safety database, the patient exposure, baseline demographics of the study population, and the adverse events which include the incidence and discontinuation due to adverse events. We will also discuss the vital sign changes, the major safety issues seen with sibutramine, and other safety information related to these changes.

The safety data presented in the discussion are from the database with a cutoff date of September 30, 1994 for the NDA submitted in August of 1995. The data we have seen subsequent to the cutoff date remain consistent with the results of this database. All serious adverse events, however, are current. That is, if we received a report since the cutoff date, it is included in today's discussion. The data from the Holter Study which will be presented later on in the presentation was obtained after the cutoff date, but was included in the four month safety update of the FDA.

Over 2,500 patients received sibutramine in obesity studies. Of these, almost 2,000 received sibutramine in controlled trials. In the comparator trial, dexfenfluramine was given to patients in obesity studies and desipramine or imipramine were given to patients in depression trials. Overall, in

the NDA database, there were over 4,200 exposures to sibutramine.

The largest group of subjects were Caucasian females between the ages of 31 and 50. Most other groups of the population were well represented. Approximately 500 males, 250 Blacks, and over 700 patients over the age of 50 years were involved in sibutramine clinical trials. Ten percent of patients receiving sibutramine discontinued due to an adverse event compared to eight percent of the placebo patients. Six percent of patients receiving placebo discontinued due to a lack of efficacy compared to four percent of patients receiving sibutramine. Approximately one-third of the patients in both placebo and sibutramine group discontinued the studies prematurely. These differences were not statistically significant.

This table presents the adverse events in placebo control obesity trials which cause discontinuation rates of at least a half-a-percent. These events include hypertension, insomnia, depression and dizziness. The incidences of discontinuation for each of the events was not statistically significant between sibutramine and placebo.

There were three deaths in the clinical program. Two were suicides in depression studies. The third was a patient with a history of coronary heart disease and angioplasty who died of a myocardial infarction 15 days after receiving his last dose of sibutramine. The EKG at the last on treatment visit was unchanged from baseline. None of these deaths were attributed to sibutramine therapy.

This slide summarizes the incidences of adverse events occurring with a frequency of greater or equal to one percent in sibutramine treated patients. The majority of these adverse events, such as dry mouth, anorexia, constipation and insomnia were predictable based on the pharmacologic action of the drug. These events were typically mild to moderate in severity and self-limiting. The incidence of adverse events by demographic subgroups was not affected by gender or race. There was no evidence of primary pulmonary hypertension, neurotoxicity, or abuse potential.

I will now direct discussion to vital signs. The topics that will be discussed include the mean change in blood pressure, analysis of outliers, the frequency of discontinuation and dose reductions due to elevated blood pressure, ambulatory blood

pressure monitoring, changes in pulse rate, and the incidence of clinical events potentially related to blood pressure and pulse rate.

Consistent with the sibutramine mode of action, there were observed increases in mean systolic and diastolic pressure in the range of two to three millimeters of mercury and three to five beats per minute in pulse rate across the dose range studied.

This slide shows a meta-analysis of placebo subtracted mean change from baseline to the last on treatment measurement in blood pressure in all placebo controlled obesity studies. With sibutramine therapy, the systolic blood pressure increased from .7 millimeters of mercury in the one milligram dosage range to 4.1 millimeters of mercury in the 30 milligram treatment group. In sibutramine treated patients who lost five percent of their initial body weight, the systolic blood pressure ranged from a decrease of 2.9 millimeters of mercury to 2.8 millimeters of mercury in the 30 milligram dosage group.

The changes seen in diastolic pressure are of similar magnitude as those seen as systolic blood pressure. The diastolic blood pressure change ranged from a decrease of .2 millimeters of mercury in the

one milligram dosage group to a 2.5 increase in the 20 milligram dosage group. In sibutramine treated patients who lost at least five percent of initial body weight, the diastolic blood pressure ranged from reduction of 1.6 millimeters of mercury for the one milligram group to 2.6 millimeters of mercury for the 30 milligram group.

It is important to point out that only patients who achieved weight loss will be treated with sibutramine. In the group of patients who lost five percent of their body weight, the change in blood pressure ranged from a decrease of 1.2 for the five milligram dosage group to an increase of 2.3 for the 20 milligram dosage group.

This slide shows the effect of sibutramine in a 12 week placebo controlled study in hypertensive patients. Both placebo and sibutramine groups had mean decreases in systolic and diastolic pressure. While there was no statistical difference between treatment groups, the decrease is numerically lower in the placebo group.

This slide shows an analysis of the data from the 239 additional hypertensive patients treated in other placebo controlled obesity studies. Hypertension for this analysis is defined in the

footnote at the bottom of the slide. The systolic blood pressure in the placebo group decreased 7.6 millimeters of mercury compared to a decrease of 4.5 millimeters of mercury for the ten milligram group, and a decrease of 4.7 for the 15 milligram dosage group. The diastolic blood pressure decreased 2.6 millimeters of mercury in the placebo group compared to a decrease of 1.4 in the ten milligram group, and an increase of .1 millimeters of mercury in the 15 milligram dosage group.

This slide illustrates the percent of patients who had increases, decreases, or no change in diastolic blood pressure from baseline to the last on treatment visit in the placebo controlled obesity studies. Thirty-seven percent of the placebo group had increases in diastolic blood pressure at the end of the study, compared to 46 for the combined sibutramine group. For the ten milligram dosage group, 39 percent of the patients had a decrease in diastolic blood pressure and 20 percent had no change. Over the whole dose range study, more than half the sibutramine treated patients had a decrease or no change in diastolic blood pressure at the end of the study. A similar pattern was seen for systolic blood pressure changes.

This slide illustrates an outlier analysis done in two pivotal trials. For this analysis, an outlier was defined as any reading of systolic blood pressure greater than or equal to 140 millimeters of mercury or a diastolic blood pressure reading greater than or equal to 90 millimeters of mercury at any visit.

In BPI 852, the six month US dose ranging study in which hypertensive patients were excluded, we can see that in the five milligram dosage group, there were 3.4 percent more outliers than in the placebo group. In the 20 milligram dosage group, there were 13.3 more outliers than in the placebo group. A similar pattern is observed in the UK one year efficacy study. In the ten milligram group, there were 5.2 percent more outliers than in the placebo group and in the 15 milligram dosage group, there were 3.3 percent more outliers than in the placebo.

This slide illustrates another outlier analysis. For this analysis, an outlier is defined as any increase of 15 millimeters of mercury above baseline for two consecutive visits. The frequency of outliers increased slightly with increasing dosage of sibutramine for both systolic and diastolic blood pressures. This increase in frequency in outliers is

consistent with the small mean change seen in diastolic and systolic pressure.

This slide will illustrate that when blood pressure is assessed by individual treating physicians, clinically meaningful increases in blood pressure are rare. In the whole placebo controlled database, there are only 17 discontinuations on -- for elevated blood pressure. In study BPI 852, the large US dose ranging study, dose reduction or discontinuation was mandated if the systolic blood pressure was greater than or equal to 160 millimeters of mercury, or the diastolic blood pressure was greater than or equal to 95 millimeters of mercury at a single visit.

In that study, 1.4 percent of the patients were discontinued because of these criteria, compared to .7 percent in the placebo group. The frequency of dose reductions was the same in sibutramine and in placebo. Approximately half the dose reductions and discontinuations were in patients taking 30 milligrams of sibutramine, a dose which is now not being recommended. If the 30 milligram dosage group is eliminated from the 852 analysis, the frequency of discontinuations would be .8 percent with sibutramine compared to .7 percent as seen with placebo.

If we now look at placebo controlled studies for discontinuation of blood pressure were at the discretion of the investigator, we see there is only .5 percent discontinuations in the sibutramine treatment group compared to two percent of discontinuations in the placebo treatment group. Overall, this indicates a discontinuation for hypertension even when mandated by protocol were infrequent with sibutramine treatment.

It is also important to be able to identify patients who have an elevation of blood pressure early in treatment. This slide illustrates the time to the first reported occurrence in patients who had an increase of ten millimeters of mercury at two consecutive visits in BPI 852. Most of these increases in either systolic or diastolic pressure occurred within the first four weeks of treatment. Therefore, patients with potentially significant elevations in blood pressure can be identified early and discontinued from treatment if so indicated.

Ambulatory blood pressure monitoring was carried out in two pilot studies. In BPI 822, a crossover study done in six normal volunteers, given 20 milligrams of sibutramine over a one week treatment period, there was no statistically significant

difference found between systolic or diastolic blood pressure between the sibutramine and placebo groups. BPI 855 was a small pilot study designed to evaluate blood pressure in hypertensive patients.

As BPI 855 was extensively discussed in the FDA medical review, I would like to comment on the technical problems encountered in this study. Information that was unknown to the FDA medical reviewer is that the instrument used to measure ambulatory blood pressure, the Takeda TM 2420, is now rated unacceptable by both the Association for the Advancement of Medical Instrumentation and the British Hypertension Society because the ambulatory measurements do not correlate with simultaneous blood pressure measurements obtained with a mercury sphygmomanometer. Our conclusion to the study is that there were no unexpected effects of sibutramine on blood pressure in hypertensive patients and that the diurnal variability was maintained.

To summarize the effect of sibutramine on blood pressure, the mean change from baseline ranged from two to three millimeters of mercury across the dose range studied. In patients who lost greater than five percent of the weight, the group of patients who received sibutramine for long-term treatment, the

increase were in the order of one to two millimeters of mercury. Patients with hypertension had reductions in their blood pressure, however these reductions were not as a great as those seen in the placebo group.

The frequency of outliers was slightly higher in sibutramine treated patients which is expected from the small increase seen in mean blood pressure. The incidence of discontinuations was less than one percent for all sibutramine treated patients. Over half the discontinuation of blood pressure were in the 30 milligram dosage group, a dose which is now not recommended. Clinically significant changes in blood pressure were rare and seen early in treatment.

I would now like to turn our attention to the pulse rate changes seen with sibutramine therapy. This slide is a meta-analysis of the placebo subtracted change from baseline in pulse rate for all placebo controlled studies. In all patients, the increase in pulse rate ranged from .7 beats per minute for the one milligram dosage group to 5.5 beats per minute for the 30 milligram dosage group. In patients who lost at least five percent or more of their body weight, the pulse rate ranged from a decrease .1 beats per minute to an increase of 6.3 beats per minute for the 30 milligram dosage group.

To better understand the observed heart rate changes, a Holter study in 21 obese patients was conducted in which all subjects had a baseline 24 hour Holter recording. Each subject received sequentially at two week intervals, the sibutramine in escalating doses of five, ten, 15, 20 and 30 milligrams. At the end of each two week period before the subject received the next successively higher dose, a 24 hour Holter was repeated. The results of this study show that there was a dose related increase in heart rate. The peak heart rate occurred approximately between four and six hours following doses of sibutramine which parallels the peak concentrations of metabolites 1 and 2. Importantly, the normal circadian pattern is maintained.

The following table shows the mean change from baseline in daily mean heart rate from the Holter study. The mean heart rate change from baseline in the five milligram group was .4 beats per minute and rose to 4. beats per minute for the 20 milligram dosage group. These data are consistent with the pulse rate data seen in the clinical trials.

In summary, the circadian pattern of heart rate was maintained. In addition, no clinically significant changes in PR, QRS, or QTC intervals were

seen in this study. No proarrhythmic potential was identified.

I would now like to present data on clinical events which may be associated with vital sign changes. The following table illustrates the incidence of cerebral vascular events including patients in ongoing clinical trials. When we look at the incidence in placebo controlled studies, we see that the placebo group had an increase of .11 percent -- an incidence of .11 percent compared to an incidence of .10 percent in the sibutramine group. The incidence in this table is lower than shown in the briefing document as one patient originally listed as a possible cerebral vascular accident has now been definitely diagnosed as having spondylitic myelopathy. Overall, the incidence of cerebral vascular events is .11 percent in over 5,600 exposures to sibutramine.

The following table illustrates the incidence of chest pain, substernal chest pain, and angina pectoris reported in all placebo controlled studies. The incidence of these three events in the sibutramine group was comparable to the incidence in the placebo group. The following table illustrates the incidence of arrhythmia seen in placebo controlled trials. The incidence of these rhythm disturbances

range from .2 percent for those classified as arrhythmia to .4 percent for those classified as ventricular extrasystoles. These incidences were similar to those found in placebo group. There have been two reported cases of super ventricular tachycardia to date, one in a placebo patient and one in a sibutramine treated patient.

In conclusion, there have been over 4,000 exposures to sibutramine in the NDA database which is equivalent to over 1,300 patient years. The vital sign changes and the most common adverse events reported were not unexpected being consistent with sibutramine's mode of action. The mean blood pressure increases two to three millimeters of mercury, and pulse rate increases three to five beats per minute across the dose range studied. The number of patients with clinically significant elevations in blood pressure are small and can be identified early in treatment. No proarrhythmic potential has been identified. There's no difference in the incidence of cerebral vascular accidents or overall cardiovascular events between sibutramine and placebo groups. Overall, these data show that sibutramine is a safe and well tolerated medication.

Thank you.

CHAIRMAN BONE: There may be one or two questions from members of the Committee.

Dr. Flack first, then Dr. Kreisberg.

DR. FLACK: I'd like for you to clarify something for me about the ambulatory blood pressure monitoring. There is a fall at night, looking at these graphs, with sibutramine. Throughout much of the night, at least with this ambulatory data supplied here in the graph, the pressure is higher. Is that a fair interpretation based on your looking at this graph? Because I'm having trouble reconciling that there's no affect on the nocturnal dip looking at this weak -- systolic blood pressure change here.

DR. SEATON: Well, we have data -- the 855 study was a very early study. It was the pilot study done in hypertensive patients. There were ten patients studied. When we did the study, the reports that were in the literature said the equipment was very good. Subsequent to that, we found the equipment was not very good. So, the conclusions we can draw from that is that there is a diurnal pattern.

I think there's another way we could also look at the diurnal pattern. If you look at the pulse rate changes which, again, also reflect a potentially similar mechanism diurnal pattern, it is maintained in

the Holter monitor study.

Perhaps Dr. Singh would be willing to comment on another way of looking at this data in the spectral analysis which again suggests that there's no reason to think why the diurnal pattern would not be maintained with sibutramine therapy.

DR. FLACK: Is it also true that the dosing for the blood pressure medications in these studies where hypertensive patients were on medication really wasn't standardized across patients?

DR. SEATON: In the hypertensive studies?

DR. FLACK: Yes, where the patients were asked to take their medicine within a narrow time range during the day for comparability.

DR. SEATON: That's true. There were a number of different medications they could be taking and there were no standards. They were not supposed to change their medication but, again, it was not standardized.

CHAIRMAN BONE: Excuse me. Exactly what was the problem with this equipment?

DR. SEATON: The problem with the equipment is that when you look at sphygmomanometer readings comparing them to the readings obtained with the instrument, they do not correlate.

CHAIRMAN BONE: Well, is there a systematic error or what kind of discrepancies were observed?

DR. SEATON: Well, maybe I could have Dr. Weber comment on that, please?

DR. WEBER: Mr. Chairman, just for the record before I comment on that question, I should declare that I am a current active member of the Cardiovascular and Renal Drugs Advisory Committee of the FDA. But I'm not here in any sense in that capacity but simply as an expert in hypertension and ambulatory blood pressure monitoring.

The problem with the Takeda instrument is that it was, according to the tests done by the British Hypertension Society, inconsistently inaccurate. They had difficulty studying it because the frequency of mechanical breakdown during tests lead to the fact that most readings, in fact, could not be obtained. They gave it a classification of "D", which meant that it could not even meet minimum standards that would allow it to be compared with other equipment.

I must say, having said that, that the design of the studies and the way in which the studies were done created so many problems that even if the

equipment was good, they would be almost impossible to interpret. I guess we'll discuss that a little later.

But one answer to Dr. Flack's questions on it was that the baseline was done institutionalized and the treatment effect was done ambulatory. That, alone, could explain the very marked discrepancy.

CHAIRMAN BONE: Well, excuse me, just to pursue this question for a minute. If I understand correctly, you said that the major reason for deciding that this equipment wasn't useful was that the instruments that were tested by the British Hypertension Society -- is that right? -- broke down frequently during the testing? Is that correct that it was the major problem?

DR. WEBER: That they identified as the biggest single concern.

CHAIRMAN BONE: Was there a problem with the equipment breaking down during the study that was conducted with this drug?

DR. SEATON: No, but at least five percent of the readings were considered abnormal. In other words, there were readings that would go from 140, 150 to shoot up to 200 on one reading and then drop back down to normal. This is a very large percentage of unacceptable readings.

CHAIRMAN BONE: Did this introduce a systematic bias or just more uncertainty in the measurements?

DR. WEBER: According to them, the comparison with the mercury sphygmomanometer was inconsistent in both directions.

I am not a huge fan of those sorts of validation studies because the sphygmomanometer itself in the hands of many observers is not exactly a gold standard either. My feeling is that the problem with the ambulatory monitoring studies, you don't need to invoke problems with the equipment to see the problems with the studies. I agree with what Dr. Seaton has said that it's very poor quality equipment and certainly would no longer be used, but I think there are other easily identified problems with the ambulatory studies.

DR. SHERWIN: And what are they because I'd like to get that straight?

DR. WEBER: Well, I think the first very dramatic problem is that there was no basis of comparability between the baseline observations and the treatment observations. The baselines were done in an institution with patients essentially at risk. The treatment readings were done with patients

ambulatory.

The second problem is that --

DR. SHERWIN: But aren't there two different groups? I mean, are you comparing one group to another group so that they were both, you know, treated the same way even though they were different baseline and experimental?

DR. WEBER: Yes, indeed that's correct.

If you'll allow me, Mr. Chairman, there is a slide with a very long number called 5440. If that could be called up, that actually shows the actual data that we're talking about.

CHAIRMAN BONE: Well, let's get that because I think there's a lot of interest in this question. It seems like a technical question, but it sounds like it's an issue about whether a lot of data should be included or excluded from our analysis. I'm not convinced yet about it.

DR. WEBER: Okay, these are the data in the placebo group. You can see that the baseline is shown in blue and the eight week ambulatory values are shown in yellow. These are the systolic data and they seem moderately similar to each other. You could argue that during the day, the patients when they're ambulatory do have a somewhat higher blood pressure.

At night, maybe they have a fractionally lower blood pressure. But you're guessing and remember the n is only ten here.

DR. SHERWIN: And this is the different between -- blue is hospital and yellow is outside the hospital?

DR. WEBER: That's correct, yes.

DR. SHERWIN: Okay.

DR. WEBER: Okay, so you can see when your ambulatory pressure is a little by day and maybe a little lower by night for what's that worth. But it's all over the place. That's systolic.

If you look at the diastolic which is the next slide -- oh, oh --

CHAIRMAN BONE: Maybe we're going the wrong direction.

DR. WEBER: Well, make it 5441.

These are the diastolic data. Now, these are actually different. What's a little scary to me is if you look at between hours 2:00 and 4:00, there is a huge plunge in blood pressure for reasons that I have no explanation for. You can see about 93 to the mid-70s, a fall of about 20 points which I suspect may have been one or two aberrant patients. Remember, these are people on placebo. Then at night, there is

a big fall in blood pressure. You didn't see it that much at baseline. You see it more in the ambulatory patients. But if you just look at the ambulatory patients and see the tremendous variability, it's really just -- to work with.

CHAIRMAN BONE: What happened in the treated patients?

DR. SHERWIN: Yes, let's take a look at the treated patients.

CHAIRMAN BONE: Can we see the treated patients' results, please?

DR. WEBER: Yes, the next slide.

These are the sibutramine patients. These are the systolic values. You can see that they are somewhat higher at eight weeks than on the baseline. But it's interesting that unlike the placebo people, there was actually a fall in the systolic pressure in the sibutramine people when they were in the institution. That's something we didn't see with the placebo group.

If we go to the next slide, we have diastolic. You can see, again, there is a slight increase in blood pressure with sibutramine compared with its baseline. But again, remember this is ambulatory as opposed to institutionalized.

Mr. Chairman, I'd have to say I'm very reluctant in a sense to start trying to analyze it and dicker with these data because I just think that the number of patients in the study, the way in which it was done, just don't allow us to reach any conclusion. If you say that to now go ahead and start playing games with it, to my mind is not appropriate. The numbers of patients are too small. There were also gender differences between the placebo and treatment group. There were just too many problems.

And I don't think the study was ever intended -- correct me if I'm wrong -- to be used for this purpose. I think it was originally intended to be --

DR. SEATON: It was the first time the drug had been given to hypertensive patients. It was a pilot study. It was really to look to make sure there would be no major untoward effects in patients with hypertension.

CHAIRMAN BONE: Well, I'm sure that we're going to come back to discussion of this issue. I think the technical question that was asked here about disqualification, in effect, of the study based on the instrumentation is hard to understand. Because it seems as though from what we've been told, the

instrument problem would have, if anything, increased the randomness and perhaps created more overlap between groups rather than less. But I think we'll have a further discussion later on about the implications of this and what weight to give the studies.

Further questions?

I know that Dr. Kreisberg and then Dr. New had questions and I think others may.

DR. KREISBERG: It seems to me that the patients for participation in these studies were -- can everybody hear me all right? -- largely selected to be free of physical or comorbid medical problems. And so, the safety data is a best case scenario. Most of these patients have comorbid medical problems and they were more-or-less systematically excluded from the evaluation.

So, the questions I have relate to do you have any information about how renal insufficiency, co-existent liver disease, or co-existent cardiovascular disease influence either drug disposal or side effects? And if you don't have any of that in humans, do you have any studies in animals with renal insufficiency or other problems that would give us an idea about how the drug might be used in obese

patients who would be candidates but would have comorbid problems?

DR. SEATON: I'd like Rod Haddock to address that, please?

CHAIRMAN BONE: Did the transcriptionist get the name?

DR. HADDOCK: My name is Dr. Rod Haddock. I'm head of pharmacokinetics of Knoll, UK.

Yes, we've carried out a standard pharmacokinetic study in hepatically impaired subjects.

Could I have slide eight, please?

This slide shows the mean plasma profiles of subjects with moderate hepatic impairment. That's Child Pugh score five to five versus normal hepatic impairment. On the top in yellow you can see the metabolite 2 concentrations. Those in red are the impaired which are pretty well superimposable. There's a slight delay in the removal of material but that did not reach statistical significance. In fact, against the standard statistical text, these two curves were superimposable.

In terms of metabolite 2 -- metabolite 1 which is the minor metabolite, as you can see below here. There was a minor difference in Cmax between

the impaired and the non-impaired. Overall, the bioavailability when you add these two curves together, there's an overall deficit in the hepatic impaired. The bioavailability is up by a factor of about 25 percent. So, in kinetic terms, the drug is handled very similarly by hepatic impaired people. And there was a minor increase in the overall bioavailability of these pharmacologically active metabolites.

CHAIRMAN BONE: Were there further studies along the lines, Dr. Kreisberg asked about, for renal impairment?

DR. HADDOCK: With regard to renal impairment, the active metabolite of sibutramine are removed from the body by further metabolism. So, we would not anticipate that renal impairment would have any effect on the termination of the pharmacological response. However, we have a study in renal impairment ongoing and a small, again, standard pharmacokinetic type study in moderate and severe renally impaired subjects.

CHAIRMAN BONE: Was that a satisfactory answer, Dr. Kreisberg? Yes.

Thanks. I think Dr. New has the next question.

DR. NEW: I need some clarification on the presentation that indicated that there were differences of one and two millimeters blood pressure. When you saw the great variability that was presented in the ambulatory --

DR. SEATON: I'm sorry, I can't hear.

CHAIRMAN BONE: Speak into the microphone.

DR. NEW: Of course, I'm sorry.

I need clarification on the one millimeter to two millimeter changes that you're reporting in the various groups. Then we've just seen that the ambulatory changes are extremely variable -- there being as much as 20 millimeters of difference. So, what I need, I guess, is a standard error or a standard deviation of those measurements to know how you came out to one to two millimeter difference.

DR. SEATON: The standard error in those measurements was similar in the placebo group and in the treatment groups and was a range between 10 and 14 millimeters of mercury. I'm sorry, the standard deviation -- that's not the standard -- standard deviation.

CHAIRMAN BONE: Just to pursue this question of the magnitude of the change in blood pressure, the largest chunk of your experiences in

terms of patient years of exposure is 852 and this extension?

DR. SEATON: Yes.

CHAIRMAN BONE: And I note from the table that was prepared that in that study -- I'm particularly referring to a couple of issues. One is, the issue of looking at the change in blood pressure across the entire dose response curve as opposed to at the doses which were efficacious. Of the doses that you were recommending, those that were efficacious were the 15 and 20 milligram dose according to the five percent criterion.

Sorry?

DR. SPIGELMAN: No, the recommended dose range is five to 20.

CHAIRMAN BONE: I think you said that you would have a starting dose of ten. If you look at the doses that actually achieved five percent mean reduction in blood pressure, they were 15 and 20 milligrams.

DR. SPIGELMAN: Depending on the study and the parameters that are used in the guidelines, then different parameters were met by different doses. If a categorical analysis is used based on five percent responders, then five milligrams even met the

guidelines in 852. If other analyses are used, then it sometimes is ten milligrams. Or if other criteria are used -- if it's five percent placebo subtracted, then it would be a higher dose.

CHAIRMAN BONE: I understand your point. For the purposes of my question, it will be the doses at which at least 50 percent of patients met the five percent reduction or where the mean was five percent. By both of those criteria, it would be 15 milligrams, I think, overall?

We can discuss what the dose is later but I'm just referring to the fact that at 15 and 20 milligrams, the changes in blood pressure in that very large study were a little greater than you've suggested at 15 milligrams, and substantially greater at 20 milligrams. And when we look at the extension phase which goes to this point about whether the changes occur early or late, they're actually greater in the subjects that participated in the extension in the six to ten millimeter of mercury range at the 18 month time point for the systolic blood pressure and five to eight percent for the diastolic blood pressure. I note that the lowest dose in that extension was 15 milligrams, apparently on the basis of efficacy. Also, at 12 months, a similar experience

was noted.

So, I guess the question here is whether using a two millimeter increase in blood pressure, as the basis for estimating the risk of the pressor effect is really as solid as it might be?

DR. SPIGELMAN: Well, I think, you know, when we looked at the extension study, this was an open label study so it's very difficult to compare what blood pressure changes would have been. I think when we look at our whole placebo controlled database, while you've not seen this meta-analysis -- this was recently completed -- we thought it was the best way of trying to capture all the data. Particularly when we see in the hypertensive studies that there was a lowering of blood pressure in the group, but the lowering was not as great as we saw in the placebo group.

We thought the best way of presenting the data was really to combine all this data in a meta-analysis to really look at what the changes were. We think that's the best way of really trying to assess what it is -- placebo controlled trials and not to use, you know, one extension trial, particularly since we have not completely re-analyzed the extension trial. Data is being cleaned up right now. We don't

have all the results back from that trial.

CHAIRMAN BONE: All right.

Dr. Sherwin?

DR. SHERWIN: Two questions. First of all, have there been any patients at all that in long-term use have had primary pulmonary hypertension?

DR. SEATON: No. There's been one case with sclera derma who developed hypertension which was attributed to the sclera derma. But there have been no cases of primary pulmonary hypertension.

Perhaps Dr. Heal would care to address this issue?

DR. SHERWIN: Is there any potential, let's say --

DR. SEATON: Well, Dr. Heal will, I think, address this issue for you.

DR. HEAL: Could I have the third carousel and slide number five, please?

CHAIRMAN BONE: Is this going to answer Dr. Sherwin's question?

DR. HEAL: I hope so.

CHAIRMAN BONE: Okay.

DR. HEAL: As I pointed out in the pre-clinical discussion, we need to think about the mode of action of sibutramine as well as thinking about the

actions of drugs which are associated with pulmonary hypertension.

Sibutramine is a seratonin and norepinephrine reuptake inhibitor. SNRIs have been around in various forms for 40 years now. We know that there are tricyclics which are selected for nordrinolin, selected for 5-HT, or they're mixed uptake inhibitors. Primary pulmonary hypertension has never been an issue with these drugs.

We know that there are new generations of drugs such as the SSRIs fluoxetine. As I showed you in my presentation, there's nothing unusual about sibutramine's actions on body weight and feeding. These can be mimicked by giving fluoxetine with a norepinephrine reuptake inhibitor. There have also been new SNRIs like venlafaxine. In fact, sibutramine's actions can be mimicked by high doses of venlafaxine.

We know of no case reports associated with fluoxetine and PPH despite the many million exposures to Prozac which have occurred. In addition, the Case Control study that showed the association between dexfenfluramine and other weight reducing agents showed no association between fluoxetine and PPH, even though there was sufficient patients exposed to assess

this.

Now, we are uncertain at present about what the reasoning behind the induction of pulmonary hypertension is. But if we take a look generally amongst the drugs which produce this, they appear to fall into two categories. They are the 5-HT releasing agents, fenfluramine and dexfenfluramine, and there are patical releasing agents like mazindol, diethylpropion, clobenzurex, phenmetrazine, and fenpropurex.

As I clearly pointed out in my introduction, sibutramine is not a releasing agent for catecholamines and it is not a releasing agent for 5-HT. Therefore, it should be thought of in terms of the other SNRIs. I believe that its potential for pulmonary hypertension will be exactly the same as drugs of that class.

CHAIRMAN BONE: Thank you.

DR. SHERWIN: That was a good answer.

My second question relates to the fact that blood pressure, as we all know, can vary enormously if you lift weights or do something like that. Blood pressures can rise dramatically, exercise has dramatic effects. Most of the focus, except for the ambulatory blood pressure readings, are resting

type blood pressure.

Have you looked systematically at factors that would promote blood pressure elevations? I would expect that in a situation where you have that, you would release norepinephrine and then you couldn't get rid of it very easily. So, my biggest concern about this drug relates to induced -- sort of physiologically induced increases in blood pressure that would occur with activities like lifting packages.

DR. SEATON: That's an interesting question. We have some data on physiological testing.

I'd like Dr. Bramah Singh to address this, please?

DR. SINGH: There has been one study with treadmill exercise, twenty-four patients with three groups. One was placebo, one at low dose, five milligrams of sibutramine, and the other one 20. The patients were given the drugs for a whole week.

DR. SHERWIN: One week?

DR. SINGH: One week and the baseline pressures were taken and all the other parameters. Now, an interesting pattern emerged that at the maximal exercise, there was no difference in terms of the 0_2 consumption. The only effect that was seen was

at the maximal exercise, the heart rate increase was about seven beats higher than compared to the placebo. Actually, the diastolic blood pressure actually fell. All the other parameters, in fact, there were no differences between the placebo responders and the responders of the five or 20 milligrams of sibutramine. And the exercise capacity was not altered.

CHAIRMAN BONE: Thank you.

DR. MARCUS: Excuse me. This was treadmill exercise?

DR. SINGH: This was on Bruce protocol, the standard kind of treadmill that we do in patients with coronary --

DR MARCUS: So, you don't have information regarding resistance activity of the sort of lifting or Valsalva, or other things which are well known to really send the systolic pressure up?

DR. SINGH: No, those were not done. This study was purely on treadmill exercise.

DR. FLACK: Right. Was this only after one week?

DR. SINGH: After one week.

DR. FLACK: Are you planning to look at them later -- this group or any other group at a later

point in time after they've been on the drug for a longer period of time?

DR. SEATON: These are all studies that are being considered for Phase IV.

CHAIRMAN BONE: But that study is done and you didn't do that, right?

DR. SINGH: No, in this particular study, that was the end of it.

CHAIRMAN BONE: Right, thanks.

Dr. Colley?

DR. COLLEY: I've got a question about the blood pressure response and age. The average age of your subjects was relatively young, although this drug would presumably be used in older patients especially if we consider this to be a treatment that would be used chronically.

Did you notice any difference in ages in terms of the incidence of blood pressure increase?

DR. SEATON: No, there is no effect of age on the blood pressure effects of sibutramine.

DR. COLLEY: How about in patients who were hypertensive versus normal, or in treated versus untreated hypertensive?

DR. SEATON: Well, in the one study where we had patients in the hypertensive trial, one-third

of those patients were on anti-hypertensive medications. The changes were no different between patients who were on hypertensive medications or off hypertensive medications. We saw the similar pattern. In general, there was reductions in both groups but the reductions were not as great with sibutramine treatment as we saw in the placebo group. They were not statistically different, but numerically they were higher.

CHAIRMAN BONE: Thank you.

I think Dr. Molitch had a question?

DR. MOLITCH: Yes. I noticed in the earlier presentation that the p450 enzymes were involved in the generation of the active metabolites. I was wondering if any medications that would induce those enzymes would result in higher blood levels? And would that then alter the blood pressure responses, perhaps, of these patients?

DR. SEATON: Yes, I'd like to have Rod Haddock address this question, please?

DR. HADDOCK: Could I have slide 11, please?

We've examined the p450 isozymes that are involved in the metabolism of sibutramine and the major enzyme involved is an enzyme called CYP3A4.

There was a minor contribution from CYP1A2 and CYP2C9. There is no contribution from CYP2D6 and a known low capacity in enzyme of genetic -- which also shows genetic polymorphism.

Because CYP3A4 was the major enzyme involved, we decided to carry out a study in vivo in LB subjects whereby we would coadminister CYP3A4 competitor substraits erythromycin or ketoconazole. The results are as indicated on the slide here. There was a negligible effect of erythromycin on the plasma concentrations of the active metabolite though there was a trend to slightly higher levels in the erythromycin treated patients when erythromycin was added to sibutramine treatment at steady state.

In respect to ketoconazole, which has a potent potential to inhibit CYP3A, there was a minor effect on the active metabolite concentrations. But this effect overall was some 23 percent increase in active metabolite concentrations when ketoconazole was added at normal regimen and to sibutramine regimen.

CHAIRMAN BONE: All right, thank you.

Are there further questions from the Committee before we go ahead with the remainder of the company's presentation?

Fine. Then I think we'll be ready to hear

the epidemiology benefit and risk analysis.

DR. SEATON: Yes. I'd like to introduce Dr. Sylvia Smoler who will present an epidemiologic risk/benefit analysis.

DR. SMOLER: To assess the public health risks and benefits of sibutramine, we used two models, the Nurses Health Study and the Framingham model. In this presentation, I'm going to concentrate on the Framingham model. The reason for doing this is that sibutramine treatment is associated with a small increase in population mean blood pressure and a concomitant improvement in lipids in those losing weight. The Framingham model allows us to examine the interrelationships between changes in blood pressure and lipids and changes in the risk of coronary heart disease and cardiovascular disease.

Now, in the absence of large, long-term clinical trials that would have these endpoints as outcomes, the only way to assess the risk is really through proportional hazards regressions and logistic regressions based on models in established populations. That's why we're using these two models. The Framingham study is one on which many national policies with regard to risk factor, control and prevention have been based. So, it's widely used and

it's a very important database.

In order for it to be useful, however, we have to demonstrate that it is generalizable. There have been a number of studies that indicate that Framingham models are generalizable to the population and I'll just mention two of them. The NHANES epidemiological follow-up study, which was the first national cohort study based on a medical examination of a probability sample of US adults and included over 14,000 people showed that the events predicted by Framingham predicted remarkably well for this NHAMES follow-up study sample.

In the Western Collaborative study group which was a prospective study of middle-aged men with about eight years' follow-up -- the NHANES had about 10 years' follow-up. But in the Western Collaborative group, again, the events -- the observed coronary heart disease events did not differ from those predicted from the Framingham equations. So, that's why we're using that.

The two events I'm going to be discussing are coronary heart disease which consist of angina, unstable angina, MI, and sudden death; and cardiovascular disease which is CHD plus congestive heart failure, cerebrovascular disease and

intermittent claudication. Now, the independent variables which are controlled in these models are age, systolic blood pressure for the cardiovascular disease, cholesterol, LDH by ECG, diabetes, and so on. In coronary heart disease, there's also the added variable of HDL cholesterol which was not measured early-on in Framingham.

We're going to have a prototype scenario which we've devised for a 40 year old woman who is a non-diabetic, non-smoker, and has no LVH, has a diastolic blood pressure of 80 millimeters of mercury, a cholesterol of 220, and an HDL of 45. Those are all the variables that are entered into the CHD model. As you can see, the risk of CHD in eight years per million for such a woman is 13,450. With an increase of two millimeters blood pressure, the risk rises to 14,260. This two millimeter increase is based on the sibutramine trial data.

Now, with a concomitant weight loss of five kilograms which would result in a decrease of ten milligrams in cholesterol and an increase of two milligrams in HDL, the risk would drop to 11,982 per million. These data are from the meta-analysis of the effect of weight loss in the publication shown here and are also consistent with the sibutramine trial

data. So, subtracting then this from this, we have a net event diverted in eight years per million of 1,468 or a 10.9 percent reduction in CHD rates.

I'm going to walk through this slide because the rest of them follow the same pattern. Here on the left, is a graph version of what I've just shown you on the prototype slide. Again, the DBP of 80, cholesterol is 220, HDL of 45. The rise in risk with an increase of two millimeters blood pressure and then the drop of risk with that decrease of cholesterol and an increase in HDL, resulting in the 10.9 reduction in CHD shown on the previous slide. This is applied to the CVD model which does not have HDL in it, and which uses systolic blood pressure. And again, the rise in CVD risk with a two millimeter increase in blood pressure, a drop, resulting in 617 events averted in eight years per million, or 4.1 percent reduction in cardiovascular disease.

This shows the same kind of data for a man aged 50. For him we have assumed he has a diastolic blood pressure of 85, a cholesterol of 230 and an HDL of 40. The scale is different here and there's no zero point. But the absolute number of events averted are greater for the man because he is at higher risk, 7,179 and that results in an 8.2 percent reduction in

CHD and a 4.4 percent reduction in CVD.

Here, we have looked at the same thing for the 40 year old woman who has no LVH, but who is a diabetic and is a non-smoker. Again, the rise in risk and then the drop in risk with the lipid changes resulting in a 9.3 reduction in CHD. Here it is for a smoker who is non-diabetic. Again, there's the rise and the drop with the lipid changes for a 9.9 percent reduction in CHD. If it's a diabetic smoker, the same kind of pattern applies.

Okay, this shows the trade-offs between an increase in blood pressure and a beneficial effect on lipids. So, the yellow line here pertains to a 50 year old, non-smoking, non-diabetic man who has a cholesterol of 230 and an HDL of 40. The percent CHD risk rises with the rising diastolic blood pressure. The green curve is the similar kind of thing for the man with cholesterol of 220 and HDL is 42.

The dashed line is the line of equivalent risk. So, you can see that the risk at 84 millimeters diastolic blood pressure for the man with the baseline lipids is equivalent to the risk for the man with the better lipid profile who has a 90 millimeter diastolic blood pressure. Meaning that this six millimeter rise in diastolic blood pressure is offset by the benefit

on the lipids of the weight reduction. We did the same thing for a woman and that amounts to five millimeters being offset by the benefit due to the lipids.

So, in summary, the increase in risk of CHD or CVD with the increase in blood pressure that results from the sibutramine is more than offset by the beneficial effect of the weight loss on the lipids alone, with a net decrease ranging from four to ten percent. Similar effects were found for men and for women, for diabetics and for smokers. These data are based on the actual results obtained in the meta-analysis of the sibutramine trials and they are consistent with the effects of weight loss as analyzed in the meta-analysis of weight loss.

So, it's wonderful when you see everything consistently pointing in the same direction. The Nurses Health Study model which you have in your briefing document yields similar results in that there is a nine percent reduction in mortality. So, in summary, all of the data really are quite consistent and for an epidemiologist, that's always a great pleasure. Thank you.

CHAIRMAN BONE: Thank you, Dr. Smoller.

I have a question. I know you said this

and I think I just missed it. You said that the estimated lipid benefit that you used for your calculation would approximately offset a five millimeter increase in blood pressure for men.

DR. SMOLER: For women.

CHAIRMAN BONE: Yes.

DR. SMOLER: Six for men.

CHAIRMAN BONE: So, five to six millimeters, okay. Five millimeters for women and six millimeters for men. Okay, thank you.

Questions?

All right, very good. Thank you.

DR. SMOLER: Let me introduce Dr. Michael Lean.

DR. LEAN: Thank you very much. My presentation is going to be from the perspective of a practicing clinician. My background is as a physician with specialist training in general medicine, diabetes, and endocrinology. I have a continuing consultant practice in a busy general hospital. I also have research training in human nutrition with a special interest in obesity. I'm the head of a fairly large, multi-disciplinary university department of human nutrition in Glasgow.

I'm heavily involved in developing

clinical guidelines for weight management in the United Kingdom and I've had clinical and research experience with most of the drugs available and under development at the moment. I've had some experience with sibutramine in the context of a double blind, placebo controlled trial in dyslipidemia which has gone on to a two year open extension which is ongoing. At present, we've recruited 150 subjects into the study, of whom 115 have proceeded into the open extension phase. In this trial, it has not been possible to distinguish those patients who are on placebo from those on active drug therapy. But my experience in the open phase of that study is that the drug is extremely well tolerated. Both the patients and the staff are extremely happy with the way it is progressing.

From the evidence I've seen presented today and from my own experience, I believe that sibutramine would be a valuable adjunct as part of a structured, multi-disciplinary program of weight management. The evidence showing the likelihood of specific benefits for patients with diabetes or hyperlipidemia is interesting and worthy of further research. But it is important to recognize that this submission, the aim of today's submission, is to

obtain a license for weight management and not as primary treatment for these conditions.

Now, in my clinical practice, I regularly see patients with important improvements, clinical improvements associated with weight loss which can be achieved routinely using our standard approaches. Clinical observations of that kind have been confirmed in a vast number of published studies. For example, those in looking at the metabolic control in Type II diabetic patients. I believe it is very important for doctors and for patients to be aware of the medical benefits from modest but sustained weight loss without the need to convert very obese people into very thin ones.

I conducted a study which was published in 1990 in Diabetic Medicine which carried out the survival analysis to look at the life expectancy in patients who were overweight and had non-insulin dependent diabetes. These subjects were recruited at the mean age of 64 and this was a total population study. So, it reflects the relative kinness of Scottish diabetic patients compared with those, perhaps, in the United States.

At that age, they had a life expectancy without any weight loss of eight years. What we found

was that those who lost weight under advice in the first year of treatment went on to a longer life expectancy and this was highly significant. The data had been controlled for pre-existing heart disease, for age, for sex, and for blood pressure. So, this study illustrated for me that quite modest weight loss, of the kind achieved routinely, was of great value for patients at high risk.

The benefits of each kilogram of weight loss were equivalent, approximately, to three to four months' survival. By the time these patients had lost nine or ten kilograms, their survival had increased to much that of the background population. So, the impaired life expectancy of non-insulin dependent diabetes was abolished by weight loss of the order of nine to ten kilograms.

This slide shows data from David Williamson from the Center for Disease Control published last year, which gives really quite striking similar benefits from relatively modest weight loss. Firstly, in people who already had obesity related diseases, those who lost five to nine kilograms of weight loss had a reduction in all cause mortality of about 20 percent. Those who had no secondary diseases, the analysis was able to find that for those

who lost nine kilograms or more, a staggering 25 percent reduction in mortality combined both from heart disease and from cancer risks. It is important to recognize that the benefits in both these groups included reductions in obesity-related cancers. A lot of our discussions today have focused on risk factors for coronary heart disease and that's only one part of the story.

More recently, we've conducted studies using dietary approaches. This is just one where a dietary study produced a weight loss of between four and five kilograms. We looked at patients with angina and those who were simple overweight and we found in the study a quite significant reduction in clotting factor VII, another factor which may be associated with long-term mortality. So, again, another factor in addition to the lipid improvements which we also found in the same study. It applied both in patients who already had angina and those with simple obesity.

Now, my patients come to me in clinical practice, really in two sorts. In the next part of this presentation, I would like to suggest that some of the risk factor analyses that we've been concentrating on today are a little bit remote from the problems that my patients present to me. If

you'll excuse the familiarity, I'm going to describe two patients.

The first one here is a hypothetical Mr. Johnstone. He's aged 60. He has developed non-insulin dependent diabetes and is on treatment with sulfonylurea. He's hypolipidemic, on treatment with lovastatin. He's hypertensive on enalapril. He also has arthritis and is on regular analgesics. He has a body mass index of 36. He's unemployed. He's unhappy and he's expensive for the health care system. I see Mr. Johnson as a new patient two or three times every week, and I think that's a familiar experience for many of my colleagues.

On the next slide, Mr. Johnstone's daughter, who we'll call Ms. Johnstone is aged 35. Her body mass index has reached 30 and she's coming complaining of tiredness, of back pain, of shortness of breath. But we note, the worrying family has a history of diabetes, hypertension and coronary heart disease.

Now, when I see a patient like the first one, Mr. Johnstone, who is already on life-long therapies for three or four direct consequences of obesity, I wish I could have done something constructive at a much earlier stage. There's, of

course, a lot that I can do for him and I have a medical responsibility to do it. But I feel that earlier treatment with an effective agent for patients like Ms. Johnstone here, who have not yet developed or required treatment for secondary complications would be more rewarding, or would ultimately be more cost effective.

The next slide shows the sort of trajectories of weight change which we see in adults as they grow older. In some ways, it is similar to the slide which was shown earlier by Dr. Pi-Sunyer which was commented on by Dr. Marcus. The patients I've described are following the trajectory of the top 10 percent. We find that in the UK at least, around 20 percent of our 20 year olds already have a body mass index which is exceeding 25. That is destined to follow this high trajectory and they'll run into symptoms before they run into the more medical, if you like, complications.

Our aim of therapy should be to reduce the level of trajectory to a lower one. We remember that less than half of all adults remain within the range of body mass index which is considered healthy or normal. I would like to think that if we could treat Ms. Johnstone when she is at approximately this point,

we could reduce her body mass index to that of a lower point. Whether we can continue it steadily or not I'm not sure. I think instinctively that it is likely that we would reduce the body mass index, and we would see it then climb up along a lower trajectory as she grows older.

I'd like to pause for a moment to look in a bit more detail at these symptoms which, again, to some extent, are neglected except by clinicians who see obese patients regularly. The list is very long. They're very familiar and often attributed to other diseases rather than being recognized as direct consequences of obesity itself. They're expensive and cause a lot of unhappiness in our patients who are already discriminated and don't like to complain directly about their symptoms and relate them to their weight.

Without professional help, the treatment for overweight and obesity are limited in success, and we heard something about that earlier. Mr. Johnstone or his daughter have only about a ten percent likelihood of maintaining a ten percent weight loss and they're referred to me after they've failed. My approach to these patients would always be to provide the very best dietary and behavioral care I can offer,

including physical activity.

Most of my patients can, in fact, lose five or 10 percent of their weight under this sort of regimen but the difficulty is in preventing regain in the long-term and maintaining that weight loss. To combat that, I would, I believe, be ready to add a therapeutic trial of a drug such as sibutramine. Hitherto, I've been unenthusiastic about the use of very low calorie diets on the basis that weight regain is usual and the long-term results are generally poor. But I have been impressed by the data we've seen today which suggests that it may be possible to maintain quite rapid weight loss, which is attractive to patients, by the use of drug therapy.

I am very attracted by being able to identify non-responders to drug therapy as an early stage. I think that's extremely important partly from the point of view of efficacy and partly from the point of view of avoiding unwanted side effects, particularly from the point of view of blood pressure, are more apparent in those who do not lose a lot of weight. I was always taught at medical school that whenever I start a drug therapy of any kind to any patient, this should be regarded as a therapeutic trial, should be evaluated at follow-up, as there are

non-responders to virtually every drug that we prescribe. The data we've seen today suggests a very simple and effective way of ensuring that sibutramine would not be given to non-responders indefinitely.

Now, some of the principles of weight management I've mentioned are relatively new. In teaching medical students and doctors, I stress the need to address our own attitudes towards obesity and its management. They're summarized on this slide.

We need to recognize the symptoms of the overweight. We need to treat the disease process and not wait for an end result which might be a body mass index over 30. We need to start management at an earlier stage, not necessarily with drug therapy. We need to treat the underlying cause, which in this case is overweight, before we treat complications for waiting for them and there are lots of them. We need to recognize the medical benefits of five to ten percent of weight loss. I would add to this slide, the need to focus on prevention, including both primary prevention and the secondary prevention of regain and the maintenance of weight loss.

In summary, I feel that the long-term benefit risk ratio is clearly of benefit and positive for sibutramine in proper clinical use. The potential

side effects are mild and they should be easily managed. I recognize that they are outweighed by the achieved weight loss and the concomitant improvement in risk factors such as lipids. There are other benefits which haven't been measured.

Obesity is a serious disease with serious consequences. I am happy to have available another anti-obesity drug for my patients. I will, of course, observe all the usual cautions and monitoring required for any new medication as a part of routine good medical practice. I recognize the need to keep an eye on the blood pressure, as I would with any other drug, and that the fall in blood pressure expected with weight loss -- which I see routinely in weight loss in other settings -- in blunted in patients on sibutramine. But I accept that the net benefit of losing weight outweighs the hazards of a fairly small elevation in blood pressure. I'm also greatly reassured by the clinical safety data that there is no increase in strokes, cerebrovascular accidents on the sibutramine treated patients.

I'm personally not very worried about the small increase in heart rate. It's not as great as that which we see when treating patients with other drugs including such things as salbutimol which we do

routinely. I would never prescribe sibutramine without recommending dietary change and physical activity which would help to lower the resting heart rate and blood pressure.

There remains some interesting questions about sibutramine which will be addressed in Phase IV post-marketing trials.

I will hand over to Dr. Spigelman to take over an outlined description of those trials. Thank you very much.

CHAIRMAN BONE: Any immediate questions from the Committee at this point? No? Thank you.

Go ahead, Dr. Spigelman.

DR. SPIGELMAN: Thank you, Dr. Lean.

What I'd like to now present is the status of our proposal regarding post-marketing clinical research with sibutramine.

Some months ago, we began to consider what were the most relevant issues that we felt could be best addressed in the Phase IV post-marketing setting. The two issues that really became most prominent in our thinking on this topic were expanding the safety database and specifically, in this regard, to beginning to look at non-surrogate and longer term endpoints and also beginning to measure what I'll call

the real world effectiveness of the compound. Although the criteria for approvability are based on showing weight loss and improvement in comorbid parameters like lipids and blood pressure, I think the effects on other non-surrogate parameters like mortality or like morbidity such as myocardial infarction or stroke, are clearly the ones that many of us are very interested in.

Similarly, it's well known that the artificial context -- somewhat artificial context really of a double blind placebo controlled clinical trial is excellent for answering certain scientific questions but really doesn't always predict exactly what will happen when a drug is placed in the real world setting of clinical practice.

In trying to approach these issues, we really, initially began by looking at three study designs that we considered scientifically valid and potentially feasible. Either following a cohort of patients on sibutramine, doing a classical case control study, or doing a large simplified clinical trial. Without going into detail, we concluded that the large simplified clinical trial, although it clearly is the most difficult and the most expensive, would also be the most likely to yield the most

valuable and unconfounded information.

Why don't we briefly just run through some of the hallmarks of large simplified clinical trials. They're usually randomized. By definition they're large. They are of relatively long duration, require innovative data collection because of, really, the sheer size of the trials. They're usually intended to measure either small important effects or long-term non-surrogate endpoints. They focus on a few critical variables rather than the massive data collection that's usually done for each patient in the Phase III clinical trial setting. Examples of large simplified clinical trials include the ISIS beta blocker trial, the metforman acidosis study, and the physician's health study of aspirin for MI prevention.

Before going further, I just want to take a minute to thank the FDA, and specifically Dr. Stadel, who really provided very constructive critique on our initial proposal.

As you're aware, in that regard, there really are very difficult decisions that have to be made in the design of any clinical trial. Today, what I'd like to present is simply our current thinking on some of the more crucial issues that surround the proposed Phase IV trial.

The first issue is that of the comparator arm. We believe that the most instructive, as well as probably the most feasible design to do a randomized trial that would compare sibutramine with what would be the only other product approved for the long-term treatment of obesity, that is dexfenfluramine. The proposed duration of the study is two years. There would be a relatively simple schema for visit schedules and follow-up which I will describe in more detail in the next slide. This would be an open label trial. Projected accrual at this time is 10,000 patients, 5,000 patients per arm. Endpoints would be all cause mortality, all cause hospitalization as a measure of morbidity, CVD mortality, CVD hospitalization, and we would measure weight loss. We have done power calculations and with this design would be able to detect differences between the arms of 19 CVD deaths or 57 hospitalizations.

After randomization and initiation of therapy, projected follow-up would consist of protocol mandated week four, eight, 24, 48, 72 and 96 recordings, exposure status, weight, history of hospitalizations, and death. Every six weeks, there would also be telephone follow-up that would include exposure status, weights and hospitalization. For any

hospitalization or death, medical records would be obtained and carefully scrutinized.

To give you an idea of the magnitude of the effort that such a study would entail, the projected requirement to do this is 500 physicians in order to recruit the required 10,000 patients. There would be approximately 34,000 office visits included, 120,000 at least completed telephone calls, follow-up of approximately 800 to 1,000 hospitalizations. Clearly, as I alluded to earlier, there are many issues regarding study design that are really judgment calls and can be subjected to a great deal of discussion. If sibutramine is approved, it is certainly understood that the process that we have undertaken must continue as an iterative one to more fully consider all the ramifications of the various possibilities. I just want to emphasize, this is a work in progress at this time.

At this point, I would now like to conclude by briefly summarizing the morning presentations on sibutramine. Sibutramine is a novel pharmacological approach to the treatment of obesity. The first seratonin, norepinephrine reuptake inhibitor that has been, to my knowledge, proposed for the treatment of obesity.

It produces clinically meaningful weight loss and weight loss maintenance, both of which meet the guidelines for weight loss. The data shows consistent reduction in waist and hip circumference, which is confirmed by the DEXA data that is present in your briefing documents that we have not actively presented today. The expected benefits from weight loss are seen in the lipid profiles and in glycemic control and additional benefits of decreased uric acid.

The adverse event profile is predictable based upon the pharmacology of sibutramine. The adverse events that have been seen are mild to moderate in severity and they are self-limited. Modest increases in mean blood pressure and pulse rate which, even though they may be clinically important, are easily measurable and easily measured.

The epidemiologic evaluations that have been performed predict uniformly that the benefit/risk will remain favorable, not only over the short period of time of one year that this drug has been studied in controlled clinical trials, but over longer periods. The benefit/risk furthermore though can be markedly enhanced through judicious clinical use which has not been factored into any of the epidemiologic models.

The proposed Phase IV large clinical trial will further expand our knowledge base and do it very importantly in an actual practice setting.

In conclusion, in light of a clear positive benefit/risk ratio, we would conclude that sibutramine is safe and effective for the treatment of obesity. Thank you very much.

CHAIRMAN BONE: All right, thank you.

Are there specific questions related to the last presentation?

Then what we'll do, obviously, is break for a shortened lunch break and return for the FDA presentations after. I don't think we're going to get through those.

Is that right? That's what I thought.

Right. Dr. Kreisberg has a question.

DR. KREISBERG: I think John was first.

CHAIRMAN BONE: Oh, Dr. Flack does.

DR. FLACK: Could you tell me which endpoint you based your sample size on for power considerations? Also, even though this is a Phase IV, is there any consideration at all given to a dummy pill group in the sense that this trial will never let you know if the treatment is actually better than doing nothing? It will simply give you the relative

difference in benefit on all the endpoints between two treatments, but both could be worse than doing nothing, or could be better, or could be the same.

DR. SPIGELMAN: Yes. No, those are excellent questions and those are questions that we've struggled through, you know, over the past period of time. The simple one, or relatively straightforward one is that the numbers that I mentioned to you were for all cause -- I'm sorry, for CVD and for all cause mortality. For those endpoints, we would be able to detect a difference of 19. For all cause hospitalizations, 57.

Now, the answer to the double dummy technique, or double blinding, et cetera, gets to the heart of what are we really trying to measure in this sort of a trial? Is it a trial that is geared toward seeing what will happen in terms of the effectiveness of the drug when used in as close as we can come to the actual clinical practice? Or are we trying to learn sort of a step removed, more theoretical questions about what the drug could do but may not necessarily do when applied to people who really will get the drug in a more normal clinical practice setting?

At this time, our thinking is that what is

needed more is to find out what anti-obesity drugs can really do when they're used by practicing physicians in as close a setting to the real life situation as possible. Therefore, our priority is to do this in an open label randomized, but not double dummy type of situations that would markedly restrict the real life extrapability of the results. But obviously, those are the sorts of issues that need to be honed in and further defined and thought through before coming up with a final study design.

CHAIRMAN BONE: Thank you.

Dr. Kreisberg?

DR. KREISBERG: Well, one of my questions is quite similar to John's. I wonder, can you tell me how many morbid and mortal events that you would project for a two year study with a population of the size that you've calculated, so I can have a frame of reference to some of the other large studies that look at similar endpoints?

It seems to me that you're going to have to have a relatively large event rate in order to do this. I wonder if you really know what the event rate is going to be?

DR. SPIGELMAN: Yes. I'm not sure I can pull the slides out right now, so I can get them to

you after the break. The numbers are calculated primarily from the Nurses Health Study which we felt was a comparable population in terms of expected events. I will pull those out and get them for you.

CHAIRMAN BONE: Other questions or comments before we recess?

Dr. Illingsworth?

DR. ILLINGSWORTH: One question concerns the need for adequate follow-up. In looking at the data that's been presented this morning, I'm struck by the lack of knowledge about what's happened to patients who drop out. I think you should look at, say, the 4S trial as the gold standard for clinical trials where everyone is identified. I compel you to do this with this kind of trial, too. So far, the data that's presented from the clinical data shows that to be lacking in my view.

DR. SPIGELMAN: Yes, no question. That is a sine qua non of the proposed trial. And again, with help from Dr. Stadel and some advice, death should be 100 percent virtually attainable through the various techniques that are available to detect death.

Telephone follow-ups are made independent of whether the patient stays on drug or does not throughout the whole projected two year period of

time. So, follow-up is intended to be independent of status on or off drug. We are optimistic that with that sort of plan, we can get as close as possible to full follow-up. But that is clearly the intent of doing this study.

CHAIRMAN BONE: Thank you.

I will reassure people that the generous allowance for Committee discussion and question time in the afternoon will allow us to finish in a timely manner because we accomplished much of that, obviously, in the course of following along with the presentation.

It's now 12:03. We, I think, should plan to reassemble here at 12:45.

Is there a problem with that? No? Okay.

(Whereupon, the meeting was recessed at 12:03 p.m., to reconvene at 12:45 p.m., this same day.)

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

12:43 p.m.

CHAIRMAN BONE: Will everyone please take their seats?

The meeting will be in order. The next order of business is the presentations by the Food and Drug Administration. The first FDA presentation will be presented by -- let me see, is Dr. Troendle here to make an introduction?

DR. REEDY: Attention to Committee members who are sitting at the table. I want to call your attention to in your folder, there is the 1997 schedule and the remainder of the 1996 schedule. I want to call your attention to the fact that the meeting that we had scheduled on November 8th has been postponed to November 22nd. In other words, no meeting on November 8th, but there will be one on November 22nd, then again in December, and then next year. Those are all firm issues including the first one in February.

CHAIRMAN BONE: I'm sorry. There's one person we're waiting for.

The introduction to the Agency presentation will be given by Dr. Gloria Troendle. We'll please be in order for that. She'll be followed

by Drs. Eric Colman, Bruce Stadel, and John Flack.

Dr. Troendle is kindly distributing copies of the current draft guidance document which this Committee considered and discussed with the Agency last year. Most of the members of the Committee participated in that discussion, although we do have one or two new members.

Thank you, Dr. Troendle for that.

Obviously, for persons who are interested in obtaining copies of the draft guidance document, they can be obtained from the Agency.

If we can turn off Dr. Colman's slides please, we will be able to look at Dr. Troendle's overheads. Okay.

Dr. Troendle?

DR. TROENDLE: Hi. A recently updated version of the Guidance for the Clinical Evaluation of Weight Control Drugs has been provided for the information of the Committee. The guidance was reviewed by this Committee and recommendations for the Committee were incorporated into it. It requires some rewriting from time-to-time principally to clarify issues about which we get questions.

The recent revisions were to ensure that the guidance does not suggest that it consists of

requirements for drug approval. It is only our current thinking and is suggestions. I believe that the basic points remain as they were originally written and subsequently modified by this Committee. The important points are as follows, subject to modification for special situations.

(1) The population study should be representative of the target population for weight control drugs and usually meet a definition of moderate to severe obesity.

(2) Trials should be of a size and duration to allow an assessment of the long-term benefits and risks of drug use because an indication for long-term use is usually desired. Double blind, randomized dose-finding and efficacy studies are generally needed to identify the optimum dose and to establish efficacy. It is particularly important to establish the lowest effective dose when the drug will be used in an otherwise relatively healthy population such as is true of many obese patients.

(3) Weight loss or maintenance of weight loss should usually be the primary endpoint as recommended by this Committee. The study of other endpoints may lead to meaningful indications in addition to weight control. Such endpoints might be

the prevention of or improvement in diabetes, hypertension, osteoarthritis or sleep apnea. Improvement in quality of life or in physical performance on, say, walking or stair climbing may be a desirable endpoint. Measurement of obesity associated cardiovascular risk factors: lipids, blood pressure and glucose tolerance can readily be done and may have a place in determining the balance of benefit versus risk for the drug. If one or more of these factors deteriorates or is not improved, the risk associated with this deviation must be considered in making a benefit to risk decision for the drug.

(4) At least two weight loss outcomes are possible. First, a demonstration that the mean drug effect is significantly greater than the mean placebo effect, and that the mean drug associated weight loss exceeds the mean placebo weight loss by at least five percent. The second one, demonstration that the proportion of drug treated patients who lose at least five percent of their initial body weight is significantly greater than the percentage of placebo patients who lose at least five percent of their initial body weight.

The second efficacy demonstration may help to identify efficacy of drugs that are effective in

only a portion of obese patients and it reflects our expectation that obesity may be a disease of diverse etiologies so that a given drug benefits only subjects with a particular abnormality. When the efficacy of any drug is established, benefits of the drug are compared to risks. Depending on the indication that is sought, several roots are possible for establishing efficacy of a drug that is broadly intended for weight control but all decisions ultimately come down to whether the population has been identified in whom benefits outweigh risks.

And that's all I'm going to say about the guidelines. Those are just a few of the points. The rest of the presentation will be made by Dr. Eric Colman on the medical aspects, then Dr. Bruce Stadel on the epidemiologic aspects.

CHAIRMAN BONE: Dr. Colman?

Thank you, Dr. Troendle.

Were there questions from members of the Committee concerning Dr. Troendle's presentation?

Dr. Marcus appears to have a question.

DR. MARCUS: I would just like to submit that I think a stronger statement about ethnic diversity should be inserted. You can not get an NIH grant involving a human study. You can not even, in

theory, get a clinical trial through an institutional review board now without paying attention to that issue. I mean, I fully understand that the studies we're hearing today came out prior to the initial guideline. But I think for the future, it would be very important particularly for a disease like obesity where, clearly, any drug action that we take over the next few months on this drug are going to be applied to Hispanic and Black populations -- that is, populations who are said uniquely to have a pre-disposition towards it. I think we need to have adequate data in those ethnic groups for sure.

DR. TROENDLE: Right. Yes, we do mention a couple of times in the guidance that minorities, Blacks and Hispanics in particular, and both males and females should be studied. But we put it very mildly, it is desirable to have that.

DR. MARCUS: I am requesting that you make it a more stringent --

DR. TROENDLE: So that it's required.

CHAIRMAN BONE: Thank you.

Are there specific questions related to today's discussion from Dr. Troendle? No?

Thank you.

Dr. Colman?

DR. COLMAN: Good afternoon. My discussion is going to focus on two main topics. The first is efficacy. I'm going to briefly discuss the results from the one year pivotal study, SB 1047. I will not comment on the second primary or pivotal study, BP 852. You heard the results from the sponsor earlier today. I'd like to spend the bulk of my time discussing aspects of the risk/benefit analysis and in particular, the effects of the drug on blood pressure and lipid levels and spend a little bit of time discussing two studies that looked at the effects of the drug in patients with Type II diabetes.

As for efficacy, once again, SB 1047 was a one year study. It involved 485 patients. These patients were randomized to one of three arms, either 10 or 15 milligrams a day of sibutramine or to placebo. The baseline characteristics of the three groups were well matched. The mean age was 42 years. They were primarily female and nearly all Caucasian and the mean VMI was 33 kilograms per meter squared.

This next slide illustrates the percent weight loss from baseline for subjects who completed the one year study. Just to give you an idea of how many people completed the study, roughly 50 percent of the placebo patients and 50 percent of the ten

milligram patients completed the one year study. Fifty-nine percent of the subjects in the 15 milligram group completed the one year study.

As you can see, there was significantly more -- or greater weight loss in the two drug treated groups versus placebo. At month 12, the differences between these two groups versus placebo was statistically significant. However, it's interesting to note that at month 12, there were no significant differences in weight loss between these two groups.

Now, in addition to looking at percent weight loss as a gauge of efficacy, one can look at the number of individuals who lose at least five percent of baseline weight. This has been called the responder analysis, or five percent responder analysis. The next slide illustrates these data. As you can see, 20 percent of placebo patients lost at least five percent of initial body weight. Thirty-nine percent of the subjects in the ten milligram group lost at least five percent of body weight, and 57 percent of subjects in the 15 milligram group met that criteria. Again, the two drug treated groups, one compared to placebo, was statistically significantly different.

Thus, to quickly summarize the efficacy

from this one year study, for subjects who completed the one year study, the 15 milligram dose resulted in a percent weight loss that was five percent greater than placebo. Regarding the responder analysis, compared to placebo, a significantly larger proportion of subjects who took 10 or 15 milligrams a day of sibutramine lost at least five percent of initial body weight.

Now, at this point, I'd like to move from efficacy and discuss risk/benefit. We've heard this morning some talk about blood pressure. I think this is the critical component with sibutramine. I'll spend a fair amount of time discussing blood pressure. I'll also discuss some aspects of lipids -- again, two studies that looked at the effects of the drug in patients with Type II diabetes.

There's a massive amount of data in this NDA regarding blood pressure and innumerable number of ways to look at blood pressure data. When I was looking at the data, I thought three questions would be reasonable to keep in mind and try to answer. The first question is does sibutramine increase mean blood pressure? The second question, does sibutramine lead to large increases in blood pressure in a subset of patients? The third question was, does sibutramine

alter the 24 hour diurnal variation in blood pressure?

Now, as far as the first question is concerned, the sponsor has stated sibutramine does increase mean systolic and diastolic blood pressure by approximately two to three millimeters of mercury relative to placebo. I'm not going to show any data to support that. I think it's a fair assessment and I will simply leave this question here.

The second question, does sibutramine lead to large increases in blood pressure in a subset of patients? That's a little more difficult question to answer, however, this slide represents data from all placebo controlled studies with patients who had uncomplicated obesity. Again, this involves all doses of sibutramine. What is shown is the number of patients who had an increase in resting blood pressure that was at least 30 percent greater than their baseline measurement at some point during treatment.

If we look at systolic blood pressure, 6.5 percent sibutramine treated patients had a significant increase in blood pressure at some point during treatment. This is in contrast to only 2.5 of placebo patients. Again, with diastolic blood pressure, 7.4 percent of patients on sibutramine had a significant increase from baseline in their blood pressure at some

point during treatment. Again, this is in contrast to only 1.9 percent of placebo patients. These p values indicate that these differences are unlikely to be due to chance.

Now, the next slide may be difficult to read, but I think it's an important slide. I'll walk you through it. These are data from the one year study, SB 1047 that I reviewed a minute ago. Again, recall that these subjects were on either 10 or 15 milligrams a day of sibutramine or placebo. This is a scatter plot of month 12 data. These are actual data points at the last month of the study. What is shown along the Y-axis is a change in body weight in kilograms. This represents a reduction from baseline body weight. Along the X-axis is the change in systolic blood pressure from baseline. Again, this direction is an increase from baseline and this is a reduction from baseline.

Now, the placebo subjects -- hard to make out, are shown by crosses here. The stars represent sibutramine treated patients.

CHAIRMAN BONE: We're going to ask for a budget increase so we can have a color slide next time.

DR. COLMAN: I'm going to help you out.

I'm going to direct your attention just to this quadrant. It's a little easier. People who fell into this quadrant lost at least five kilograms of body weight or more. Yet, at the same time, they had an increase in systolic blood pressure of greater than ten millimeters. Now, once again, I'll test your visual acuity. There's only one placebo subject in this quadrant. This individual represents roughly 1.4 percent of all placebo patients on the graph. The 20 or so sibutramine patients represent 12 percent of all sibutramine subjects on this graph. If you want to be statistically proper -- we did do statistics -- comparing 12 percent versus 1.4 was statistically significant. P equaled .006.

Now, this was a concern to me. These are individuals who have gone through a year of treatment on 10 or 15 milligrams. They've had a significant reduction in weight, anywhere from five kilograms all the way up to over 20. Yet, at the same time, they've had substantial increases from baseline in systolic blood pressure, 20 millimeters here, 25, et cetera. Again, these represent single measurements, but this is somewhat worrisome. A clinical question is can you effectively and easily and early-on in treatment screen these individuals out so that you don't expose

someone to potentially a year of blood pressures in this range? But I think these data, the data on the previous slide, suggests that there is a subgroup of patients who have a substantial increase in blood pressure and that is of concern.

Now, back to our favorite study. The third question I asked was does sibutramine affect the diurnal variation in blood pressure? This question may be answered, to some extent, in this study BPI 855. This was a small study. It was eight weeks. It involved 20 patients with a history of hypertension and they were controlled on a single, anti-hypertensive. Most were on a diuretic. Half the subjects received 20 milligrams a day of sibutramine, half received placebo. In addition to having a manually measured or cuffed measured blood pressure, they had 24 hour ambulatory blood pressure monitoring.

I should also mention that part of the protocol specified that weight loss be minimized. They actually had dieticians instructing the patients to eat enough so that the weight loss was minimized. The idea behind that was to try to isolate the effect of the drug and not have the confounding effect of weight loss.

Now, again, we heard this earlier. Aside

from the difference in the gender distribution, the two groups were fairly well matched to baseline. The mean age was 50 years. Half the subjects were African-American. This was a bit different from the standard studies we've heard about. It did not include this number of African-Americans. As far as weight loss, this slide illustrates a change in body weight from baseline to week eight. Again, as specified in the protocol, there was a small amount of weight loss in the sibutramine group. This was not statistically significantly different from placebo.

Now, this slide represents the baseline values, or day zero values prior to drug administration for 24 hour ambulatory diastolic blood pressure. At this point, let me explain how these numbers were derived. From the hours of 6:00 a.m. to 10:00 p.m., during the daytime blood pressure was taken every 15 minutes. From the hours of 10:00 p.m. to 6:00 a.m., the nocturnal readings, a pressure was taken every 30 minutes. From those values, hourly means were calculated and then a single mean was calculated for the daytime value and a single value for the nocturnal time period. What you can see here is that both groups at baseline, prior to drug administration, had the expected nocturnal reduction

in blood pressure: 86 to 80, 84 to 73. Again, you could argue that these two groups weren't matched ideally and statistically that it wasn't significant. But again, these were not perfectly matched.

Now, following this procedure they were randomized to drug or placebo and the patients had repeat ambulatory measurements on day three and at the end of week four and the end of week eight. I'd like to show you the results on the next slide. Again, these represent the mean change from baseline in ambulatory diastolic blood pressure.

I'd like to direct your attention to the nocturnal readings in yellow. You can see as early as day three, the placebo group had a reduction from baseline in nocturnal blood pressure, while the sibutramine group had an increase of one millimeter. This was significant. This pattern becomes more exaggerated as time goes on. At week four, the placebo group has a 12 millimeter reduction in blood pressure while the sibutramine group has a four millimeter increase from baseline. Again, significant. The same pattern was seen at week eight.

Now, this overall pattern was mimicked with mean arterial pressure. It was not seen with systolic blood pressure. And as the sponsor

mentioned, the manually measured blood pressures or the cuffed blood pressures were not significantly different between the two groups. So, there was a discrepancy.

Conclusions from this study: 24 hour ambulatory blood pressure monitoring indicated clinically significant increases in blood pressure associated with the use of 20 milligrams a day of sibutramine compared to placebo. In addition, sibutramine eliminated the expected nocturnal reduction in blood pressure. In some sense, it reversed it.

So, if I were to summarize the effects of sibutramine on blood pressure, I would say that sibutramine increases mean systolic and diastolic blood pressure by two to three millimeters relative to placebo. I think we all agree on that. I've shown some data that indicates sibutramine does, indeed, induce large increases in blood pressure in a subset of patients. This is worrisome. We need to be able to screen these people adequately to lower their risk. The final study suggests that sibutramine may eliminate the expected nocturnal reduction in blood pressure. Again, we've heard about the problems with the technology and so forth. It was a small study and

I certainly agree that you can not make any definitive comments about this but it does raise some questions.

Now, at this point, I'd like to move on to lipids. There were a lot of studies in this NDA that measured lipids, however, they were not primary or secondary or even tertiary objectives. There was only one study, one study that had as its primary objective, to measure lipid levels following sibutramine treatment in patients with hypercholesterolemia. This is important to keep in mind. This is the only study that was prospectively designed to look at lipids.

I'm going to review this study. This was a 16 week study conducted in Spain. It involved 182 patients. Half the patients received ten milligrams a day of sibutramine and half received placebo. The entry criteria included a total cholesterol of 200 to 300 and/or a TG level of 200 to 400. Now again, both groups were well matched for baseline characteristics. The mean age was 46. They were primarily female, all Caucasian. They were quite heavy -- mean BMI was 35 kilograms per meter squared. This next slide illustrates the baseline lipid levels. This demonstrates that, indeed, the two groups had comparable baseline lipid values. They might be

considered to have mild to moderate hypercholesterolemia.

Now, as far as weight loss, this slide illustrates the change from baseline to week 16. As you can see, there was an impressive weight loss in the sibutramine group. A mean weight loss of over eight kilograms or nearly 18 pounds. The placebo group lost 5.7 kilograms. The difference between the two was statistically significant.

How did this weight loss translate into lipid effects? This slide illustrates the mean changes in lipids, mean values with standard deviations in parentheses. Again, despite greater weight loss in the sibutramine treated patients, there were no significant differences between any of the lipid parameters. It's also interesting to note that despite a mean weight loss of nearly 18 pounds, the mean HDL level didn't budge.

In conclusion from this study, despite greater weight loss, obese hypercholesterolemic patients treated with 10 milligrams a day of sibutramine had no significant improvements in lipid levels when compared to subjects treated with placebo.

Now, again, the lipid question has become somewhat cloudy. I mentioned that a lot of studies in

the NDA had measured lipids. They weren't primary or secondary objectives of the study. Some post hoc analyses have been done. I've listed here on the left side, the studies in which a favorable or significant improvement in lipids were noted in the sibutramine group. On this side, there are studies where no significant improvement was noted. Again, these studies are very heterogenous. They range anywhere from eight to 12 weeks up to one year. Some have multiple doses. Some were done in the US. Some were done in the UK. One was done in Spain. It's difficult to make a general conclusion from the variety of data.

In any event, the two largest studies, the two primary or pivotal studies, BPI 852 and SB 1047 -- I think it's important to show you the actual lipid data from these two studies. Again, this was a six month dose ranging study. This shows the mean percent change from baseline to month six in mean lipid parameters. Now, the sponsor has mentioned they are going to drop the 30 milligram dose. When you do that, you see some sporadic improvements in some of the lipid parameters, primarily triglyceride. You don't see a dose response here. There was a dose response with body weight, but there doesn't appear to

be a dose response with lipids. It's also interesting to note that LDL, numerically it looked as though the drug was beneficial. But statistically, nothing showed up for LDL.

Now, turning to SB 1047, again, this was a year long study. This study only measured total cholesterol in TG. HDL and LDL were not measured. It's interesting to note that in this study, total cholesterol actually increased from baseline in all three groups. TG was reduced in all three groups. None of these differences were statistically significant.

Now we heard the sponsor present a meta-analysis of the lipid data. Unfortunately, I can't comment on that meta-analysis simply because no details of that study have been submitted to the Agency for review. So, I am left reviewing the data in the NDA. Simply my conclusion from looking at the data is the data are inconsistent regarding lipids. I think I've shown that.

Now, finally, I'd like to finish up with a brief discussion of two studies that studied the effect of sibutramine in patients with non-insulin dependent diabetes.

This was a small study, a pilot study. I

guess we didn't hear about this study. This is a 13 week study. It involved 18 obese patients with Type II diabetes. It had somewhat of an interesting study design. For the first four days, 12 patients were randomized to 30 milligrams a day of sibutramine and then placed on 20 milligrams a day for the remaining 12 weeks. Six patients were on placebo for the entire 13 weeks. Now, aside from the placebo group having a higher fasting c-peptide level -- which was 40 nanograms per ml versus 24 in the sibutramine group -- both groups were fairly well matched for baseline characteristics.

To save time, I'm just going to show you the results of the study in one slide. This shows the mean change from baseline in body weight, hemoglobin A1C, fasting glucose, and the two hour glucose concentration after an all glucose tolerance test. There was a modest mean reduction in body weight in the sibutramine group. This was not significantly different from the placebo weight loss. As you can see, there were no significant improvements in any of the metabolic parameters. Not only were these differences not significant when compared to placebo, but within group comparisons, were also non-significant.

Now, the larger study was a 12 week study. It involved 91 patients. Half were randomized to 15 milligrams a day on sibutramine, half to placebo. Again, these groups were fairly well matched to baseline. In the interest of time, I'll show you the results. Again, this shows the mean change from baseline to the end of the study in body weight, hemoglobin A1C, fasting glucose. This represents the change in the glucose area under the curve following a test meal. The test meal was a standard breakfast, 520 kcals. This is the change in fasting insulin and the change in the insulin area under the curve following a test meal. Once again, there's a modest reduction in body weight in the sibutramine group. In this case, it was statistically significant. Yet again, there were no significant improvements in any of the measures of glycemic control.

To conclude, the treatment of obese diabetic patients with sibutramine had minimal effect on body weight and no significant effect on glycemic control.

As an overall summary, I have two slides to conclude with. Regarding efficacy, the five percent responder analysis: compared to placebo, a significantly larger proportion of subjects who took

five through 30 milligrams a day of sibutramine lost at least five percent of initial body weight. In general, there's consistent evidence that sibutramine has a pressor effect. More importantly, it appears that this pressor effect is independent of the change in body weight. Also, in general, there's a lack of consistent evidence that sibutramine improves lipid levels. Finally, there's no evidence that sibutramine significantly improved glycemic control on patients with Type II diabetes.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Colman.

Are there any questions now from the Committee to Dr. Colman concerning his presentation?

Dr. New?

DR. NEW: Dr. Colman, how do you know that in the illegible graph that had the quadrants -- how did you know that in the right lower quadrant, those who had lost weight but yet were hypertensive, how did you know that they were different individuals?

DR. COLMAN: How did I know they were different individuals?

DR. NEW: How do you know they weren't the same person? Since you said they are single blood pressure measurements, how do you know that they're

different people?

DR. COLMAN: Because it only represented the people --

DR. NEW: Once?

DR. COLMAN: -- once, yes.

DR. NEW: In other words, the data as submitted was by individual?

DR. COLMAN: Yes. There was a plot for each individual, the change in their body weight versus the change in their blood pressure. They came out as one point.

DR. NEW: So, what point did you select to plot?

DR. COLMAN: Well, we took the arbitrary -- we made two measurements. We said if someone lost five kilograms of body weight, we consider that a reasonable amount of weight. We decided that ten millimeters of blood pressure was significant clinically, and that's how we came up with that quadrant. Simply to illustrate that there appears to be a subset of patients who lose weight on the drug, yet have a substantial increase in blood pressure.

DR. NEW: But supposing I asked you what was the blood pressure of those who lost significant amounts of weight at night? Because there is an

ambulatory record which you showed.

DR. COLMAN: Yes.

DR. NEW: So, could you have plotted a different hour of the day? Because these are single individual blood pressure measurements. How about if you plotted the mean blood pressure for those people?

DR. COLMAN: Well, we could ask the company to do ambulatory blood pressure monitoring in 1,000 patients, but I don't think they'd probably go for that.

DR. NEW: Okay. Could you have given me a mean blood pressure of those patients in that right lower quadrant?

DR. COLMAN: A mean blood pressure?

DR. NEW: Rather than an individual blood pressure.

DR. COLMAN: A mean of over what time period?

DR. NEW: Twenty days.

DR. COLMAN: Oh, I'm sure we could do all those things. I don't have the data set to do it. And again, my point was to show that there clearly is a subset of patients who lose a substantial amount of weight, yet at that time point, they had an increase in blood pressure.

DR. NEW: And what confidence have you that that time point represents the blood pressure of that person, in general, on this drug?

DR. COLMAN: Well, also, the point is that there was only one placebo patient in that quadrant and there were 20 or so sibutramine. So, there's an issue of comparing groups.

CHAIRMAN BONE: Those were the endpoint changes in blood pressure and endpoint changes in weight, is that correct?

DR. COLMAN: Not endpoint, over month 12.

CHAIRMAN BONE: I'm sorry.

DR. COLMAN: Endpoint, I would --

CHAIRMAN BONE: So, it was only for completers?

DR. COLMAN: Right.

CHAIRMAN BONE: So, do I understand correctly for the benefit of everyone, that that analysis was performed on subjects who completed the full 12 weeks --

DR. COLMAN: Months.

CHAIRMAN BONE: Twelve months, I'm sorry. Pardon me, 12 months. Excuse me. Completed the full 12 months, graphing the change between baseline and 12 months in body weight and the change between the

baseline measurement and the 12 month visit measurement in blood pressure?

DR. NEW: So, it was the 12 month visit?

CHAIRMAN BONE: Yes.

DR. SHERWIN: But what's important is it doesn't include those people who were withdrawn because of hypertension. Is that correct?

DR. COLMAN: Very few people were withdrawn from that study for hypertension is my belief.

DR. SHERWIN: Okay. Do you have the numbers on that?

DR. COLMAN: I don't. The sponsor might want to address that.

CHAIRMAN BONE: Perhaps somebody can be checking that unless they have an immediate answer.

DR. SPIGELMAN: Well, the incidence -- that was one of the protocols in Dr. Seaton's curve in which there was no mandatory discontinuation. The discontinuation in that whole population, as I remember it, was in the order of about .5 percent, much less than one percent. So, I can't tell you for that one study specifically.

Okay, nobody was withdrawn for high blood pressure in that study.

CHAIRMAN BONE: Thank you very much.

I believe Dr. Flack and then Dr. Kreisberg have questions.

DR. FLACK: I think another important point about that right lower quadrant is that those were people who had unfavorable blood pressure changes and lost a fair amount of weight, but it really underestimates what happens in reality because everybody is not going to lose a fair amount of weight. That's really sort of taking the paradoxical smaller group and putting it together which is, I think, what that slide is showing.

CHAIRMAN BONE: Dr. Kreisberg?

DR. KREISBERG: Well, that was, I think, my point as well. I would be interested in people in the right upper quadrant because those are people who had blood pressure that went up but didn't lose weight. That looked to be a pretty heavy quadrant as well, is that not right?

DR. COLMAN: Right, yes.

DR. KREISBERG: So, these are people that were maintained on the study for the 12 months and actually were not getting any benefit from weight reduction but were presumably deriving some detrimental effect from an increase in their blood

pressure?

CHAIRMAN BONE: Dr. Critchlow?

DR. CRITCHLOW: Do you know if blood pressure tended to increase right away and plateau, or did it steadily go up among those whose blood pressure increased?

DR. COLMAN: Specifically with this data, I don't know. My impression from the NDA is that -- well, first of all, I don't think the blood pressure has been well characterized as far as questions like this. In general, I've seen statements from the NDA such as the peak blood pressure effect may not be seen for six to eight weeks. At that point, it may plateau.

CHAIRMAN BONE: Other questions or comments?

Dr. Sherwin?

DR. SHERWIN: I just want to get it straight in terms of the right upper quadrant. I couldn't see -- you didn't point out stars and --

DR. COLMAN: Do you want to go back to that?

DR. SHERWIN: Well, in other words, stars versus whatever they were, crosses?

DR. COLMAN: I don't know what number

slide that is.

DR. SHERWIN: Because it looked like both groups were in that quadrant. I just don't know --

DR. COLMAN: Keep in mind, again, another way to look at this is to look just simply at who increased, who decreased from zero. You know, the zero here and then zero here. We thought it was more clinically relevant to pick a point where people would be attracted to the drug because they did lose at least five kilograms. That's over ten pounds. Then we arbitrarily chose ten millimeters as saying this is significant. Some people may argue this is not significant. And again, it's only a single measurement.

The point is, there's only one placebo patient here and there are roughly 20. Quite a difference in the proportion. But you're right, people are scattered all over the place. Again, that gets back to the point that there doesn't appear to be a correlation between the change in body weight and the change in blood pressure.

DR. SHERWIN: Were these evenly divided groups? I can't tell from this. There were more people on drug originally?

DR. COLMAN: Well, yes, there were --

DR. SHERWIN: You don't want to skew it too much.

DR. COLMAN: No. There were roughly 166 sibutramine patients who completed and approximately 71 placebo. But again, if you look at the proportion, it was significantly different.

CHAIRMAN BONE: Thank you.

Dr. Colman, one of the questions I asked earlier based on some of the tables that were prepared for us had to do with what the estimated magnitude of this increase in blood pressure might be for patients on doses that are likely to be clinically effective. You said that, particularly with regard to the study 1047, you thought the estimate of two to three millimeters was a realistic estimate. That does fit with the -- I think it's the 15 milligram dose in that study.

DR. COLMAN: Yes.

CHAIRMAN BONE: But looking at the other large study 582 -- I mentioned earlier that looking at the table, it looked as though to me, the magnitude of the increase in blood pressure was somewhat greater for those doses that were likely to be clinically effective.

DR. COLMAN: Right.

CHAIRMAN BONE: And it seemed to be higher yet if anything with chronic exposure -- which gets to this question about acuity of the effect. Was your comment about the two to three millimeter estimate pertinent only to the 1047 study or to taking all the data together?

DR. COLMAN: That is an overall estimate taking all the data altogether.

CHAIRMAN BONE: Are you confining that to the doses of 10, 15, and 20 milligrams, or to what extent is that influenced by the one and five milligram doses?

DR. COLMAN: No, and again -- yes, again, this would probably be better addressed by the sponsor because the sponsor has -- actually, that's a quote from the sponsor and I tended to agree with it. I don't know all the specifics of it and they might be able to better address that.

CHAIRMAN BONE: Well, all right. We've heard the sponsor's description, so I guess we're just agreeing with it, or not disputing it.

Are there any additional questions or comments concerning Dr. Colman's presentation from the Committee?

Thank you, Dr. Colman.

I guess the next speaker will be Dr. Bruce Stadel.

DR. STADEL: I got drawn into this in early August because some of the discussions about possible effects of blood pressure were brought forward in the forms of epidemiologic models and I was asked to look at those. Then this has progressed. So, I tried to put together some of the information on the big picture of where we are with appetite suppressive drugs because I think it does have some relevance to some of the issues for this drug in particular.

These figures are from IMS America which is a database used by industry and by the Agency for measuring drug use nationally. The left-hand column shows numbers of prescriptions and the right-hand column is a demographics column drawn from a file that asks physicians about patients they've seen and what drugs have been discussed and so on.

I put up the years that I have because the current episode of interest in anti-suppressant drugs really got its impetus in 1992, the publication of the paper by Weintraub and colleagues on long-term weight control NHLBI had sponsored. There were 62 patients on drug in that study. It was a long study, but

small. Sixty-two patients on study and 59 originally randomized to placebo. This was on a combined fenfluramine/phenteramine regimen. Now, that was in 1992.

Well, you can see that what's happened here with the prescribing of the two drugs that are used in that regimen for phenteramine -- there's lots of brands. But it has gone from two million prescriptions written in 1992 to just under 10 projected for this year on the basis of the first few months' return. And for fenfluramine from 69,000 up to 6.3 million prescribed. Now, these aren't always used together but I think they probably are a lot even though there really isn't a marketed and labeled regimen of that kind. But I wanted to show this because I think it provides some background for what's happening in the world of appetite suppressant drugs. Then, of course, in April of this year, the redux dexfenfluramine was approved. We anticipate -- I mean, my expectation is that it will supplant fenfluramine which is only one brand, pondimin, and continue rapid growth.

I have some personal opinions about this growth and what I've been able to learn about the appetite suppressant market and that is that I think