest of time, I'll show you my summary slides only. We're

right near the very, three or four from the very, end.

The hypertension is one that is of interest, particularly since many of the anorectic agents have been implicated in producing hypertension. And what is reassuring from these studies is that there was no increase in blood pressure in any of these subjects.

Why don't we just go from the last one forward? We'll do that. One may have slipped out because these are shiny and slippery.

There were three studies in which blood pressure was measured. Again, these are three-month studies. The Cameron study. The upper graph is systolic blood pressure. The lower graph are the diastolic, the mean plus or minus standard error of the mean.

Institution of the diet and control showed a trend of a slight rise in systolic blood pressure in the drug-treated group and no effect in the placebo group. By the end of the study, there was no difference between the subjects, although initially the subjects on drug had lower systolic pressure.

The same pattern appears to be present in the diastolic pressure in the Cameron study with a gradual rise over the course of three months in the

drug-treated group of no statistical difference from the placebo group. The placebo group remained relatively stable.

The next one forward from that. Then we'll go into the back forward. I believe we had three studies with -- the one on your bottom.

The other studies essentially showed similar findings with no negative effects of the drug on blood pressure. In the Stewart study, blood pressure was measured at the start and at the finish. And so we had no way of detecting trends.

There was no change in systolic pressure, no significant change in systolic pressure in the drug-treated group, and no significant change in systolic pressure in placebo group. Diastolic pressure showed a drop --

CHAIRMAN BONE: These are --

DR. LUTWAK: These are mean plus --

CHAIRMAN BONE: Those are glycosolated hemoglobin slides.

DR. LUTWAK: I'm sorry. Those --

CHAIRMAN BONE: That's a glycosolated hemoglobin slide.

DR. LUTWAK: I'm sorry. Did I mislook at that one? I cannot see. I'm sorry. I cannot see the

title from here. Fine. Let's leave that there because that's another point that was made.

Okay. The Stewart study shows the patients on drugs started out with lower glycosolated hemoglobins, but not significantly different from the placebo group. Placebo group rose. The patients on dexfenfluramine did not drop.

The drug group showed a drop in the lower slide, which I believe the lower one I think is glycosolated hemoglobin. There was a drop in the Stewart study, yes.

Next one. Now we're looking at the Cameron study of the blood pressure. Okay. We see no significant differences. There was a drop in blood pressure in diastolic blood pressure in the first and second months but a return to previous levels by the third month, which is difficult to explain.

This is the Bremer blood pressure. And there are no differences noted in this one.

Okay. Let me just summarize. In terms of co-morbidity, we were not able to see any confirmed significant effects on lipid metabolism. The effects on carbohydrate metabolism are suggestive of a possible decrease in glycolated hemoglobin in one of the studies.

As you can see in combining the Cameron and the Stewart studies using just the fasting blood glucose, the two populations were quite different at start, placebo and the drug groups. And the changes are not strongly significant for either.

We can conclude from this there were no negative effects on co-morbidity of lipid metabolism, no negative effect, co-morbidity, on blood pressure, no negative effect on lipids. There is no clear-cut evidence of any beneficial effects on any of the co-morbidities.

The risk factors studies are reassuring. There is no evidence for any changes in cognitive behavior. There is no evidence for changes in mood behavior. The data for primary pulmonary hypertension are reassuring in that primary pulmonary hypertension is of minimal significance, although probably related to the use of the drug.

And so it's up to you, ladies and gentlemen, to derive a balance between the efficacy and the safety of this drug. Thank you.

CHAIRMAN BONE: Are there questions or comments for Dr. Lutwak? Dr. Borhani? And Dr. Marcus next.

DR. BORHANI: Yes. Would you be kind

enough to just clear in my mind? I see a little bit of difference between what you just showed, the weight loss at six months between actively treated and placebo.

I see autographs and tables that I have been given. And this document I have says I can make it the best at 12 months, less than 2 percent in the placebo, more than 6 percent in the actively treated. When I take six from two, I don't get the kind of figures you showed. What's the discrepancy?

DR. LUTWAK: Which? Which are you talking about?

DR. BORHANI: I'm talking about the efficacy.

DR. LUTWAK: I showed one slide of the efficacy, the index study. I think it was the --

DR. BORHANI: 3.2 percent, but the figures I have in this green book, which is the sponsor's book that I received, shows somewhere between 5 to 6 percent.

DR. LUTWAK: No, no. You mean on the index study?

DR. BORHANI: That's where I'm confused.

DR. LUTWAK: Are you talking about the index study or the -- see, these are three-month

studies.

DR. BORHANI: No, no, no. I'm talking about the index study.

DR. LUTWAK: Okay. Now, which number, Dr. Borhani?

DR. BORHANI: The graph showing dose response effect, 12 months.

DR. LUTWAK: Do you have a graph?

DR. BORHANI: Yes.

DR. LUTWAK: Okay. well, these are the numbers that --

DR. BORHANI: Yes. But then that's where my confusion is. I make a parallel line from the point in graph from placebo and then one for the actively treated. And then I take them back and forth. I end up with a four to six percent difference between placebo and active in weight loss. And your data at best shows 3.2 percent difference.

DR. LUTWAK: Well, these are the data that our statisticians --

DR. BORHANI: So you're talking about the same data that --

DR. LUTWAK: Well, we're talking here about completers and less observation carried forward. And I don't know which graph you, what you

specifically -- okay. Dr. Nevius?

DR. NEVIUS: Thank you. Ed Nevius from Biometrics.

I think the discrepancy may be that you're looking at a graph of medians. And if you look at the medians, instead of the means, you do get a slightly larger difference. So maybe the sponsor can clarify that. But the statistics on the slide in front of you are means. And the medians were a slightly larger difference.

CHAIRMAN BONE: All right. Any questions? Dr. Sherwin? And then Dr. Marcus. Is that right?

DR. SHERWIN: I just want to be sure to get this summarized. We have about a little over three percent effect. And there is not clear evidence of benefit with co-morbidity factors.

Now, with respect to risk, there was data that we saw the last time that there were 100 patients from Europe reported with primary pulmonary hypertension. And is that correct? I just want to be sure I get that straight.

DR. LUTWAK: I believe Dr. Cooper or Dr. Faich showed that their experts have reviewed those cases and have thrown out many of them. These were the cases that were -- Dr. Cooper, let me answer this,

please. You --

DR. SHERWIN: Yes, I understand that some were thrown out by the company.

DR. LUTWAK: Right.

DR. SHERWIN: But that doesn't necessarily mean that they -- what I'm looking for is that --

DR. LUTWAK: See, we haven't evaluated the --

DR. SHERWIN: So that's what I'm -- Okay.

DR. LUTWAK: We have not. We're using the numbers that were reported as spontaneous reports.

DR. SHERWIN: Now, the final question and the most crucial to me is about the power in which you can detect in a small number of patients using psychological tests differences.

My impression is that you need extremely large numbers of patients when you evaluate, as opposed to a glucose, which is a very defined number of cholesterol. Looking at behavioral endpoints, they're very soft numbers. And so that you would always have no significant difference unless you have an enormous effect.

So my question is: Has anybody done a power analysis and assessed what would be a significant behavioral change and whether we have

enough patients in these studies to assess significance?

I mean, you're telling me it's not significant. And that's fine. But I don't know how many patients I would need to see to determine that. And that's the key question because as far as the animal studies are concerned, I am not convinced of it, but I would like to be convinced that the human data is nonsignificant.

DR. LUTWAK: The only way I can answer that, Dr. Sherwin, is that we asked Dr. Rapoport about 10 days ago to review these studies. And she concludes she found no evidence for any effect.

DR. SHERWIN: Well, there is no evidence for effect. I would agree with that. The question is: Has there been a statistical analysis? You're raising your hand. I don't know.

DR. NEVIUS: Thank you.

That is a very valid question. And the sponsor should be able to tell you the power in the design of their study, what differences they were designed to detect. And you could on the basis of that determine whether that's really a clinically meaningful difference that they were designed to pick up.

CHAIRMAN BONE: Has the agency's statistical review addressed that question?

DR. NEVIUS: Well, for us to address that question, the experts in the field have to tell us what would be a meaningful difference in these parameters. That's a clinical question.

CHAIRMAN BONE: So it hasn't been. Right. All right.

I believe Dr. Marcus has the next.

DR. MARCUS: Yes. Well, I'll pursue that. I think that's more important than what I had to ask. I'd like to hear the sponsor say how the power analysis was done for those studies.

DR. COOPER: I may draw on some of my colleagues here. Keep in mind that with the exception of the Noble long-term study, all the other studies were retrospective analyses of parameters that were put in for safety monitoring features. So formal power calculations were not done for those studies.

Nevertheless, when we showed the design of these studies and the results of these studies to really the six or seven of the leading experts in the field who deal with these kinds of issues every day, "Are these studies powered enough to determine X, Y, or Z factor?" that there was essentially a uniform

opinion from these experts that, in fact, there was adequate power here to detect a difference.

And, if you could see that, some of the sample sizes for some of the primas were extremely large.

DR. MARCUS: Well, excuse me. Twenty-five people in a group is not a large sample size if you're trying to find a five percent difference. You tell me what's meaningful, but let's not say that these are large samples.

DR. GAMMANS: That's a fair comment. But I think your answer to your question will really go by test or by disorder. Just to give you an example, antidepressant trials get meaningful differences with groups as little as 35 to 50 per treatment.

The studies that I told you were 80 to 160 for treatment on those studies. So those are very meaningful. The profile of mood states and the DSST studies are typically that small and are state-dependent. And they typically detect differences of as little a deficit as that associated with taking chlorofenaramine with sample sizes that were used, the 12 and 15.

So it's true across the board, but you have to answer each one specifically.

DR. SHERWIN: But that's in depressed people. I mean, these are not depressed people. So you may need to have a larger number to use depression, as opposed to treat existing depression.

DR. GAMMANS: Well, no. I'm giving you the number that will lead to the ability to detect a meaningful change in the amount. It would not be directional in that regard. And I'd offer again the view, as I recall telling you, that the scores are extraordinarily low. They're values of three.

And we're looking to get anybody to a value of 18. In addition to looking at group values, I looked at the individuals. And, in fact, it doesn't happen.

Likewise for the suicide analysis, those were based on evaluations in over 160 people on the single item analysis, that that's more than enough of that. And, really, the powerful data is the post-marketing exposure. And that's very striking and not giving indication of increased incidence. I won't try to defend that it's lower for a meaningful reason, but it is certainly unequivocally not higher.

So I think study by study the findings are, in fact, very convincing for that purpose. It's typical in these studies, actually, that they're only

8 weeks long and have groups of 30 or so. So that's usual.

CHAIRMAN BONE: Just further to this, Dr. Cooper a moment ago referred to having had several experts review these and comment. I read the letters that were sent in. None of these that I recall specifically addressed the question of power.

DR. GAMMANS: They did not address in their letters power. That's correct. But three of them are here if you wish to ask their independent opinions there.

DR. SHERWIN: Is Dr. Mann here?

DR. GAMMANS: Dr. Mann had another commitment. I'm sorry he's not here.

DR. SHERWIN: Because that was one of the letters that hit me when I read it. It said that the neuropsychological tests that have been carried out do not have a great deal of sensitivity to the kind of abnormalities one might predict. For example, the MSE, his raphe sensitive test, relative sophisticated memory tests, and tests of disinhibition or impulsivity have been carried out so that, although blah blah blah.

So that one of the concerns that I had when I read the letter was: Were the tests that were

done sensitive enough to pick up the kinds of effects you might see?

I agree with you the suicidal data are pretty convincing to me. I mean, that's an endpoint that you can't argue with. I'll buy that very --

DR. GAMMANS: I would argue that the depression data are equally persuasive to my view. And I certainly offer others an opportunity to opine on that.

The cognitive performance testing data there are sensitive, and they're typical of that size. And I believe they would detect very small deficits.

CHAIRMAN BONE: Were any of these studies specifically designed with the primary endpoint to test any of these variables? The sample size --

DR. GAMMANS: Well, the Noble study was designed with that primary goal in mind.

CHAIRMAN BONE: Okay.

DR. GAMMANS: The study protocols defined these instruments with their primary goal to test these parameters.

CHAIRMAN BONE: But the sample sizes in the other studies were determined by the primary endpoints for which the studies were designed?

DR. GAMMANS: Correct. And those are

larger than would be designed by the psychometric. The weight loss parameters would lead to larger study sample size calculation.

CHAIRMAN BONE: Further questions concerning -- actually, this is really all from Dr. Lutwak's presentation. Any further questions for Dr. Lutwak from the Committee?

(No response.)

CHAIRMAN BONE: Fine. Then I think we can proceed with a presentation of Dr. Stadel.

I will ask at the request of the transcription people that members of the sponsor organization please remember to identify yourselves as you speak. There apparently have been some questions about exactly who was speaking.

EPIDEMIOLOGY AND PHASE IV STUDY CONSIDERATIONS

DR. STADEL: My comments were called "Epidemiologic and Phase IV Considerations." While I was listening here at the end, I decided to turn it around and talk first very briefly about how we go about dealing with, would plan to go about developing a Phase IV study on any issue the Committee was concerned about because it's a process, rather than a specific thing.

And I just outlined. Gee, can't we get

that bigger? Well, I'm sorry about that. I thought that was -- that was the way I've made them before. Something must be different before.

Basically, what we would do for any issue would be to begin -- we've done this before, and some members of the Committee have participated in this with regard to the metformin Phase IV trial development.

And I would send a letter to the sponsor defining the issues that needed to be addressed in any Phase IV protocol, the outcomes that would be measured, why they think the outcomes that would be measured would be appropriate, the representativeness of the intended study population in relation to the intended marketing population, the procedure for control confounding, whether using a blinded trial or if one was doing an observational study what procedures would be taken to confounding, the power considerations, validation of data, and then timeliness and feasibility in relation to a market launch because those are very practical issues in actually making a Phase IV study work. And lastly would be simply qualifications of the investigative team.

We would ask a sponsor to develop a

proposal which gave their plan for addressing an issue and address each of these kind of categories. Then we would request ad hoc written peer review by appropriate members of the Advisory Committee and if the Advisory Committee so felt by ad hoc experts if there were areas where that was necessary; and then go through a process of written exchange with the company of the review material; of response to the review material; and, finally, try to come to a negotiated final product.

I thought it was worthwhile to say that at the beginning because I think that that kind of procedure can develop a more solid Phase IV study agreement than has sometimes been the case with some issues over history.

So, then, with that comment in general about the development of Phase IV studies, I really have only a couple of main points that I'd like to try to make on the epidemiologic issues.

The first is I reviewed and talked about my perspective on the pulmonary hypertension study at the last meeting of this Committee. And I feel that it clearly meets the criteria of causality that are appropriate to a serious but very rare adverse event. The study methodology that is possible for such an

event has been employed, really, at its maximal capacity. And I think we have to take that as the best that can be done.

I estimate that for women over a body mass index of 30, that one would expect between 20 to 30 cases per million per year because the study showed pretty clear evidence of synergy between the increase in risk that is related to body mass and the increase in risk that's associated with the drug.

So the figure I came out with per million women is somewhere between 20 and 30 cases expected. Excuse me. That was deaths expected. Excuse me. Deaths expected. That was mortality risk, not total cases.

Nevertheless, we are dealing here with a rare phenomenon. And that's a point estimate, which clearly would have a fairly wide margin of error about it. A confidence interval really isn't even computable for that kind of statistic. But there is some evidence of synergy.

Having said that, I think that it's also a couple of other things that need to be noted. Those are just not readable. And I don't know why because that's the same way I made the ones I showed you last time and they were readable. They're the same

magnification. I don't understand that. But I can deal with the issue without showing those. And so I would ask not to show them if you can't read them.

I think that in evaluating the drug itself and speculating about its possible impact on mortality, one does have to consider that any reasonably organized weight loss treatment program could reasonably be expected to have the placebo effect of the index trial.

So that one must subtract the placebo values. And when one does that, there is a memo that is in the Committee's packet where I reviewed the model. I cited those figures and pointed out, then, that this substantially reduces the magnitude of the effect of dexfenfluramine itself, causing perhaps 11 percent of treated participants to lose 15 percent of body mass index, 8 to lose about 10 percent, 2 to lose about 5 percent, and 79 percent to be in the range of less than 5 percent or more.

Nevertheless, one could go ahead and factor those kinds of figures against the mortality rates in the nurses' cohort study. I did not do that because I feel that there are some reasons for concern that it's unduly speculative.

I relate to some ways the comments that

Dr. Borhani made about what the focus of the approval criterion is. I do feel some of these things just need to be said.

The one study which has looked at the relationship of intentional weight loss to mortality, which is the Williamson study, showed, I think, a couple of important findings.

First off, in the patients without preexisting illness, no co-morbid conditions, there was no overall effect of intentional weight loss in that group on mortality one way or the other.

There was a reduction in mortality if they lost some weight within a year, but there was an increase in mortality if they lost the same amount in longer than a year. And when you netted it out in the data for that part of the data, the relative risk of dying if you lost more than 20 pounds was .98. Okay? And that was a large data set.

So, on the other hand, in the group with preexisting illness, with obesity-related disorders, intentional weight loss was associated with a 20 percent, 19-20 percent, reduction in mortality subsequently, which would be an enormous number of deaths.

There's a caveat here. In this one study

that's available, the loss, the reduction in mortality was 20 percent, for a loss of 19 pounds. And it was 19 percent for loss of 20 pounds or more. That is, the amount of weight lost in this particular study was not predictive of the reduction in total mortality, making one think that other things related to intentional weight loss. Exercise, lifestyle, and so forth, may have played in these data as much a role as the loss of weight itself.

I do not say these things to disparage the importance of weight loss, but, rather, to give my reasons for not being inclined to speculate numerically about the potential savings of lives that could occur here. I don't think that that is pivotal to the issue before us, but I did want to give that position because it's background for my main point.

My main concern is this. If the drug is approved, there will assuredly be cases of pulmonary hypertension. And they will be reported to the Food and Drug Administration because it's a visible event. It's received a fair amount of publicity. It's rare enough. The association is striking it up. We will receive reports.

Okay? That's the one hand. Now, on the other hand, if we have a Phase IV study that gives a

good, rigorous assessment of benefit versus risk for mortality, those reports can be seen in perspective.

One can say, "Well, we have these reports. But what does it show in a rigorous study as the bottom line for benefit versus risk?" That's what I see as the attractive feature myself of having a Phase IV study that looks in a way that is acceptable through a review process that I described at the net effect on mortality.

In the absence of such a study, there are circumstances that have arisen before at the Food and Drug Administration where you have a drug which people believe has benefits. But, remember, benefits that people receive from a drug are never reported in the spontaneous reports because the individual experience did not know they experienced that benefit. On the other hand, adverse events are. So it's intrinsic to the system that it does not provide a way of weighing benefit against risk.

I'm not disparaging it. It's an important surveillance system for seeing early warning signs. But circumstances like this, if one does not have a context for evaluating such reports, they can pile up and become difficult to deal with.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Stadel. Are there questions from the Committee members for Dr. Stadel? Dr. Critchlow?

DR. CRITCHLOW: Dr. Stadel, do you think with current data that one could speculate for a particular patient, for example, what the expected mortality benefit, say, of losing an average of one BMI unit could be compared to the risk of PPH or other serious event --

DR. STADEL: I think there's a difficulty. There's one slide, which was actually Table 13 from the sponsor's submission, that had a nice summary of their efficacy data.

One of the things that you see there is among the portion of people who lost more than 10 percent, actually, a fair portion of them lost way more than that. It's almost like there's a quantum phenomenon. There's a group in there where some sort of like step function occurs. And those people seem to lose a lot of weight.

If that persists, I would expect it to have some beneficial impact. I just don't want to speculate on it numerically without having numbers that I feel comfortable about using. But in group with responders, the extent of response is fairly

impressive.

I think there's one other issue that we don't know about from the pulmonary hypertension study. It's a question they didn't think to ask when they designed it. I understand that because I've done that. And that is whether the people who developed pulmonary hypertension did or did not have a history of responding well in terms of weight loss early in the course of the drug.

I think that's an extremely important question. And certainly if the drug comes into use, that's the kind of thing that follow-back investigation can be done on spontaneous reports and will provide extremely useful information to find out: Is this something that happens when people keep taking the drug when it doesn't work or is it something that happens in people for whom the drug produces a substantial weight loss?

But I don't know a direct way to answer your question. I'm sorry.

CHAIRMAN BONE: Are there other questions for Dr. Stadel from members of the Committee? Are there any other questions from other members of the Committee for any of the FDA people? I actually had one if Dr. Contrera is available concerning the review

of the neurotoxicity question.

DR. CONTRERA: Yes.

CHAIRMAN BONE: I'm reading a review which I thought was very helpful. And there are two points at which a discussion of this margin of safety question is addressed. And either I don't understand the difference or there is a discrepancy. And I would appreciate having this clarified.

On Page 37, in the third paragraph, it's stated that the discussion leading up to the conclusion that the systemic exposure is not significantly in excess in the rat which produces a long-lasting alteration in 5HT biomarkers is, therefore, no significantly in excess of the human systemic exposure at the recommended clinical dose, which would imply to me that there was not a significant margin of error.

On the other hand, on Page 40, Summary Conclusion Number 3 states that the clinical margin of safety is approximately 15.

DR. CONTRERA: Yes.

CHAIRMAN BONE: I would appreciate it very much if you could clarify that.

DR. CONTRERA: Those are two different estimates. The one on the preceding page, the 35 I

think that you mentioned --

CHAIRMAN BONE: Thirty-seven, actually, for the --

DR. CONTRERA: Thirty-seven.

-- is based on a consultant toxicokinetic analysis of the available plasma data in animals and humans. This was done by Dr. DiGeorge at the FDA. And it was done early in this process before we had the direct brain concentrations, the MRS data.

So we were trying to get a handle on comparative systemic exposures in animals and humans to get an idea about margin of safety. So his estimates were based on the then available data of plasma levels of dexfenfluramine or dex in rats and a dose that gave long-term depletion and what we knew about the clinical plasma levels.

And the estimates that are in the summary conclusions are based on brain concentrations in humans that the sponsor already alluded to, the average of around four micromolar concentration in humans and the brain concentrations in a recent rat study where we used the 13-week depletion as our standard. And we got the 10 from the 8 milligram per kilogram values for the brain in rats compared to the brains in humans.

CHAIRMAN BONE: Thank you.

Now, some of the literature we've read has suggested that, rather than directly comparing either plasma or brain concentrations, --

DR. CONTRERA: Yes.

CHAIRMAN BONE: -- the dosage should be compared as multiples of the anorectic dose. Would you care to comment on that? Dr. Seiden's group particularly made that suggestion.

DR. CONTRERA: I think the anorectic dose varies with species. For example, the anorectic dose in mice is really high. In fact, they were fairly resistant of weight reduction.

I think in rats it was around two and a half milligrams per kilogram. And so the multiples of the anorectic dose would be what, from two and a half to eight.

CHAIRMAN BONE: He suggested in his writings that the multiple was quite low in which toxicity emerged. The question I'm asking you is your opinion of the legitimacy or meaningfulness of adjusting in that way. Does that somehow add something to what we see from brain levels?

DR. CONTRERA: I don't know if it would really add much. It's just another way of looking at

the information we have. I think now that we have the brain levels in humans, the clinical steady state level in humans, I think everything is based, no matter what species you use, I think everyone agrees, including the sponsor and the agency, that the neurochemical, whatever you want to call it, neurotoxicological effect, we use the marker of long-term depletion. And that means for weeks after use cessation of dosing. We use that as a marker for some unusual effect of this drug. Then you get a ratio of around 10-15 if you use the values that we have in rat and calculate that to humans.

Then, no matter what species you use, probably -- and, I mean, this is my estimation -- a 40 to 70 or so micromolar concentration in the brain will give you this long-term depletion effect, --

CHAIRMAN BONE: I see.

DR. CONTRERA: -- and whether it's a human, a monkey, a mouse, a rat, or anything of that sort. And so in the humans, right now the clinical level is only four. So you can, you know, use judgment in terms of that.

CHAIRMAN BONE: Thank you. I just have one or two more questions related to this if you don't mind for you.

DR. CONTRERA: For me?

CHAIRMAN BONE: Yes. The comments were made earlier, a representation was made earlier, and I did take a moment during the presentations to look at the prior transcript, that the information presented suggesting the failure of the axons to regrow or the tangles were actually not dexfenfluramine. Is that your understanding as well?

DR. CONTRERA: No, no. Well, I know that there is work in the literature, including some work in Mario Negri, I believe, that showed that dexfenfluramine can cause swelling and abnormal axonal terminals. So by immunohistochemical --

CHAIRMAN BONE: Well, I guess specifically the reference was to the comments by Dr. Molliver where he showed some slides and he was talking about tangles. And we heard earlier the comment that that was not based on dexfenfluramine, that those weren't dexfenfluramine slides. Do you know for sure one way or the other?

DR. CONTRERA: He never gave me his slides, and I never saw his. But he mixed examples of MDMA and fenfluramine. I could see people getting mixed up at which one was which in that discussion.

CHAIRMAN BONE: I see. Are you prepared

to accept the sponsor's consultant's explanation of that, then?

DR. CONTRERA: Well, the word "tangled" is -- I think there's enough evidence in the literature that said that dexfenfluramine can produce morphological changes when evaluated by immunochemical means that show swollen, abnormal axons and an absence of fine fibers.

Now, there were theories that this could be due to the serotonin that's released and things of that sort. There are all kinds of explanations. But there is evidence in the literature. That's all I can tell you.

CHAIRMAN BONE: I see. Which do you think is the meaningful figure, then, for us from your -- do you think the 15 is the figure we should be using for a margin of safety for our estimation?

DR. CONTRERA: Well, you see, the way toxicologists -- I get criticized form many of my colleagues. They say, "You're talking margin of safety. You can't use the lowest toxicological effect for margin of safety." You really want to talk margin of safety, you have to use the highest no-effect level.

So then you look at the data. Well, in

that case it would only be four or five if you use the lowest effect that caused no long-term depletion ever. And I didn't think that was fair either in this case because there are a lot of unknowns.

One thing I could say is that if you have long-term depletion, even if the axon has survived, is there, a nerve axon without a transmitter is like an electric circuit without current. If we turned off the current now, this building, this room is perfectly normal except that we won't have any lights. I mean, it's essentially the same thing for a nerve.

So that goes on for 13 weeks or 16 weeks. That's unusual. That's all.

CHAIRMAN BONE: Thank you very much.

Were there other questions? Dr. Cara?

DR. CARA: Forgive me for perhaps asking a very simpleminded question, but is there a way that you can do, for example, a meta analysis and look, for example, at patient years on drug versus placebo and get some idea of morbidity and mortality?

DR. CONTRERA: Well, that's probably outside my area. I'm in the neurotox and neuropharm area. That may be another --

CHAIRMAN BONE: Would Dr. Stadel want to

--

DR. CONTRERA: Dr. Stadel might be able to answer that.

DR. STADEL: Understand everything is short-term except the index study. I mean, you can meta analyze away, but you still won't answer the question.

DR. CARA: Thank you.

CHAIRMAN BONE: Any further questions for the agency personnel? Dr. Critchlow?

DR. CRITCHLOW: I was going to ask Dr. Contrera. What relative importance should we place on the amount of data from the monkey model in terms of trying to assess margin of safety versus the relative overabundance of data that we have to look at in the rat or mouse?

DR. CONTRERA: The more we've struggled with this, the more we realize that probably species isn't as important as the concentration of dexfenfluramine and nordexfenfluramine as attained in the brain of that species and that perhaps it's a threshold effect. As long as you're below that threshold, you probably won't see many of these effects. And you exceed that threshold, you will see the effects.

So we don't have enough data in the

monkey. And the squirrel monkey reports that were published unfortunately didn't include a wide enough span of doses so that we could see a no-effect dose in that monkey and an effect dose in the monkey. So all we have is the 10-milligram per kilogram level that caused considerable concentration of the brain in the monkey, like 130-micromolar concentration.

So that in the monkey perhaps one or two milligrams probably give that effect. I mean, I would guess that if I were to do the monkey study, I'd shoot for 40 or 70. And I'd get it at 40 and 70. If I went down to the human level, I wouldn't get it. But that's my conjecture.

CHAIRMAN BONE: Are there further questions from Committee members for the agency?

(No response.)

DISCUSSION AND QUESTIONS

CHAIRMAN BONE: Now, I think this is the opportunity for the members of the Committee to discuss amongst the Committee about questions that we may have, I think, points that we want to raise or discuss amongst ourselves.

I think the best way to do this based on our prior experience is to ask everyone to make comments. We'll eventually go around the table and

make sure everyone has had an opportunity to make comments or remarks.

And then when we get to the voting on the questions, I'm going to really ask everyone to just confine themselves to the answers to the questions. I would like any remarks to be made, particularly any remarks at any length to be made, during the discussion period so that we do not have any confusion during the voting.

Dr. Bilstad?

DR. BILSTAD: Well, I just wanted to make a comment to your question to Dr. Contrera --

CHAIRMAN BONE: Oh, I see.

DR. BILSTAD: -- about the point that the sponsor was making on whether the studies that Molliver had done were conducted with dexfenfluramine or fenfluramine. I went over the transcript quite carefully on that point, and I interpreted it to mean that the study, the slides that showed the tangles were not, in fact, done with dexfenfluramine or fenfluramine. So I agree with what the sponsor said on that issue.

CHAIRMAN BONE: That's just what I was trying to get to. I wanted to distinguish between whether there was language in the transcript that

might confuse us or, in fact, that was the case.

DR. BILSTAD: I think it was fairly stated that he had not done the studies.

CHAIRMAN BONE: Okay. Dr. Cara?

DR. CARA: I would like some clarification on the questions before we get to them. I don't know if you want to do that before or after we comment.

CHAIRMAN BONE: Well, why don't we have a little general discussion and then come back to the questions and clarify it just before we answer the questions? Because some of the questions we have about the questions may be resolved in the discussion and there may be discussion-emergent questions as well. All right.

Let's see. Why don't we just start around the table, if that's agreeable to anyone? Any comments or remarks you'd like to bring up at this point, Dr. Critchlow? We'll go around again after everyone has spoken.

DR. CRITCHLOW: I think the take-home message for me in having reviewed the materials and listening to further presentations is my impression would be that there's probably a beneficial effect of the drug for certainly just a subset of patients for which it would be prescribed and that, unfortunately,

with all due respect to Dr. Faich, I think the benefit to risk ratio was probably vastly overstated in his presentation, although I think for a group of patients, it probably would still come out on the positive side, but certainly not for all.

CHAIRMAN BONE: Yes. I had the same concern. It was raised by Dr. Stadel's comments. And I think I had exactly the same concern.

Dr. Borhani?

DR. BORHANI: Yes. I have two short comments I would like to make. First, as I said earlier, I hope that we can concentrate and focus on the questions of efficacy and safety based on what I understand the claim of the sponsor is for this drug; i.e., losing weight.

And all the related advantages or disadvantages that may be associated with losing weight by having this drug in the market I would like to submit, respectfully, that is a separate question, must be dealt with separately. And I hope that we will not confuse the two at this time.

And my second comment has to do with this issue of neurotoxicity. I was very concerned last time. I'm glad that Dr. Bilstad brought it out, and I'm glad the sponsor identified it. And I'm glad I

read the transcript because that was indeed my understanding, that the presentations we heard dealt with a different kind of drug and not this drug. And I'm very happy to see this clarified. Thank you very much.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: I guess I've said about as much as I want to say. The issue, I guess, that we all have to wrestle with is it's relatively unique to have a weight-reducing agent indefinite use. I mean, that, to my understanding, is the issue that we're trying to deal with today.

And we don't have any data to know what the long-term impact is on that other than one study that has been used for lots of purposes during the course of this presentation. And I think we all are going to have to wrestle with the fact that we don't have a lot of information to look at the long term, although we have a lot of data presented to us over the short term.

I guess with respect to pulmonary hypertension, just a remark. And that is that it's a very subtle disease that can develop insidiously. And it may take, I suspect, a while to appreciate it exists. So we may be underestimating the full

presence of pulmonary hypertension over a relatively short period of observation.

So, again, my biggest concern is related to the long-term course of events. And I wish I had more information.

And my other concern, just to mention, that I mentioned before was that we don't have a lot of powerful data with respect to cognitive functioning. In my view, having done these tests on different occasions, they're not robust tests. And 25 patients in a group is totally inadequate to assess that. So, consequently, we're dealt with inadequate data in terms of evaluating a long-term effect on brain function.

And so I am a little bit stuck because I don't see major problems here, but I don't -- there's a big window of unknown that I'll have to wrestle with in my vote.

CHAIRMAN BONE: Dr. Kreisberg?

DR. KREISBERG: I'm not sure that I'm going to say anything that hasn't been said. I think the issue of the efficacy is what concerns me most now.

I think the sponsor did a terrific job, although it was much too long, of dealing with some of

the issues that were raised at the last meeting of this Committee and which concerned us all. I feel reassured, even though I agree with Dr. Sherwin that we perhaps would like to have seen more data and data on longer follow-up.

One of the points that I'd like to make in favor of the drug, even though I am not sure that it's across the board as effective as I would like it, I don't think it's a breakthrough in the treatment of obesity personally. I hope nobody is offended by that. But there is a subset of patients for whom it is very effective, for whom it appears to be very effective.

And I think the analogy is that when you take a population and try and change their cholesterol, you treat a lot of people in whom the cholesterol doesn't change, but there are some people who benefit from cholesterol lowering. And that's reflected in a substantial reduction in population-related disease. But not everybody benefits.

And I think the issue here with obesity is that this is a spectrum of response and that if we could only better identify those who are going to get the benefit from it, that that would allow us to limit

the use of the drug to those people.

I think the suggestion that weight loss in the first month might be a predictor would be excellent. But what I would like to emphasize is that I think that people will read instructions very superficially, that the physicians may, in fact, not look very carefully at the fine print and that the company would need to conduct an extensive education program to make sure that physicians knew that the drug had limitations and that if there was no evidence of an adequate response within a short period of time, that the drug should be discontinued.

CHAIRMAN BONE: Perhaps I'll pass and speak last.

DR. MARCUS: Thank you.

I'll try to be brief. And I will not reiterate the points that have been made by Dr. Sherwin and Dr. Kreisberg, both of which I agree with. However, there is a new point that I don't particularly expect a response to, but just to register a concern.

Something has been stated during the course of the afternoon that this drug has been shown not to have a high abuse potential. The way that abuse was described was I think within relatively

narrow constraints, including manifestations of addictive behavior, et cetera.

There are people in this population where there's another epidemic. It's not the epidemic of obesity, but maybe obesity standing on its head, and that is anorexia nervosa and other eating disorders. There are college-aged gymnasts, dieters, cheerleaders, and other people who are being encouraged all the time to get down below some arbitrary weight, be it 100 pounds or something like that.

I see heavy potential for let's not say abuse. Let's just say inappropriate use of this medication in those particular quarters. And I think it's incumbent upon the sponsor and upon the people particularly in the marketing arena to come up with some sort of a strategy to try to minimize that and make sure that these sorts of inappropriate prescriptions of this medication are not easily done.

CHAIRMAN BONE: Dr. Colley?

DR. COLLEY: I would agree with Dr. Marcus' point that the potential for usage of this drug is going to be far beyond the indicated population. And, for that reason, I was going to discuss more with regard to labeling that there should

also be some patient labeling, some patient education.

I know just since last year, when there was a Reader's Digest article on weight loss drugs published, I've received a number of questions from patients about "Well, what about these pills that help us lose weight? Where can we get them?" And the perception is still that there is a pill that helps me lose weight.

And the emphasis I think is, unfortunately, removed from the other changes. And, for that reason, an educational effort directed towards patients I think is important as well.

DR. CARA: I agree with many of the comments that have been said, especially Dr. Sherwin's. I think he put it very eloquently. I think he voiced very eloquently the struggle that we're all dealing with right now.

I want to mention a couple of other things that I myself am struggling with at this moment. And that is the fact that this is, quote, unquote, "the only thing we've got."

On the one hand, it would be nice to have something available. On the other, what's available may not be all that great not so much in terms of short-term efficacy, but in terms of the questions

related to long-term efficacy.

The other issue that I'd like to raise is my concern about this drug being seen as a magic bullet and the fact that the success rate with this kind of therapy will be much less than we will anticipate based on the observations that we've heard today simply because of the fact that people will see this as a, quote, unquote, "magic bullet" without really recognizing the need for adjunct therapy in the treatment of obesity.

CHAIRMAN BONE: I agree with many of the comments that were made, would like to make one or two additional comments. Firstly, I think it's important to bear in mind that the specific issue here is the long-term indication.

If we were talking about an application for the drug to be used for the same period as either anorectic agents which are already approved, we would probably not be talking because we would be looking at the comparison between this isomer and the racemic mixture, for instance. But we are talking about essentially an unrestricted duration of treatment and the differences that we need to take into account here.

Also we have had a recent recommendation

that the drug be delisted as a controlled substance because it was regarded as not being a drug of abuse but perhaps of misuse, as Dr. Marcus was talking about. And that's a factor that does weigh as well into the likely applications.

I think that we have to look heavily at the long-term data; that is to say, the evidence that we have over the one-year study. And that is the only long-term data we have, the index study, in terms of controlled trials.

We did see that the drug is marginally efficacious overall in that category in comparison with the guidance but does have a subgroup of patients who have a significant weight loss.

I think we have had some mitigation of concern at the very least with respect to the question of neurotoxicity. It is now apparent that some of the most worrisome information that we were presented the last time, in fact, may not be characteristic of this particular agent.

There I think is still some residual information that there is a potential at higher doses for neurotoxicity. And we have some question about whether the margin between the no-effect dose and the clinical dose is 4 or 10, something like that.

The information on the emergence of neuropsychiatric abnormalities in clinical trials where certain of these were evaluated and in the clinical database, it is somewhat reassuring that nothing emerged. On the other hand, we can refer, I think, with benefit to Dr. Mann's letter to the sponsor at their request, the letter that they solicited.

And I think the point was made earlier by Dr. Sherwin that, as Dr. Mann says, although there is a vast clinical experience suggesting that the drug does not produce detectable abnormalities, the neurocognitive testing that has been employed has been of rather poor quality at this stage. It goes to mention those points that have been made before.

So I think it would be very bad if we saw something with relatively insensitive measures. It is not absolutely reassuring that nothing has emerged so far for reasons mentioned by others.

We have had I think what appears to be a reasonable estimate by Dr. Stadel of the risk of deaths from pulmonary hypertension. We need to understand clearly that it's quite likely that if a million patients take this drug, at least a couple dozen of them will die annually as a result of this

complication. That seems to be the best estimate. This is something that has to be weighed seriously.

The sponsor, as we are asked to take into accounts risks and benefits, has made some calculations about benefits. But, as Dr. Critchlow, Dr. Stadel, and others have pointed out, one might take issue with some of the premises on which this calculation is based.

The first question is whether one can give the drug-treated group the drug credit for all the reduction in mortality; whereas, probably two-thirds or something like this was seen with the placebo group.

So a very substantial reduction in the imputed benefit has to be made in order to account for the fact that we are only to look at the difference between the placebo group and the treatment group, not looking at all of the other effects.

Secondly is a question of whether this extrapolation is warranted at all. Of concern is the fact that we have very little information about the actual reduction in mortality from weight loss programs and, as far as I can see, no information at all about actual reduction in mortality from anorectic use.

The suggestion has been made by Dr. Stadel -- and it seems to be a legitimate interpretation, if not the only interpretation -- that since the magnitude of the weight loss was a poor predictor of the degree of reduction in mortality, the hygienic measures employed, such as change in the composition of the diet, increase in fitness, and other measures which might have been introduced in that trial, may have had as much to do with the mortality reduction as the actual weight loss. Beyond this is a question of whether weight loss achieved in one way is equivalent to weight loss achieved in another way.

So I think the suggestion by Dr. Marcus, I believe, that the calculation may have looked at the most optimistic case is once again at least a legitimate suggestion. And it's one for which we do not have information at this point.

I guess the point I'm reaching here is that it may be that the actual difference in mortality -- one further point is that most of the benefit seemed to be in patients who had improvement in co-morbid or obesity-related conditions. And we have precious little information about the long-term effects of this drug on those conditions specifically.

So I think that, for these three reasons,

there is considerable concern that, in fact, the reduction in deaths in the obese group that might be expected strictly as a result of the use of the drug over and above other measures may not be very much greater than the risk of pulmonary hypertension. We can't calculate those with precision. I would be very surprised if the confidence intervals for those estimates, if calculable, did not overlap substantially.

One of the points that Dr. Kreisberg made was that it would be very nice if we had a way of confining the use of this drug to people who really got a major benefit from it. The sponsors referred earlier to the recent action by the French regulatory authorities in which extended use of the drug is now contemplated.

What was not really emphasized was that the French regulatory authorities are in a position to and, in fact, have restricted the initial prescribing of this drug to specialists in metabolism and obesity. And the patient to get a refill must present not only the prescription from their general practitioner but also the original prescription from the specialist. And, if I understand the French document correctly in its translation which I read, it's implied that an

annual review by the consultant or specialist is required.

This gives the French regulatory authorities a way of, in effect, making sure that the drug is used only in those patients who have the greatest benefit and that specialist attention is paid on an ongoing basis as well, but particularly in selection of patients for treatment and for continuation of treatment after the initial response is determined.

This is not something which the laws of the United States permit. There is simply no mechanism for doing this except in the advisory sense in which the labeling by the sponsor and the promotional efforts of the sponsor and educational efforts by the sponsor are undertaken to guide physicians in this way.

So these are my amplifications -- I'm sorry for going on a bit -- that we'll have to weigh as we're thinking about the actual votes on this application for long-term approval.

Have we reestablished communication with Portland? We lost our telephonic correspondent during the question period. And I was hoping to ask if he had questions. Okay.

DR. KREISBERG: Could I make one?

CHAIRMAN BONE: Yes, Dr. Kreisberg?

DR. KREISBERG: And I don't mean to correct you, but I think there's a misunderstanding. The Williamson study is not an intervention study. It's an observational comparison.

CHAIRMAN BONE: That's right.

DR. KREISBERG: And it's not randomized, not prospective. And it has a lot of limitations to it as a result of that --

DR. STADEL: It's not randomized. It is prospective. It's not randomized. It is prospective. It is not randomized. I did not represent it as a --

DR. KREISBERG: No. I know you didn't. But, I mean, sort of the assumption around was that it had more significance than it really does.

CHAIRMAN BONE: No. I didn't mean to imply that at all. Pardon me if I did.

Let's see. Dr. Deitch is reminding us that the company made some commitments at the Drug Abuse Committee meeting about commitments for education and its appropriate use. Thank you, Dr. Deitch, for reminding us of that.

Are we back in touch with Dr. Illingworth? Dr. Illingworth?

DR. ILLINGWORTH: Yes. I'm back with you guys. Thank you.

CHAIRMAN BONE: Did you have additional comments or questions?

DR. ILLINGWORTH: Yes, one comment or question for perhaps Dr. Lutwak. Any correlation between the magnitude of weight loss and the changes in either glycemic control, lipids, or blood pressure? Because if you put it all in the intent to treat base, then you'll dilute the effect of people in whom the drug does work with those in whom it did not.

DR. LUTWAK: We only have means that were reported.

DR. ILLINGWORTH: Right.

DR. LUTWAK: And we don't have the individual case reports in those studies. So I cannot answer your question.

DR. ILLINGWORTH: Okay. Thank you.

CHAIRMAN BONE: Thank you.

Further comments or questions? Let's see. One last time around the Committee. And then we'll review the questions. And then we'll vote. Dr. Critchlow had a question.

DR. CRITCHLOW: I mean, I would agree with Dr. Marcus that the potential for misuse may be

sufficiently high as to argue against widespread availability. I mean, how much teeth, if at all, does labeling restrictions or labeling comments have?

CHAIRMAN BONE: Well, people from the agency may wish to comment. As a practitioner, I can say that once the drug is approved, the agency regulates, I believe, the distribution of the drug and the advertising, promotion of the drug, but does not in any way regulate the actual prescribing of the drug. Would that be a correct statement?

DR. SOBEL: That's right. The practice of medicine in this country dictates a lot. The only restraint that a doctor may feel is that if he goes too much against labeling, he exposes himself to medical liability. But practice of medicine is a fairly liberal thing in this country.

CHAIRMAN BONE: It's not regulated by the federal government. It's regulated by the states.

DR. SOBEL: We do not regulate the practice of medicine. The states, as Dr. Bone said, state licensing authority, may pursue physicians that they feel have used their liberal state unwisely.

DR. CRITCHLOW: And the other comment is it's of some concern that we basically have one long-term study, even though that is among a large

number of patients.

And I don't know if it's feasible to either suggest or perhaps it's just not feasible to try to do another long-term study which would or might specifically evaluate effects on co-morbid conditions or again try to look among other subsets of patients for some benefit.

CHAIRMAN BONE: I'm sure it's always possible to do another study. Certainly the magnitude of the indication, the enormous volume of expected sales there I think would reward a successful application that had such a study in it. So I would think that would only be a question of time and effort, rather than possibility. That's my own view. Others may disagree.

Just one last time around, then. Dr. Borhani, any other comments before we go to the votes?

DR. BORHANI: No except that I just want to bring to your attention that, especially since Dr. Marcus was not here, last time we met jointly with the other committee. I can't remember the proper name, but there was another advisory committee and this committee.

CHAIRMAN BONE: Drug Abuse.

DR. BORHANI: We met. And they

deregulized or decontrolled it. I don't know what the proper name is for that single drug. And there were lots of testimonies by sports medicine people and other people who expressed concern about the issues Dr. Marcus raised. And this issue, despite that, the Committee recommended approval that that drug be removed from controlled substance.

I think this issue becomes an issue of labeling and physician and patient education. And I hope that, as we heard, this will be done. And hopefully that will take care of it, I think, if they do a lot of physician education properly, as they said they would, and public education.

But that issue is a labeling issue. We may want to consider it later in the labeling suggestions perhaps.

CHAIRMAN BONE: Just before we vote, one more round for comment.

DR. SHERWIN: I have just one question.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: If we approve dex for long-term use, how does that affect fenfluramine? And will then both drugs be utilized for that purpose?

CHAIRMAN BONE: As far as I know, that's used -- I don't know if anyone can speak to the

question of how it might be used, but it would not automatically affect the labeling of racemic fenfluramine. Actually, the same company will be marketing both drugs.

DR. SHERWIN: Right. One is -- yes? Go ahead.

DR. SOBEL: Well, the racemate, of course, has some other characteristics, which the company has conveyed to me as having different effects on sedation, et cetera.

There are issues that arise for the company who has done -- not taking into account the fact that Wyeth-Ayerst and Interneuron will control both, but ordinarily when a company has done a clinical trial that has resulted in data that have led to a particular clinical usage and in this case, as has been emphasized, the real issue is long-term use, then there will be exclusivity issues revolving on that.

There is one other issue that we will have to answer definitively, we think we will answer definitively. When you have an isomer, how much exclusivity is granted? Is that given a new drug status or is the isomer not?

I think our current thinking is that the

isomer itself does not give it a new molecular entity status. So the exclusivity issues will not be as large as they might have been. So let me just get clearer on it.

There is some exclusivity that would be gained by the fact that the dexfenfluramine has done clinical studies. This exclusivity could carry three years perhaps.

Whether one would apply findings in the dexfen to the fenfluramine labeling, I think in certain areas we tend to apply things. That would be on safety issues discussed in the dexfen. I think we would insist going into the fenfluramine.

The efficacy part of it I don't think is that readily transferable, both because of true scientific considerations and because of exclusivity issues. Perhaps Dr. Bilstad wants to amplify a bit.

DR. BILSTAD: Well, I just wanted to say that any consideration of exclusivity would be -- I mean, obviously there could be agreements made between the concerned parties.

CHAIRMAN BONE: But I think the direct question was: Would you extend the period of treatment for the racemate? And I guess the answer to that is no?

DR. BILSTAD: Right, not without an application and data to support it.

CHAIRMAN BONE: Right. But this wouldn't do that?

DR. KREISBERG: Can we advise the FDA to limit long-term use contingent upon additional information? In other words, we have been presented data that extends out about a year in the very best study.

We are all concerned about long-term use of this drug. So it would seem to me that we might be able to both provide a recommendation and at the same time expect more information for continued long-term use.

DR. SOBEL: Yes. I'm glad you brought that up. I sort of mentioned it briefly in my morning elucidation or clarification. You certainly could put that in a section of the labeling, either "Dosage and Administration" or perhaps "Warning." You have to have a level of concern.

If you feel that it's a dosage and administration thing, as we did for alandronate, we said that safety and efficacy in the "Dosage and Administration" section have not been established beyond four years.

On the other hand, if you feel the long-term considerations are such that they have more problems, you might want to put that in the "Warning" section.

So there are different ways you can express your degree of anxiety and concern. And I feel that you'll come to that in both Questions 1 and 4, proposed use by a sponsor and labeling.

Yes. To give you a short answer now, yes, we can place some form of limitation of long-term use and make it sort of a rolling issue pending future results. And that is one of the things I did want the Committee to consider.

CHAIRMAN BONE: But that would be in the nature of an advisory, rather than nature in the labeling, rather than any --

DR. SOBEL: Well, it would appear in the labeling. You know, we have ways of giving signals as far as our degree of concern as to where it appears. It could go all the way from "Contraindications" to "Warning" to a mild shrug in the "Dosage and Administration." But that's the type of judgment, you know, we'd like to hear about.

CHAIRMAN BONE: Okay. Let's see. Dr. Marcus?

DR. MARCUS: I have nothing to add.

CHAIRMAN BONE: Dr. Cara?

DR. CARA: Clarification of a question.

CHAIRMAN BONE: Can we get to that in just a minute? This is your last round of questions before the questions.

DR. CARA: Just one other question of Dr. Sobel, if I may.

CHAIRMAN BONE: Please.

DR. CARA: How do you interpret or what is your read on the French government's guidelines regarding use of anorectics, especially dexfenfluramine?

DR. SOBEL: Well, it's clear they differentiated between the so-called amphetamine series from the dexfenfluramine. They felt that the amphetamine-like drugs have a poorer status. And they do not recommend those for long-term use.

They did permit, as Dr. Bone explained, under certain conditions a long-term use of dexfenfluramine with the initial evaluation by a specialist and subsequent ability for general practitioners to write on it with periodic review.

So if you ask me "What does the French position say?"; the French position seems to say that

they feel the drug is probably safe. They express no concerns in regard to neurotoxicity. In France the main issue was the primary pulmonary hypertension. And their action appears to dismiss that as an important issue.

So my read of the French regulators was a favorable one for dexfenfluramine, but, as Dr. Bone says, they have a lot more filaments and strings that they can attach than we can. So perhaps you have to view it in that way. They have a little bit more feeling of control.

CHAIRMAN BONE: Well, several of us have expressed a little frustration about the limitation on the amount of long-term data. The sponsor has commented that several thousand patients have been exposed in clinical trials and the large number of patients exposed in non-trial settings.

But I think we do have to consider the enormous scope of use of this drug. You're talking about tens of millions of people who potentially will take this drug. And it is I guess somewhat disappointing that a drug which has actually been around for such a long time doesn't have much more extensive long-term information of the kind that would help us to resolve of these questions about: What is

the long-term effect in Type II diabetes on morbidity and so forth?

I think it's a point where we have perhaps admonished sponsors in general that it's really incumbent on them to do this kind of work as they go along and so that when we get to this kind of point we don't have this recurring frustrating problem that's been around forever and we don't have the data in rigorously controlled studies.

Dr. Cara?

DR. CARA: I'd like to extend on that that the Phase 4 studies are not the solution --

CHAIRMAN BONE: Absolutely.

DR. CARA: -- because generally they lack the rigor and the incentive to really get any worthwhile data.

CHAIRMAN BONE: I share your concern about that, although people can do very good Phase 4 studies at times.

Dr. Illingworth, any further comments before we specifically go into the meaning of the questions and then vote?

DR. ILLINGWORTH: No. Thank you.

CHAIRMAN BONE: All right. Now --

DR. ROSENWALD: Excuse me. Dr. Bone? I

apologize, but --

CHAIRMAN BONE: Who are you?

DR. ROSENWALD: Dr. Rosenwald, a member of the Board of Directors. There's a very serious misunderstanding that Dr. Critchlow has that I wanted to make clear.

When we licensed the drug, it had a very short patent life. We thought that because of the human data that is available, it is highly unlikely that further studies would be done because of that.

CHAIRMAN BONE: I see. Thank you.

A representative of the company says that because of the short patent life, he doesn't think they would do additional or major studies, if required to, prior to approval. Is that correct? Did I correctly summarize your comment, sir?

I was just asked the relevance of your comment or the point you're making. I was trying to summarize as fairly as I could that I didn't catch your name, but you --

DR. ROSENWALD: I'm Dr. Lindsey Rosenwald.

CHAIRMAN BONE: Dr. Rosenwald.

DR. ROSENWALD: I'm sorry? Dr. Lindsey Rosenwald.

We licensed it because it was one of the

most heavily used and experienced drugs in history and had a huge experience in safety.

CHAIRMAN BONE: Sir, please. His comment was that he wasn't planning to do more studies or that he might not.

Is the meaning of the first question clear to all of the Committee? Dr. Cara says the meaning of the first question is not clear.

DR. CARA: No.

CHAIRMAN BONE: Dr. Sherwin. Others feel that's too bad. Let's see if we can clarify it. The first question is: Based on currently available safety and efficacy data and considering the overall benefits and risks of the use of dexfenfluramine as proposed by the sponsor, do you recommend approval for marketing?

DR. CARA: The trouble that I'm having with it is the "as proposed by the sponsor." I just reread the labeling, the draft labeling. And all it says is "indicated for the treatment of obesity."

CHAIRMAN BONE: That's the proposal from the sponsor.

DR. CARA: That's it? That's --

CHAIRMAN BONE: I mean, as far as I can understand, that's the proposed.

DR. COOPER: We have caveats of the --

CHAIRMAN BONE: Please stand and quickly identify --

DR. CARA: It says BMI greater than 27.

DR. COOPER: We have modified today, I believe. We proposed that the BMI be set at 30 for patients without co-morbidities and 27 with patients with the co-morbidities.

In terms of the duration of use, which is I think what you're getting at -- is it not?

DR. CARA: Well, both.

DR. COOPER: Yes.

DR. CARA: Specifically what sub-population you're --

DR. COOPER: Clearly the population is patients with a body mass index of 30 or greater in the absence of diabetes, hypertension, or dyslipidemia or a body mass index of 27 in the presence of those co-morbidities. And that's a shift from the original labeling that we submitted back in September because I think we understood from the Committee discussion that there was a fairly strong desire to see a higher threshold for that.

In terms of the duration of use, I think we've taken the obesity guidelines to indicate that

long-term therapy is equated with clinical trials of one year in duration. And we certainly can --

DR. CARA: You lost me there. Can you translate what you just said? I'm sorry.

DR. COOPER: I'm sorry. The long-term use of obesity, I believe, by this Committee has been defined to be clinical trials that show safety and efficacy for a period of time of one year or longer. And that's what we've provided.

We certainly are very willing to adequately describe the database in the package labeling session, as Dr. Sobel has suggested in terms of adequately describing what, in fact, the recommendations are based upon.

CHAIRMAN BONE: But, essentially, it's for indefinite use as it stands in terms of the duration of the treatment?

DR. COOPER: Long-term or indefinite use, yes.

CHAIRMAN BONE: Does that answer your question, Jose?

DR. CARA: Yes, sir.

CHAIRMAN BONE: Thank you.

Are there further questions about Question 1?

DR. SOBEL: I just wanted to add a bit to Dr. Cara's concerns. And since I want the use to be clear, what about the contingency about early response? Is that going to be something -- and also issues that we have discussed concerning monotherapy and the other things that have come up.

The proposed use, it's sort of a blend of 1 and 4. We may get back to it when we get the labeling indications. But I just want to say that proposed use should have those dimensions.

DR. COOPER: Yes. And I think we agree with that very strongly. We think that the responders' analysis is a very important tool for coning down on those patients who are most likely to respond and eliminating those patients who are lease likely to respond. And I think that's the sensible way of approaching the pharmacotherapy of any condition and obesity, in particular. So we would like to see that prominently highlighted in the package insert.

With respect to the monotherapy you mentioned, I think that this drug has been tested as monotherapy versus placebo with diet in both groups. And that's certainly what we will recommend.

We think it would be a large mistake to

combine the drug with another serotonergic agent. We had this discussion briefly the last time. We think that's a fertile ground for synergistic serotonergic adverse events, and we don't think it's rational with respect to noradenergic agents, such as phentermine or others. There's no clinical data to bring to bear on that.

We certainly would not recommend a combination therapy in the absence of clinical data. We think this is monotherapy.

DR. SOBEL: I have one more thing. In your response to Dr. Cara's question about the duration of use, you stress properly the database, but you sort of shied away from saying what you would actually say in the labeling about how long this drug should be used.

DR. COOPER: Well, we certainly would be very comfortable in describing that efficacy has been seen for one year in duration, which describes, I think, the clinical trial database.

And, further, further descriptions or limitations we would be very obliging to work with the Committee and the agency in defining the best way to describe the database, on one hand, and the need for chronic therapy in this commission, on the other hand.

CHAIRMAN BONE: But apart from discussions of the database, we are, as we talked about before, talking about long-term or indefinite use, as opposed to the restricted use from before. That's the major distinction here.

DR. COOPER: I think the major distinction is that previously all approved drugs today have only very short-term indications, a few weeks, at the most a couple of months. And this is a substantial shift from that paradigm.

DR. CARA: I'm still not clear on what you're saying. What you're saying is that you're recommending treatment for a year or indefinite use?

DR. COOPER: I think our --

DR. CARA: I feel like you're hedging here.

DR. COOPER: No, I'm really not hedging. I'm trying to acknowledge that we're very interested in the Committee's and the FDA's input into the proper labeling for this agent, but we've taken the past deliberations of the Committee to indicate that one-year clinical trials showing efficacy for one year is, in fact, a surrogate, a very rational surrogate, for long-term use.

DR. CARA: I.e., greater than one year?

DR. COOPER: I.e., greater than one year, yes.

DR. CARA: Okay.

CHAIRMAN BONE: Are there further questions about the meaning of Question 1? Dr. Illingworth?

DR. ILLINGWORTH: Would you like me to go first?

CHAIRMAN BONE: No. I'm just saying: Do you have any further questions? Are we clear?

DR. ILLINGWORTH: The question is clear to me.

CHAIRMAN BONE: Sorry?

DR. ILLINGWORTH: The questions are clear to me. Thank you.

CHAIRMAN BONE: Perfect. Okay. Great. I think what we'll do, then, is just ask -- now that we've clarified Question 1, I think we should vote on it as quickly as possible.

(Laughter.)

CHAIRMAN BONE: And we'll start around. We started at the right-hand side of the room several times. And we'll start at the other side of the room. But since we always think of the Pacific Coast as the left coast, we'll start with Dr. Illingworth for his

vote on Question 1.

DR. ILLINGWORTH: My response to Question 1, "Based on currently available safety and efficacy data, overall benefits and risks in the use of dexfenfluramine, would you recommend approval for marketing?"; yes owing to Question 2 being positive, being --

CHAIRMAN BONE: I can't do that, Roger. I'm sorry, Roger.

DR. ILLINGWORTH: I vote yes on Question 1.

CHAIRMAN BONE: Okay. The point that was made earlier, before we go around, by Dr. Bilstad is that we cannot make a recommendation for approval contingent upon something that happens in the future or how something comes out.

So the Question 1 is based on the, has to be based on the, data. The law requires that this be done based on what's in the NDA, currently available safety and efficacy data. Okay? Are you still --

DR. ILLINGWORTH: It will still not change my vote. I vote yes.

CHAIRMAN BONE: Fair enough. Thank you.

Dr. Cara?

DR. CARA: I have to vote no.

CHAIRMAN BONE: Thank you.

Dr. Colley?

DR. COLLEY: No.

DR. MARCUS: Yes.

CHAIRMAN BONE: No. That was Dr. Bone. This is Dr. Kreisberg. Dr. Marcus was the one before me. I'm sorry. So it's Dr. Colley was a no vote. Dr. Marcus was a yes vote. Dr. Bone was a no vote.

Dr. Kreisberg?

DR. KREISBERG: Yes.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: No.

CHAIRMAN BONE: Dr. Borhani?

DR. BORHANI: Yes.

CHAIRMAN BONE: Dr. Critchlow?

DR. CRITCHLOW: No.

CHAIRMAN BONE: We have votes from Dr. Zawadzki and Dr. New. This is Dr. Reedy.

EXECUTIVE SECRETARY REEDY: Dr. Zawadzki is yes, and Dr. New is yes.

CHAIRMAN BONE: Thank you.

What was the count, please? Six to five in favor of approval.

The second question is, "If dexfenfluramine were to be approved," reminding

everyone that the Advisory Committee advises and the agency decides about these things. So the Advisory Committee has voted six to five in favor of approval, in favor of making a recommendation for approval, recommendation for approval.

The next question is, "If dexfenfluramine were to be approved for marketing, should the approval be contingent on a commitment from the sponsor to conduct post-marketing studies?" and "If so, what should the objectives and essential features of those studies be?"

Is this question clear to everyone? Are there any questions about the question?

(No response.)

CHAIRMAN BONE: Okay. Dr. Illingworth previously said the question was clear to him. For the sake of variety, we'll start with Dr. Cara, if we will.

DR. CARA: My answer to Question Number 2 is yes. And objectives and essential features of those studies, there's continued monitoring of long-term efficacy, the continued monitoring of long-term safety with special reference to neurotoxicity, and continued monitoring of associated co-morbidities.

CHAIRMAN BONE: The next answer will come from Dr. Colley.

DR. SOBEL: May I?

CHAIRMAN BONE: Doctor?

DR. SOBEL: May I have some input, as I asked earlier in the day, on issues of numbers of patients, times for inception and completion of study, and particular emphasis for duration of study? I know you just want "Yes" or "Nos," but --

CHAIRMAN BONE: Well, I think it's "Yes" and an essay.

DR. SOBEL: And an essay.

CHAIRMAN BONE: Yes. So Dr. Cara has given us a yes and an essay.

DR. SOBEL: Yes. That's fine. Yes. That's a yes plus an essay, which does not include duration?

CHAIRMAN BONE: How long should those studies be?

DR. SOBEL: And what numbers, things like that? These are just, I know --

DR. CARA: I can't tell you that off the top of my head, but I think that's fair. I mean, that's a very serious consideration.

DR. SOBEL: Right.

DR. CARA: And I don't think we should be casual about those factors.

DR. SOBEL: No. That's right. I just wanted you to know. I wanted to know if you want to wait until the protocols are distributed or you wanted to have some input as far as what was very important to you during the day. If you want to avoid that now, that's fine, but there are some very important issues of numbers and duration, which we can defer to our review of protocols.

CHAIRMAN BONE: Do I understand correctly, Dr. Sobel, that what you're asking us to do is if we have recommendations pursuant to an affirmative answer to the second question, --

DR. SOBEL: Yes.

CHAIRMAN BONE: -- would we make some general comments now to help get started with the clear understanding that nobody is designing the protocol at the --

DR. SOBEL: Exactly, just general, just the general. I mean, it would be foolish for you to make swift power calculations in there.

DR. BORHANI: But I have a question. Sorry.

DR. SOBEL: But I want you to express

yourself a bit on this.

CHAIRMAN BONE: Okay. I think for each person, then, we will ask for, I guess, a new answer to the first part and then additional comments if you have them. And if you don't, you don't. Okay?

DR. BORHANI: Mr. Chairman, I have a point of order question. I'm sorry.

CHAIRMAN BONE: What's your point of order, Dr. Borhani?

DR. BORHANI: The point of order question is that this Committee at this time of the day is in no position to tell the FDA experts what kind of a protocol or what parameters within that protocol they should imply to have.

That beautiful statistician, epidemiologist projected slide. And he had the parameter on the screen. And I hope that when we say yes to this question, the FDA will accept their responsibility, with all due respect, to see to it that the power calculation for answering the questions that we have expressed is enough to dictate the duration, the number of the people, the kind of randomization. These are the things that you have expressed --

DR. SOBEL: The power calculation will not

have that strong a bearing on duration. Those are two separate issues.

DR. BORHANI: No, sir. I beg to differ with you.

CHAIRMAN BONE: Dr. Borhani, I think we've noted your comments, and I appreciate them. I think what we will do, though, since the agency has asked for our advice, is those who wish to give it on this point can. And we take into account the fact that nobody is trying to decide what the protocol should be here.

Is it critical, Dr. Stadel?

DR. STADEL: Only to say that if there are comments, they can be provided in the solicitation of a proposal as comments from the Committee aimed at expressing directions or guidance.

CHAIRMAN BONE: Thank you. Yes. I think that was clear.

Dr. Cara, do you have anything further to say?

DR. CARA: Just one other thing. Continued monitoring of risk-benefit ratio.

CHAIRMAN BONE: Thank you.

Dr. Colley?

DR. COLLEY: I would say yes. And, as Dr.

Cara mentioned, monitoring for efficacy and co-morbidity, continued efficacy and co-morbidities. And, in addition to the neurotoxicity, also the primary pulmonary hypertension and possibly in which patients that occurs. There's a question of whether that might occur in non-responders, as opposed to responders.

CHAIRMAN BONE: Dr. Marcus?

DR. MARCUS: The answer is yes. And, in addition to the statements that have been made by my colleagues, I think that it's important to carry out these sorts of studies for at least multiples of five years.

We're talking about people who may be taking this medication for 30 years or more. So it would not be inappropriate to do a study for at least 5 or 10 or 15 years. And I think that a long-term study is not inappropriate.

CHAIRMAN BONE: I'll go last. Go ahead, Dr. Kreisberg.

DR. KREISBERG: I'll just say yes to that, and I don't have anything to add in terms of suggestions for long-term monitoring.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: Yes. Obviously we need to

know more about co-morbidity and really about risk. And I would suggest that the FDA get the help of some people who were experts in neurobehavioral studies and assess the various instruments that are used for the purpose of evaluating specific questions related to this drug and hopefully utilize those instruments in a powerful way.

And the other thing is in terms of duration, it should be as long as you can feasibly do it, but presumably about three to five years would be a minimum.

CHAIRMAN BONE: Dr. Borhani?

DR. BORHANI: Yes.

CHAIRMAN BONE: Dr. Critchlow?

DR. CRITCHLOW: Yes. And I would say an absolute minimum of three years, if not five or more. Also I would think as far as power calculations, one thing that would probably be of most interest is to monitor PPH incidents.

And it should be powered to detect an increase over whatever you think the appropriate background weight might be expected and I would think also to monitor maintenance of both weight loss as well as maintenance of improvements in markers associated with co-morbid status.

CHAIRMAN BONE: All right. Dr. Illingworth? Dr. Illingworth?

DR. ILLINGWORTH: Yes. I would vote yes and emphasize also that they provide in writing the need to concurrently evaluate co-morbid conditions, specifically glucose, lipids, and blood pressure. And it should include adequate numbers of patients so reliable statistical data can be obtained on either a correlation between percent reduction in body weight and improvement in these metabolic parameters and also make sure that they are assessed during ideally two to five years of follow-up to make sure that the hopefully improvements are not short-term, that they're maintained with long-term therapy.

CHAIRMAN BONE: Thank you.

My own comments are -- yes. Okay. There were comments from the two people who had to leave. Dr. Reedy?

EXECUTIVE SECRETARY REEDY: Dr. New's is yes and no additional points that hadn't been mentioned. And Dr. Zawadzki's was yes and with a number of those and another point that hasn't been mentioned yet, "with significant patient and physician education."

CHAIRMAN BONE: I would also certainly

vote yes to this. I think there are two kinds of studies in two broad categories that need to be conducted.

One is the observational type of study that several people have referred to. We may require a register in some form to carry this out in a rigorous way. And all of the observations for safety and efficacy, particularly safety, that were mentioned earlier should be included.

In addition, I think that as a contingency to approval, the kinds of studies which would be required to meet the current guidelines should be absolutely required. This would mean the two-year study, one year randomized, one year extended observation, at a minimum in large numbers with looking at the effects not only on weight loss, but specifically addressing the question of reduction of morbidity and mortality, if possible, in co-morbid states.

We're talking about patients with hyperlipidemia and cardiovascular disease. We're talking about patients with Type II diabetes and complications. We're talking about hypertensive patients with significant disease.

One of the major problems here has been

the utter lack of information over the entire history of this drug and whether the drug actually makes these people healthier. And this question should absolutely be answered.

The resources required to carry out such a study, considering that the patients will have the alternative of not participating in randomized placebo-controlled trials are considerable. That is, the resources required are considerable but will be minor compared to the revenues from the drug and should be a requirement on the manufacturer and a burden that the manufacturer should bear without undue hardship.

The third question. The next question has to do with if the dexfenfluramine were not to be approved. The Committee has recommended by six to five that the drug be approved by the FDA. It is still within the power of the FDA to decide whether or not to approve it.

So I think, even though the hour is late, we could briefly consider whether we have important suggestions about Question 3. And perhaps we'll start with Dr. Critchlow for that.

DR. CRITCHLOW: Well, I think the point you made, Dr. Bone, is a good one. And that is that

if the drug were not approved, then an additional study that would be in line with current guidelines should be required.

CHAIRMAN BONE: Thank you.

Dr. Borhani?

DR. BORHANI: I agree with that.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: I don't have anything to add.

CHAIRMAN BONE: No comment. Dr. Kreisberg?

DR. KREISBERG: I think the company ought to back off. And I think they ought to revise what they want, to accept one year of chronic therapy contingent upon the provision of other information. Otherwise, I think you're going to find yourself in a crack, to be blunt.

And so my recommendation is that they rethink what they want.

CHAIRMAN BONE: Thank you.

Dr. Marcus, if the drug is not approved, what's your answer to Question 3?

DR. MARCUS: I think that it would clearly take another plateau of understanding about the drug. If it were not to be approved, given everything that

we've heard now, that it would take yet the next step forward, which is quite a substantial step and encompasses all the things that have been described; in particular, the longer-term analysis using properly controlled psychometric testing and power analysis and so forth.

And I would say it would have to go for that and it would have to be at least a three-year study to satisfy it.

CHAIRMAN BONE: So you think meeting the guidelines efficacy study would not be sufficient?

DR. MARCUS: That's correct.

CHAIRMAN BONE: Thank you.

Dr. Colley?

DR. COLLEY: I would say in reference to that question that a study which also looked at co-morbidity to at least give more weight to the benefit-risk ratio, which I think made my decision to vote no, some co-morbid conditions and also more information on changes in body composition in addition to simply weight alone.

CHAIRMAN BONE: Thank you.

Dr. Cara?

DR. CARA: I agree with Dr. Critchlow's statement. I also would like to add a continued

evaluation and a very close monitoring of risk-benefit ratio, especially in regards to primary pulmonary hypertension.

CHAIRMAN BONE: Thank you.

Dr. Illingworth, if the drug turned out not, for some reason, to be approved, what would you think would be additional data that should be obtained prior to approval?

DR. ILLINGWORTH: A one-year placebo-controlled trial just functioning on weight loss and ideally a smaller trial in patients with a BMI level of over 27 who are hypertensive placebo-controlled, a similar population with Type II diabetes and a similar population with triglycerides over three or four hundred.

With smaller numbers on those, but using a lower BMI for entry, those were to address in specific populations the metabolic methods to be accrued from weight loss.

CHAIRMAN BONE: Thank you.

For myself, I would basically endorse the previous suggestions and also say that if it turned out that dexfenfluramine were not approved, then I think one of the other things that would be very helpful here would be if with expert advice closure

could be reached about what is actually necessary to settle all of the residual neurotoxicologic questions.

And that would mean that the people who were concerned who spoke to us in the past and the company's specialists would agree on what needed to be done and then get it done so we wouldn't have to have that argument anymore.

The final question is, "If dexfenfluramine were to be approved, what recommendations would you have regarding labeling?" And perhaps we'll start this time with Dr. Borhani.

DR. BORHANI: I think we have covered everything. My hope is that the labeling will indicate these issues that have been raised today and before. And I'm sure the FDA is expert in this field. And they can work with the company and develop the labeling in that direction. I don't think I can add anything to that.

CHAIRMAN BONE: Thank you.

Dr. Sherwin, specific comments about labeling?

DR. SHERWIN: Yes. I would feel most comfortable if the suggestion and a trial and early response was put into the labeling because it seems to me that the benefits are marginal.

And clearly there's a subgroup of people who do very well. And you really want to isolate that subgroup in the labeling since we don't know about all the long-term potential problems.

So it seems to me that it should be geared for a subgroup of people to respond. And what's what should be the emphasis.

CHAIRMAN BONE: Dr. Kreisberg?

DR. KREISBERG: Yes. I think the labeling should emphasize that this medication is an adjunct to diet, lifestyle, and behavior modification. And I agree that it should be limited to use in responders as defined by the company.

CHAIRMAN BONE: All right. Just to take a slightly different turn here as we go around the table, Dr. Illingworth, do you have any comments on labeling?

DR. ILLINGWORTH: I agree with the previous comments. I think mention should be made of the need to respond with a certain degree of weight loss before it's to continue on therapy.

There should be something about the pregnancy issue. The drug shouldn't be used. And there probably should be some information about the use in children.

CHAIRMAN BONE: Thank you.

Dr. Marcus?

DR. MARCUS: I have nothing more to add specifically about the label except that it occurs to me that it may be possible to have some early indications of problems in the pulmonary vascular tree, perhaps by some relatively inexpensive, non-invasive methods, neuroximetry or something.

I don't know. I'm not a cardiologist, but I would ask that either something like that -- that could be explored by the agency. And if something appropriate is found, a recommendation to that could be put in the label.

CHAIRMAN BONE: All right.

Dr. Colley?

DR. COLLEY: I would agree with previous comments. What I would add to it is that, in addition to the contraindications in pregnant women, also lactating women and, in addition, contraindicated with use of other serotonergic drugs.

CHAIRMAN BONE: Dr. Cara?

DR. CARA: I agree fairly much with what everybody else has said. I think pediatrics. I think it should be contraindicated bottom line in anybody less than 18 years of age until enough data is

obtained.

I think that it really needs to be underscored that this is an adjunct therapy or combination therapy if you want to call it that. I think that there ought to be a statement that the long-term effects of this kind of therapy on co-morbidities is not known. And whether it decreases the risk of morbidities and mortalities associated with obesity is not known. I think that's an important point.

I think that the other important point that ought to be mentioned is that the efficacy of this drug beyond one year of treatment is also not known.

CHAIRMAN BONE: All right. Do we have comments on labeling from the absent members?

EXECUTIVE SECRETARY REEDY: Drug interaction. This is Dr. Zawadzki, drug interaction and that weight change should be reassessed at least every six months.

CHAIRMAN BONE: In addition, Dr. Zawadzki concurred with the sponsor's recommendation about a BMI greater than 30 for no co-morbidities, greater than 27 with them and a trial of one month, if they don't lose 4 pounds discontinue and your comment about

drug interactions.

Did Dr. New have any comments on labeling?

EXECUTIVE SECRETARY REEDY: Nothing that hasn't already been mentioned.

CHAIRMAN BONE: Thank you.

For myself I would strongly endorse the comments on contraindications, particularly pregnant and lactating women and juveniles, and Dr. Cara's comment about the long-term effects on co-morbid conditions not being known.

I think the issue of the early responder being the only patient who should receive long-term therapy should be made extremely strong. In fact, I think it should state that the drug is not indicated in patients who do not exhibit an early response. There's absolutely no evidence that this drug is of least use in those patients and that the potential risks outweigh the benefits, certainly in the category of non-responders.

I think there should be a black box warning for primary pulmonary hypertension to make the maximum possible statement about that in light with Dr. Marcus' comments.

Just to briefly summarize the --

DR. BORHANI: How about the abuse? How

about the abuse that Dr. Marcus said?

CHAIRMAN BONE: Well, what would you suggest?

DR. BORHANI: I think that that goes to the issue of education, that I hope -- I don't know if it is proper or not in the labeling or the negotiation.

CHAIRMAN BONE: It's specifically in the package insert here.

DR. BORHANI: That's right, about the education of the people, about the warning.

CHAIRMAN BONE: Thank you.

To summarize, the Committee has by a vote of six to five recommended the approval of the agent dexfenfluramine as we understand the proposal by the sponsor with a unanimous recommendation that this approval should be contingent on a commitment to conduct post-marketing studies and extensive recommendations for rather rigorous post-marketing studies of both the observational and prospective randomized placebo-controlled trial type, also of long-term duration. And particularly emphasizing co-morbid conditions has also been made as a recommendation as a contingent, that that agreement be a contingency of the approval.

In response to the third question, the comments I think speak for themselves. The same kind of information should the agency decide not to approve the drug would be required prior to approval.

And the labeling recommendations from the Committee have been unusually strong ones in a number of instances with respect to selection of patients in whom the drug is efficacious and also its pressing concerns about identifying those patients in whom safety problems might be especially prominent.

With this, we will conclude the 61st meeting of the Endocrinologic and Metabolic Drugs Advisory Committee with great thanks to one and all for their patience and concentration.

(Whereupon, the foregoing matter was concluded at 7:34 p.m.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING #61

Before: HENRY G. BONE, III, M.D., CHAIR

Date: NOVEMBER 16, 1995

Place: SILVER SPRING, MARYLAND

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

Irene Gray

IRENE GRAY