it is somewhat unlikely to represent a very, very narrowly selected prescribing to individuals with clearly labeled obesity indications over comorbidities. I see more reason to believe that this rapid growth involves a wider prescribing to people with varying degrees of obesity, many of whom do not have any comorbidity that is going with the obesity. So, that's just sort of a little bit of background information.

Now, the second topic I'd like to talk about is what do we know about intentional weight loss and its effects on mortality? There's only one large published study that I've been able to find. It's cited in the NDA, but it's not discussed. It's a study by Williamson and colleagues, a perspective study of intentional weight loss in mortality in never smoking, overweight, US White women, aged 40 to 64 years. It was restricted to never smoking women to separate out the confounding effects of smoking from the others in the data.

This is based on the Cancer Prevention Study Number 1 of the American Cancer Society. It's a follow-up study of 43,400-plus women who had a BMI over 27. They were never smokers, aged 40 to 64 years, who in 1959 to '60 filled out a detailed

baseline questionnaire about their medical history, personal health practices and so on, including a history of weight loss practices. Vital records status for 91 percent of the population was determined through 1972. The mortality outcomes were all cause cardiovascular, all cancer, obesity-related cancer and diabetes related.

The questionnaire about weight at baseline included current weight and height, and a series of questions about weight change recently. Whether there had been a weight change, whether there had been a gain or a loss. If it had been a loss, had it been an intentional or unintentional, and what length of period of time it had occurred over. Analyses were then grouped by intentional weight loss in one to 19 pounds and 20 pounds plus. Their potential confounding by pre-existing elements was controlled primarily by stratifying on the baseline history.

Now, this that I put up here refers to women who at baseline, reported obesity related health conditions. That is, they had at baseline heart disease, stroke, diabetes, high blood pressure, or a history of severe shortness of breath or chest pain. Persons with prevalent cancer were not included in this group. Now, the group with no pre-existing

illness which we'll get to in a moment after I talk about these was no to all disease and severe complaint categories, and said they felt well at baseline.

Now, what this shows you is the all cause mortality rate. About a third of the patients, you see, 15 out of 43,000, reported that at baseline they had obesity related health conditions. This shows you their all cause relative risk of dying during the subsequent many years of follow-up through 1972. I draw your attention to the column -- let me find my little pointer -- labeled "fully adjusted". Now, the no change means they had no change in weight and that's used as the reference group. The unknown weight loss, unintentional loss, unintentional gain, and then intentional loss. So, what you see here is for people with clear obesity related comorbidity, there was about a 20 percent reduction in mortality over the subsequent year.

Now, this doesn't look very different by the amount of weight loss but this is a pretty wide interval. And remember, this is questionnaire based so I think it's more important simply to note here that there is in these data, for this group, with clear comorbidity -- now, these are not necessarily all the people who are taking appetite suppressants.

This is a portion clearly needing medical treatment for various problems and obesity may be one of them. In further analyses, this is clearly accounted for by a reduction in the mortality from obesity related cancers. They were mentioned earlier: breast, endometrium, ovary, gall bladder, primary sites, and in diabetes related deaths. So, it made sense. Obesity related cancer, especially breast cancer, is well known in relationship with obesity and with endocrine alterations that are produced --

Let's go then to the next slide, next transparency, which has to do with the people who did not have any pre-existing baseline illness, okay? Now, they didn't report any baseline. That's two-thirds of the people. These people had uncomplicated obesity as most of the people in the large sibutramine trials had where people with NIDDM and hypertension and so on were excluded. They didn't have histories of heart disease and so on because serious illness -- and this, I think, is probably a large part of the appetite suppressant using population. So, I just think there's a need to get down to earth about like what modeling means and so on with regard to large mortality savings.

I don't think that an appetite suppressant

drug necessarily has to accomplish those things to be worthwhile, but I did just want to bring some perspective on some of the things that have been said. There was no effect of intentional weight loss on subsequent mortality in people who didn't have obesity related health problems at baseline. Now it may have done them a lot of good in other ways, but it did not reduce their subsequent all cause mortality in this study.

Now, some of the strengths and weaknesses -- I think the study is strong in terms of controlling for potential confounding by variation in baseline health. They had a very good questionnaire on health status and I think they did a good job of controlling for that. I think it's strong in terms of having large numbers and having full ascertainment of mortality and having an endpoint of mortality that is quite firm.

However, on the other side, one of the problems with big studies like this is that it's a questionnaire based. You don't have a lot of measurements on people. You do have a certain amount of problems with coding data from questionnaires with unknowns and so on. So, you could have missed some small effect here in this intentional loss group here,

I suppose.

But I just draw your attention to the difference in findings here versus those on the preceding transparency where there was a clear association for people with obesity related conditions. And that's the only study I know of in the literature that looks in the large numbers at the consequences of intentional weight loss. I emphasize intentional because the models that have been discussed -- the Framingham study is a wonderful study, but it's looking at naturally occurring variations. It's not looking at drug induced variations.

Likewise, of the Nurses Health Study which has been -- not talked about much here today but has been talked about a lot in terms of obesity. It looks at over 100,000 women who in 1976 were enrolled and followed for 16 years. It classifies them by their weight at baseline and looks at their later mortality. Well, that's the relation of naturally occurring variations in body weight and mass with weight or mortality. I have no reason to question the data from that. But naturally occurring variations are not the same thing as intentional weight loss, whether it's by dieting or by drugs and so forth. The preponderance

of evidence is that intentional weight loss does not produce large changes in mortality -- large savings.

That's going to be important when we're talking about counterbalancing the pressor effect of this drug. The argument is that the effects of weight loss as reflected through their effects on lipids in your model -- but the argument is that the effects of weight loss are counterbalancing any risk related to pressor effect. I submit that that argument is not strong.

Before I go on to talk about the model -- just on the Nurses Health Study, I'd like to make a quote from them. They had a small amount of data about weight change in addition to looking at the variations. They said that they examined the role of weight change during adulthood in relation to the overall and cost specific mortality which was later. Women who had lost weight did not have significant changes.

Now, in the sibutramine modeling that's been done, we're looking at -- I'll look at the one at the right. These are referred to as scenarios having been developed for coronary heart disease using the actual mean change of scene in the sibutramine studies. Now we tend to agree that there is a two to

three millimeter mean change in both systolic and diastolic. Now this, of course, refers to eight years of follow-up which is kind of a long time I think to be talking about in terms of drugs that have been studied for one year. But in any case, I think that as a standard for trying to look at benefit/risk tradeoff, it's reasonable.

I agree with this. I have no question about the Framingham data themselves. I think we're all in agreement that there's a two to three millimeter mean increase in blood pressure. So, that would say "well, if you took the drug for eight years and it sustained that level, then you would expect these kinds of risks per million." This change from here in the before drug to the three millimeter here would come out -- it's hard to get that on a yearly basis because this would change with the age of the women. But if I do it just dividing by eight, basically, we'd come out into an increase in risk of about one in 6,000. You'd have an increase in coronary heart risk. And you'd have added on to that, whatever other vascular disease risk beyond coronary that was related to that. We'll try to get an order of magnitude of what this means down to numbers that are easy to think about.

So, our big question is, okay, well that's what happens when the blood pressure goes up from 80 to 83. Now, is the weight change, as reflected through its lipid effects as shown up here -- are we really confident that that counterbalances this blood pressure risk? I submit that I am not. The reason I am not is two-fold. One is, I don't see the other evidence on intentional weight loss supporting the idea that intentional weight loss, as it might be reflected in lipids and so on, really produces these changes in mortality. That's not what the other evidence says to me.

The other is that I don't see in the NDA data, and reviewing Dr. Colman's review -- now I've seen the later submitted material but, again, it has not been submitted in detail for review under the NDA. I don't think the evidence for the lipid effect has the kind of consistent and pervasive nature here. I think there clearly is a lipid effect in people who lose a lot of weight. They're a relatively small fraction of the total exposed population but all of the population gets blood pressure effect. So, one -- weigh two different categories of information. Whereas here, they're entered into the regression models if they have the same weight. That's my

understanding. That if this effect were counterbalanced by an effect the magnitude of which pervasiveness and statistical significance that these were the same, why then that's true in Framingham.

But I don't think that there is a pervasive effect shown up through lipids that's really a weight loss effect that is in studies of people without prior comorbidity. I don't think the preponderance of evidence supports the concept that this counterbalances this, so I'm left with this. And saying, "well, we could be talking about an increase in risk that would have a denominator in the tens of thousands as opposed to the kind of increase in risk the other drugs have been approved and have had a denominator in the hundreds of thousands." So, I remain concerned about the issue of the blood pressure effect in terms of the mean, but I think it's a potentially solvable problem.

If we could go on to the next transparency? Whoops -- let's skip that. This is the calculations that were made from the Nurses Health Study based upon the naturally occurring variations in weight. What would happen if intentional weight loss using the drug produced those changes and was maintained over the 16 years of follow-up in the

study? I just don't feel that there's a need to go into detail about that.

Okay, if we could go to the next slide? Yes -- well, you've seen this before. We obviously have a certain enthusiasm for these data. And there has been some questions about them. Maybe I can give my opinions on them anyway.

Why are we focusing on this group? Well, because they lost a lot of weight and they would therefore be likely to stay on the drug, okay? These people -- yes, they had changes in systolic, but they didn't lose weight so, they're not going to stay on the drug. They'd have a short-term risk related to the blood pressure but it wouldn't go on for a long time. That's why we focused on this group. The point here is that it almost seems like to be a dynamic relationship between the weight loss and the blood pressure increase, at least in this one cut. Now that's not entirely true. There's quite a few stars over here and only -- a few more crosses, but not too many more.

The point in pointing this out is not to draw some ironclad end of the road conclusion. In my opinion, what it says is that there needs to be more work done on screening criteria with regard to the

issue of there being some people that look like they have substantial pressor responses. There's a statement made in the NDA submission that they didn't think there was very many people who had clinically important blood pressure increases. I don't agree with that from what I've seen.

It looks to me like the existing database, large database, could be used to test blood pressure screening scenario. For example, simple ones that have potential for being clinically useful: baseline resting blood pressure, blood pressure at two weeks. Let's say if one sets some scenarios, say a criterion of over five diastolic increase and/or over 10 systolic. If you made that cut and then you look at the residual population, are you able there to really get out a group of people? You have enough data to track that group. Say if you made that screening cut, would that strand out a group of people who really are having a clinically relevant pressor response?

Remember, you know, in blood pressure epidemiology, as I understand it, it's just as important what your rise is from baseline here to here as it is from here to here, in terms of the overall analyses. So, cut off the deal with things like diastolic over 90 and systolic over 140. Represent an

older thinking about blood pressure than is currently state-of-the-art.

So I'd say if you take the database and you say, "okay, what's your baseline blood pressure? What's your blood pressure at two weeks?" Subtract them, run various scenarios that look at tradeoffs. Does that identify and screen out? It's clinically practical. I think there's a reasonable chance that using such data, one could identify a screening strategy that was practical and that cut a chunk of the blood pressure response out. That kind of thing then could possibly be tested in a short, large, simple study that looks simply at the effect at, say, eight weeks. How effective is that screening scenario? In other words, generate the hypothesis from the data that are available and test it. I personally think that sort of thing really needs to be done with this. That's my response to the data.

My last comments I really would like to address -- Dr. Spigelman and his colleagues had come and met with us and we had what I felt was an immensely productive discussion about the potential for a Phase IV trial were this drug to be approved. I thought the suggestions made were extremely good and I think that large simple trials have an enormously

valuable role in evaluating therapies including drugs. I do think, of course, a lot of details would have to be worked out. This discussion was August 30th, so it's really an end principle. But nevertheless, I think it represents an admirable coming forward in statement and principle towards a very valuable idea. I do think myself that this blood pressure issue needs to be sorted through more before then.

So, that's really the essence of my conclusions about this. I think we've got a rapidly growing marketplace for appetite suppressant drugs. At present, we've got a more -- concern about the pressor effect and its being pervasive than about there being a weight loss lipid effect that really confidently from a model -- that's enough and that counterbalances it. I think there is good reason to believe that with some more work on the existing database that a practical hypothesis could be developed for blood pressure screening which could be fairly rapidly assessed in a fairly simple study and might well get this then into shape to say, "if you do these things" and they're simple enough to be done in widespread practice, that the benefit/risk tradeoff would be considerably improved.

Lastly, were that to occur and then the

drug were approved, I would, of course, greatly support the idea of a large Phase IV trial. Thank you.

CHAIRMAN BONE: Are there questions from the Committee for Dr. Stadel?

Dr. Kreisberg?

DR. KREISBERG: Dr. Stadel, it's my understanding that the Williamson study was an observational study and there was nothing -- it was a prospective study but it was not randomized. As a result of that, there could be confounding factors that lead to the observation that there was a reduction in mortality in those women with coexistent medical problems who intentionally lost weight, such as other healthier practices that they may have had.

I just wonder if you recall from reading that article, were all the confounding issues excluded as a possible explanation?

DR. STADEL: I thought they were pretty -- it is an observational follow-up study. I guess in terms of hierarchy of rigor, I would say randomized trial first, observational follow-up study second, and synthetic model third. Yes, it's an observational follow-up study.

I think the way that that issue was

approached was pretty good. There are two levels. One was stratification on baseline history with clearly different results in study using the same methodology for those two groups. That is, those that had a history of baseline were analyzed.

Baseline obesity related health conditions were analyzed as one group. Those that did not were analyzed in as a separate group. The results are different. The study methodology in the two groups was the same. The finding is specific to obesity related cancers and to diabetes related death. It's not pervasive across all causes of death which is what I might expect if there were uncontrolled residual confounding.

Also, in addition to the stratification on baseline history, there was a good deal of covariate data taken in the history that was used for some fairly extensive regression modeling. It didn't change much of the conclusions. It's always kind of comforting when you do these things -- if you take these kinds of studies, if you take the crude and you do regression modeling on possible confounders and it doesn't change much. It's always possible, but there's some point at which you get tired and you say, "well, it looks like that's probably true."

Lastly, after stratifying on the baseline history, they omitted the first three years of mortality follow-up precisely to get away from things that were related to uncontrolled confounding during that period. So, I think on a big brush stroke, on a big picture thing, I'm reasonably comfortable that it's a pointer in the right direction. I think like with all these big observational studies, you trade generalizability and size for precision. That's a tradeoff.

CHAIRMAN BONE: Other questions from the Committee concerning the content of Dr. Stadel's presentation?

The Chair has a question. It's a similar question to the one I've asked a couple of other times. I keep hearing this figure of two or three millimeters of mercury increase in blood pressure as the estimate of the pressor effect. But when I look at particularly the larger studies -- and particularly the 852 study which is by far the largest study. It also accounts for the long-term observation in the extension -- it looks to me as though the pressor effect may be somewhat larger if one confines oneself to the doses that are likely to be employed in clinical practice.

Did you analyze this from that perspective, or has anyone else in the Agency made any kind of formal estimate of the pressor effect based on likely clinical dosage?

DR. STADEL: I think that the answer is I didn't. My focus here has been on -- you have a mean increase. It could be three millimeters. It could be four millimeters. It's more important to me to say is there a meaningful path towards a screening procedure that gets out of group. Then if you subtract them out and recompute the mean, you can play that against your model on the mean.

So, my focus in the time I've had available has been to try to say what can be done here to separate -- it looked pretty clear to me that there is a blood pressure responding group with all -- some people don't agree with that and that's what I see. So, that's where I put the focus of the attention. I guess I'd want to say if the mean in that study was four or five, again, the question to me becomes if you take those data and you run some screening scenarios, and you look at what if I strip out this response group? -- and there's still a group in which the drug is working well and it's a matter of, like with so many things, of screening out some people for whom a

particular treatment isn't necessarily the right thing and saying for the residual group, are you getting that mean down somewhat? That is the direction I went.

So, I have not looked study-by-study to say was there significant variation in the mean because I personally think the more important issue is the other end.

CHAIRMAN BONE: It does have an impact on the magnitude of effect predicted in these models though.

DR. STADEL: I agree with that.

CHAIRMAN BONE: Thank you.

DR. STADEL: And it makes quite a bit difference if you go from two to four and you don't have any counterbalance. Then you're talking instead of one in 6,000 in here, you're talking one in 3,000. It's a big absolute risk -- I don't want you to think that I'm diminishing the point, I'm just trying to answer --

CHAIRMAN BONE: But you haven't addressed that systematically?

DR. STADEL: -- what I focused on.

CHAIRMAN BONE: Right. Thank you.

Okay, other questions from members of the

Committee?

Fine. Then we'll go ahead. In addition to having presentations --

Thank you very much, Dr. Stadel.

In addition to having presentations by members of the Agency staff, we also have a guest member and consultant. Dr. John Flack, who is sitting here, as I mentioned, as a guest member and consultant with the Committee will make a presentation on the hypertension aspects of this problem as well.

DR. FLACK: Can you hear me in the back? Okay.

Can I have the first slide, please?

I want to clear up one thing before I start and that is, I'm not a surgeon. I'm not a person who goes in and tucks stomachs out and makes people lose weight or stuff like that. I'm actually an internal medicine doctor, cardiovascular epidemiologist and hypertension specialist. My perspective is going to be, really, taking one foot on the more global approach, thinking about the entire group of patients and risk in an overall group of people who have received this drug, as well as more high risk approach. Can you screen out individuals who might be harmed or might not receive benefit from

the more clinical approach. I'll have a foot in both camps.

This is a tremendous problem. My talk today is really not to go back and rehash a lot of numbers. I'm going to really synthesize what's been said because virtually everything that you need to have seen to understand what I'm going to tell you, you've seen, maybe with the exception of one slide which I apologize for not having made.

I live in a region of the country where obesity is rampant. Seventy-two percent of African-American women in the Southeastern part of the United States in the stroke belt are overweight. I live in a state, North Carolina, where physical activity ranks last in the country. We're actually 49th. The only reason we weren't 50th is because Rhode Island didn't report. We're also maybe the vice capital of the world outside of Las Vegas too, because we make a lot of cigarettes.

So, I am very familiar with the clinical problem as well as the epidemiologic problems with obesity. Clearly, obesity influences hypertension and influences blood pressure, and affects certain populations more-so than others. As a clinician, I am very, very interested in the ability to treat obesity

with safe and effective therapies with more than just behavioral modification, which does work but is tough to actually implement over the long-term.

Well, there's some major questions that got in my review of this extensive amount of data that was supplied to me. I actually consider it a privilege to have had the opportunity to do it because it was very -- it was a lot of information and it was, I think, a very important task.

The first question is, is the pressor effect of sibutramine clinically relevant? Certainly not for everyone. In a population, even a two or three millimeter mercury shift may be significant. In a clinical setting, that's not going to be relevant for all the patients. But for a subset of patients, people who are not necessarily at the central tendency of blood pressure change but are in the outliers, it may be very important.

If so, in what patient subgroups would you wish to avoid this effect? Some of what I'm going to say today really is predicated on the assumption that if the drug were to be approved, how would I like to see it used and labeled, and what I think is reasonable based on what we've seen. Because some of the decisions we're going to have to make, we simply

don't have information at this point in time on certain subgroups.

There's several manifestations of the pressor effect that you can demonstrate with sibutramine. The first is increased resting blood pressure, clearly a dose related phenomenon. Both systolic and diastolic pressure tend to go up. Now, there's been a lot of talk about the ambulatory blood pressure, problems with the machine, random error and problems with dependability of the machine that was used in the very small ambulatory blood pressure studies.

I would agree with Dr. Bone that random variability should simply affect both groups and not one group preferentially over the other. Therefore, it shouldn't really create systematic differences between groups. In fact, random variability in a study usually kills study power and blurs differences. And so, the differences that we saw in ambulatory blood pressure which in some hours of the day were in the double digits, higher on sibutramine, are a cause for concern and further study.

The amelioration or the attenuation of the nocturnal fall in blood pressure is as well an issue that was surfaced in the ambulatory blood pressure

monitor studies, again, with the stated problems and with the device and the study design. Again, this is something that did come out. When we're treating high blood pressure, certainly one of the things we want to do is control the pressure throughout the 24 hour period of time.

Now, there's data discussed by the sponsor -- are the blood pressure change distributions by the sponsor discussed and there's a talk that it's a shift of the distribution, a blood pressure change to the right, which would give you a small average increase. Certainly that does occur, but there's something else that happens with the drug that's going to have direct clinical and practical implications. And that is, not only is the distribution shifted but there's a dose dependent flattening of the distribution with an increasing size of the right tail. Basically meaning that if the distribution of the blood pressure change looks like this and this is a zero change and it's shifted over a couple millimeters of mercury, what we're basically seeing is that with giving the drug, the right part of the curve gets fatter and you get more outliers along with that, giving it a central tendency.

That gets you to the more high risk

strategy that makes that important, and how do you identify these patients who are likely to have sizeable increases in blood pressure who you clearly up front, wouldn't even want to be exposed to the drug. People who it might be worth taking that risk, how do you identify them and monitor them once they're on therapy?

What are the implications of this right tail shift in the blood pressure change distribution? To me, what it really means is that the random variability of the blood pressure is occurring at a higher absolute level. That's not terribly exciting, but true. The variation in blood pressure from looking at the distribution curves or the change curves really is still random. But it actually is more often in an upward than in a downward direction, particularly as you push the dose up and flatten the central tendency and make the increase a part of the curve fatter.

In the material, the editors talk about outliers at three standard deviations --

CHAIRMAN BONE: Just a short intermission while we're correcting the microphone.

DR. FLACK: There's talk about three standard deviations. Probably a more routine

definition of an outlier is two standard deviations. Two standard deviations away from the central tendency, you're pretty much sure that that kind of change -- whether it be an increase or a decrease -- is not random and does not belong to what we call the zero change distribution. Those are people who are true outliers.

If you took everyone in here as they walked out of the room, measured their blood pressure today, brought you back a week, a month later and measured your blood pressure again, we would see a change distribution that would be bell shaped, okay? It would be greatest around zero, the zero change distribution. But if you were two standard deviations or more away from that zero change distribution from the central tendency of that, then we would call you an outlier. Certainly, this is an epidemiologic and statistical principle that the frequency of true outliers is related to the central tendency. There's also an exaggeration of the effect out in the tails where there's smaller numbers of people that are having larger changes that we would be concerned about.

The epidemiologic risk/benefit of the analyses, I think the models themselves, the

Framingham data, is a very valid data set. The analysis is fine and is certainly the appropriate methodology to look at the overall impact. Not to identify high risk people, but to look at the overall impact. One shortcoming of the Framingham data is obviously they're not meaning minorities. The risk functions are likely to be different, but still, I believe it's a valid population to make estimates from.

I do though think that the information included in these models with the improvement in the lipid profile with weight loss, really, across the studies is not consistently observed. So, I would agree with the previous speaker than Framingham estimates really should be redone without the favorable changes in lipids included. Because there's clearly not a demonstrable benefit across the studies in the lipid profile. That will change some of the tradeoff risk estimates that were made.

Now, here's what I'm going to extrapolate because there's really not a lot of data based on the clinical trials to make these firm -- you can't go to the bank with this, but you can know from your experience as a clinician in understanding the pathophysiology of disease or people who are likely to

not do well with a pressor effect from a drug or from activation of the sympathetic nervous system. You could really come across several disease categories that you'd be concerned about.

One, I would be definitely concerned about poorly controlled hypertension. The sponsor mentioned this and it's very appropriate. I would suggest that anyone with a systolic pressure over 160 or a diastolic over 100 or both who fit what we call stage two hypertension -- have anything above stage one hypertension -- this drug really should not be used in them. Patients with known coronary artery disease, angina pectoris. Certainly a lot of patients have a calcoronary disease. You're more likely to have it the older you get. But if you have known coronary artery disease, I believe that that is a very clear marker for caution, or perhaps even a contraindication.

Congestive heart failure is very prevalent amongst the elderly. So is obesity. Congestive heart failure is clearly a disease state where activation of the sympathetic nervous system is problematic. Mortality reduction in many studies is related to the sympathetic nervous system suppression. Does that mean that sympathetic nervous system suppression is

causing it? No. But we do know that the more uncompensated congestive heart failure is, the higher the activation of sympathetic nervous system is. So, it would make sense in those patients not to overload the ventricle with the pressor response and/or an increase in sympathetic nervous system activity which is already high in this group.

Patients who have had stroke or TIA -- again, I think would be a cautionary group. I'm not suggesting that every condition up here is an absolute contraindication, but I think these are the conditions that should be in the discussion when contraindications are derived and labelling is being decided. Cardiac tachyarrhythmias clearly are a group of people -- perhaps even atrial tachyarrhythmias as well as ventricular arrhythmias -- the drugs should either be avoided or used with extreme caution.

Now, diabetes -- said earlier didn't appear to be any specific harm with the drug in diabetic patients, but what was evident to me in the studies that were provided was that the efficacy appeared to be less in the diabetic population. Dr. Sherwin pointed out this morning to me that in diabetic patients, there's already a concern about sympathetic nervous system activation. So, you would

not want to necessarily undertake the use of this drug if there's not a proven efficacy there. A select few patients with hyperthyroidism as well, you would not want to activate the sympathetic nervous system.

My final slide, in conclusion -- I maybe even going to go a little bit further and try to tie all this together. I think that the total daily dose of sibutramine should be 20 milligrams per day or less and 15 milligrams per day or less would be ideal or preferable to that. Because a lot of the things that you see with the blood pressure are dose related. There's a dose related flattening of the curve -- more extreme values are going to be seen at the higher doses. And yes, there is an increase in efficacy but it's a tradeoff. It's a balancing of making the drug available for people who have a very important problem. I'm not trying to say that all of the benefits have got to be cardiovascular, but trying to prevent harm from certain people who might experience cardiovascular problems.

The number of conditions for which this drug is contraindicated should really be expanded, in my view, based on what I've seen in the NDA submission. More investigation into the effects of this drug on ambulatory blood pressure should be

performed. Future studies really should standardize blood pressure medication dosing, look at peak trough ratios, which are very important we believe in evaluating the efficacy of anti-hypertensive agents. I would echo the comment made earlier about studying African-Americans, Hispanics, and if possible American Indians because each one of those populations is disproportionately affected by disease. This is not about being politically correct or anything. This is about really providing clinicians with the kind of information that's needed for subgroups when these drugs come to market.

Because if you come to my practice in Winston-Salem, North Carolina, a lot of the people who are going to be asking for this drug -- yes, there will be White women and maybe a few White men, but a lot of African-American patients. I live in a town that's 40 percent African-American. I think we can make the same kind of statements for Hispanics and American Indians. I think for the sponsor, it was a very important market for them as well. So, I'd like to see that data and not just referred to, but actually presented to us where we can look at dose response cards and look at efficacy.

You know, for blood pressure drugs, there

may be differences in dose response curves. It doesn't mean the drugs don't work across different groups, but there may be differences in dose response curves as well as modifying factors that influence dose response.

Finally, I'd like to make a strong pitch for more work to be done in older people. Older people are going to have a lot of conditions which I would believe that may cause us to at least use a drug with caution. And as well, older people in this society are becoming increasingly obese. There's a lot of overweight older people. Less than one percent of the available database in the submission that I saw was from people, I believe, over 65 years of age. I think beefing up the database there would be important.

So, what I tried to do was to really give you an overview as a clinician as well as a clinical researcher with one foot in both camps, and provide you a balanced view of what I really thought should happen with this drug. My impression of this drug was that it clearly lowers -- reduces weight. There are some issues though with blood pressure that are going to be much more magnified in subsets of patients. But it doesn't negate the fact that yes, even in the

overall population, the two to three millimeter mercury shift will be an issue but it's not the immediate clinical issue that it is in subgroups of patients that I described. I think we should focus there.

Thank you very much for your attention.

CHAIRMAN BONE: Are there questions from members of the Committee for Dr. Flack concerning his presentation?

Dr. Illingsworth?

DR. ILLINGSWORTH: Would you also potentially add peripheral vascular disease, recognizing that patients with coronary disease often have peripheral vascular disease?

DR. FLACK: Yes. Yes, your point is well taken. That was inadvertently left off. People with peripheral vascular disease could potentially be harmed by the pressor effect as well as by raised blood pressure.

CHAIRMAN BONE: Dr. Kreisberg and then Dr. Marcus.

DR. KREISBERG: John, you mentioned it but you passed over it pretty quickly. It seems to me that you've identified obvious cardiovascular risk factors but there are many people who are asymptomatic

who actually are at very high risk for events because of multiple risk factors --

DR. FLACK: Right.

DR. KREISBERG: -- sort of on the threshold of an event, but not yet there. I just wonder whether you thought that you should expand your recommendation to include those?

DR. FLACK: Well, certainly you can say that the people who have these conditions and peripheral vascular disease are patients you'd want to avoid the pressor or the SNS effects of the drug. There are clearly people who have these problems that we don't really know in clinical practice.

I guess that's what you're getting at, people who maybe have multiple risk factors or high risk for vascular disease but yet have never declared themselves clinically. I think you have to use the drug there with more caution. I'm not saying you don't use it in those patients who haven't really declared themselves because ruling out something is probably one of the hardest things to do in medicine because there's always one more task you can do in a widespread, even a clinic population. Watch for screening of people, say, with echoes to make sure they don't have heart failure is probably not going to

be feasible to do.

So, I think that's where clinical judgment is really going to come in and I'm not sure that that can be well proscribed from here but should be discussed.

DR. KREISBERG: Well, it seems almost like a paradox that the people who are at the least risk are the best candidates and the patients who are at the greatest risk who might derive the most benefit, if there is health benefit of weight reduction, are the ones that you're less inclined to use it on.

DR. FLACK: Yes. There is a paradox. I guess the main benefit of the drug is weight loss. For all the psychological and feelings of well being and all that that brings -- produces discrimination and things like that. We focus on the cardiovascular effects but the cardiovascular effects are probably limiting the use of the drug in some of the higher risk people.

But you're right, the primary benefit for weight loss and where you're going to use the drug where the competing risk and benefits of the drug are going to get you into least trouble are those who are at the lowest risk.

DR. KREISBERG: Thank you.

CHAIRMAN BONE: Dr. Marcus had a question.

DR. MARCUS: I didn't notice in the NDA materials. Has anybody looked at an interaction between smoking and the hypertensive effect? Do we know anything about that?

DR. FLACK: I don't know. I think you'd have to ask the sponsor about that. I honestly don't know the result on that.

Kind of as a follow-up to that, there also may be differences in blood pressure drugs which influence sympathetic nervous system activity in one direction or the other versus those that don't. Again, I don't know that information. Maybe the sponsor does.

CHAIRMAN BONE: I'm just going to ask Dr. Spigelman to specifically answer, if he has the information, on interaction with smoking. If you don't, you don't.

DR. SHERWIN: Or caffeine.

CHAIRMAN BONE: And what about with caffeine?

DR. SPIGELMAN: No.

CHAIRMAN BONE: The sponsor states that they have not looked at those interactions specifically.

Are there other questions for Dr. Flack from the Committee?

Thank you very much.

DR. FLACK: I'd like to make one final comment.

CHAIRMAN BONE: Oh, yes, please.

DR. FLACK: I don't know if I said this or not but clearly, in addition to the subgroups I've proposed that ought to be looked at in further detail, the ambulatory blood pressure monitor studies definitely need to be reconstituted and redone as well because I think there are some issues that were raised that we're in limbo about.

CHAIRMAN BONE: Thank you.

Dr. Colman, can you tell us when -- or perhaps the sponsor can -- when was the ambulatory blood pressure monitoring study completed? When was that completed? All I need to know is the date.

DR. SEATON: 1991 it was done.

CHAIRMAN BONE: Thank you.

Oh, Dr. Sherwin?

DR. SHERWIN: Time, let's get to that, yes.

CHAIRMAN BONE: Okay, the time has come for discussion for discussion amongst the Committee.

Just to clarify one point, Dr. Flack and Dr. Zawadzki are both here to participate in the discussion but are not members of the Committee as it stands, so will not vote. But they are invited to participate in the discussion with the regular Committee members.

I'm going to just briefly summarize the four questions that the Committee will be asked to vote on. We're going to discuss for however long it takes amongst the Committee. Then we will vote on each of these questions in turn. The Committee members will be asked to vote yes or no on each of these questions based on the data in the NDA, based on the data that have actually been submitted and reviewed. The Committee members may wish to add additional comments about what additional data they would need or what might modify their position if the data became available but we will be voting the established data.

The four questions are firstly, does sibutramine meet the guidance criteria of effectiveness for weight loss? Secondly, is the pressor effect of sibutramine clinically important? Thirdly, do the benefits of sibutramine outweigh the risks? Fourthly, if sibutramine were to be approved

for marketing, should there be a Phase IV study? And I presume that people will be asked to briefly comment on what they thought the elements might be in light of prior discussion.

I'm now going to open the floor for discussion and comments on any of these issues by members of the Committee. It seems that there is not a dispute about whether there is a pressor effect. That seems to be established through some discussion about the other implications here that we have before us.

Perhaps what we might do if the Committee is agreeable is just go around the table for comments to get the discussion going. Perhaps we'll start with Mr. Molitch.

DR. MOLITCH: You mean on question one?

CHAIRMAN BONE: No, you're not confined to the structure of the question. This is a general discussion at this point. You're certainly welcome to discuss any points that have occurred to you or you can pass if you want to and talk later.

DR. MOLITCH: I don't think there's any question, at least in my mind, about the effectiveness of the drug for a substantial portion of the population. I think the pressor effect is of concern.

Actually, one thing that did occur to me as I was listening to this on one area that was really not addressed very much today but in some of the materials that we were sent were some of the comparison studies with dexfenfluramine. Looking at the weight loss studies, I was actually interested to know what happened to blood pressure in those studies in the placebo versus the sibutramine studies, versus the dexfenfluramine studies? Did the blood pressure rise in the dexfenfluramine treated studies in those comparison studies? Do we have that information?

CHAIRMAN BONE: That's a specific question for the sponsor which we'll ask them to answer very concisely.

Do you have the data and what was the result?

DR. KELLY: I don't have any data to show you but I can tell you that the blood pressure changes on sibutramine and the two dexfenfluramine studies were consistent with the overall blood pressure changes in the overall database. The patients on dexfenfluramine had small decreases in both systolic and diastolic blood pressure and in heart rate.

CHAIRMAN BONE: Thank you. Very concise.

Let's see, Dr. Zawadzki, perhaps you'd

like to comment in general at this point? Do you have anything that you'd like to introduce into the discussion?

DR. ZAWADZKI: I have a question I've been wondering about as we've been discussing here. This is a drug that potentially would be approved for chronic use, but we know that most people do not take medication indefinitely. One set of data that I have not seen is what happens to blood pressure after discontinuation of the drug, specifically to those individuals in whom blood pressure becomes elevated during the use of the drug?

CHAIRMAN BONE: I think it's a very interesting question. Can the sponsor specifically answer that exact question? In patients who experience an increase in blood pressure on drug, what happens to the blood pressure when it stops?

DR. SPIGELMAN: It goes down.

CHAIRMAN BONE: Thank you.

Does it go back to baseline?

DR. SPIGELMAN: We have variable periods of follow-up. By three months, certainly it's back to baseline. By one month, it was almost there. We'd have to go through the data to give you the details.

CHAIRMAN BONE: Thank you.

Dr. Kreisberg?

DR. KREISBERG: Well, I don't know how much of the comments will actually relate to the questions or not.

CHAIRMAN BONE: It doesn't matter.

DR. KREISBERG: I have a question for the sponsor. That is, do we have any data on plasma catecholamines during the course of the administration of sibutramine acutely to patients to get a sense of the magnitude of the change, if any? Or urinary metabolites?

DR. SPIGELMAN: Could I just introduce Dr. Danforth whom we've asked to look at that specific question, or to look at that area and some of the diabetic related questions?

DR. DANFORTH: This is an interesting question. One might expect that a drug that causes a reuptake block of norepinephrine might actually produce an elevation of circulating concentrations of norepinephrine depending on the degree of the block.

The company has done five studies to look at this issue. If I could have the red carousel number 17?

CHAIRMAN BONE: Okay, please be extremely concise.

DR. DANFORTH: Well, the bottom line is, in the five studies -- concentrations of norepinephrine, epinephrine, dopamine were measured and were not different from placebo. And there were two studies in which urinary event mandelic acid was measured and in both of those studies the actual values were lower in the drug treated versus the placebo.

CHAIRMAN BONE: All right, thank you.

Urinary, epi and norepi as well, were they also measured?

DR. DANFORTH: They weren't measured.

CHAIRMAN BONE: Thank you.

DR. KREISBERG: I'd like to just modify the presentation of the sponsor. I think they used the modifying word "very effective" in talking about medication. I think it's mildly effective. I think it is comparable in its effect to dexfenfluramine which is also mildly effective contrary to what the press seems to think about dexfenfluramine.

I'm concerned about the issue of the Phase IV study. I think you said we could have the opportunity of commenting on what we think it ought to include. I think I can tell you what it should not include and I don't think it should include the study

as proposed by the sponsor. I have a great of difficulty with there comparing their drug to another mildly effective drug that is by no means the goal standard for promoting weight loss. That drug has never been demonstrated to have any effect on the clinical endpoints. It seems to me that that's more of a marketing strategy than it is a real interest in determining whether there's a difference or a benefit from weight reduction on cardiovascular endpoints.

CHAIRMAN BONE: Thank you.

Dr. Stadel, did you have something short to add to that?

DR. STADEL: Yes, I'd like to make a short comment in response to the evolving thing here. The only pressor that I've been involved with is the Phase IV trial of metformen where the comparison is the standard of care. You either add metformen randomized or you manage the patient as you would otherwise. To some degree, I think one can see this as along dose-wise. That is, what is required of a company in using a Phase IV trial to compare their drug to the safety -- - I think there is an argument -- to the safety of currently approved therapies.

DR. KREISBERG: I thought we were looking at efficacy. And the question was whether lowering

body weight would reduce clinical endpoints? Therefore, we need a control group, don't we?

DR. STADEL: That's not the question for which the study was proposed to me. It was proposed to me in response to our ongoing concern about pressor effects and about whether this would convey a greater net risk in the population than existing proposed therapy. It was a response to that concept.

CHAIRMAN BONE: So, there's really two different objectives here. Dr. Kreisberg is really addressing the objective of the effect of on comorbid conditions and the overall health impact, and the other addresses, let's say, a more circumscribed issue.

Dr. Critchlow, did you have a comment at this point?

DR. CRITCHLOW: Just at this point, I wanted to concur with Drs. Flack and Stadel with respect to their analysis of the epidemiologic model.

Another quick question, given the titration schedule which I think is good in keeping patients on the lowest dose possible, is there any data to suggest that the approximately third of the patients who do not respond to the ten milligram dose in losing four pounds in four weeks, do they have the

same probability of responding when they go up to 15 as those initially put on the 15 and then 20?

CHAIRMAN BONE: That's an interesting question. Comments from the sponsor were somewhat contradictory in the morning. One suggestion was that patients who were started on the drug and didn't lose four pounds in the first month should be discontinued. The other suggested that the dose should be increased.

Now, do we have specific information -- specific information -- on the likelihood of a response as a result of dose escalation after four weeks?

DR. SPIGELMAN: I think the fact that I didn't come across clearly is a problem that I really would like to clarify just to make sure that the Committee understands what the position is, if I could?

CHAIRMAN BONE: Please.

DR. SPIGELMAN: The dose titration is geared both toward safety and efficacy. It probably wasn't picked up but one of the overheads that Dr. Seaton showed was that, in fact, if you look at elevation of blood pressure as measured by a rise of ten millimeters or more in two consecutive visits -- which is perhaps arbitrary, but we feel more

clinically relevant than a single visit -- the vast majority of those are detected within four weeks of starting therapy. Seventy-five percent of those patients who ultimately will have, during the course of the total therapy, two consecutive visits where blood pressure rises either systolic or diastolic by ten millimeters of mercury or more, can be detected within the first eight weeks of therapy. Over 50 percent within the first four. That was the overhead that Dr. Seaton showed.

The titration schedule is geared around enhancing both efficacy and safety. So that, in fact, if a patient is noted to have an increased elevation that is clinically not acceptable to the treating physician -- and in the vast majority of cases, those will be detected early. Not at 12 months -- then that patient should be discontinued.

CHAIRMAN BONE: I don't think that was Dr. Critchlow's question though. Thank you for that information.

Dr. Critchlow's question was we've had two proposals about what to do with a person who doesn't lose at least four pounds in one month. One is to discontinue the patient and the other is to increase the dose. The information suggesting discontinuation

seems to be clearer. The response rate, we were very convincingly shown, was very poor if patients don't lose four pounds in the first four weeks.

Is there any evidence that increasing the dose at that point is likely to result in a response?

DR. SPIGELMAN: The evidence comes from the response curves in the prospective study by subtracting what patients respond at ten versus five, at 15 versus 10. We do not have a titration study in which we have studied those patients who do go from 10 to 15, but we have no reason to think that the data that gives subtracted differences -- there is a population who do not respond at 10. There is a population who do not respond at 15, similarly at any dose.

CHAIRMAN BONE: So, your assumption is that the response rate at 15 minus the response rate at 10 would be the incremental response rate?

DR. SPIGELMAN: That's correct.

CHAIRMAN BONE: But there's no actual trial of any kind to test that so far?

DR. SPIGELMAN: That's correct. It comes from the data that we presented.

CHAIRMAN BONE: Thank you.

Dr. Marcus, do you have questions or

comments?

DR. MARCUS: Yes. Once again, it's on the issue of blood pressure. I think that I'm sufficiently concerned about that that I think a formal and good study of blood pressure as a primary endpoint needs to be undertaken. And I think it should be undertaken in a way that the usual sorts of anti-hypertensive big trials would endorse. It should have readings of supine sitting standing blood pressure. I don't know what the current status is of what they call random zero readings to get out -- ways to get out the bias of the interpreter in reading the results. To go into it in a formal and established method that the hypertension community would accept.

Furthermore, there's many questions about interactions of this drug with such every day events such as alcohol, anti-hypertensive medication of various sorts, diuretics, caffeine, tobacco, probably a zillion others that simply have not been addressed and need to be. The final issue, once again, is to explore the interactions with blood pressure and efficacy in an ethnically representative population.

Finally, I remember maybe a year-and-a-half ago when we had the first meeting to discuss guidelines. I remember Dr. Bray saying, "listen,

folks, if you're looking for these markers of cardiovascular risk, that's not where the action is in the drugs we're asking you to consider for these patients." That if the patients we're talking about with profound obesity had those risk factors, they would have died. We're talking about a completely different set of risks. We're talking about sleep apnea. We're talking about the need to lose 40 pounds so that a patient can undergo surgery.

Dr. Bray made a very eloquent and powerful presentation to focus this Committee on that particular aspect of obesity. I haven't heard a single word about that aspect of it in the entire presentation ever since that meeting. It's kind of like that was it, you know? It's got my vote. Then ever since then, it was completely ignored. I would make a plea that we should consider also some of the aspects that were contained therein.

CHAIRMAN BONE: Dr. New, do you have comments or further questions?

DR. NEW: Perhaps my comments will seem like being perseverant or perhaps reflecting the fact that I take care of very young subjects in which blood pressure is extremely variable. It really depends on whether the child or adolescent is sitting, standing,

supine, has rested for five minutes, has had an anxious episode because blood has been taken, the size of the cuff that's being used when the blood pressure is taken, whether the child is screaming, performing a Valsalva maneuver and other things.

I looked at the methodology for the measuring of blood pressure here and it says that they used the Krackoff sound disappearance as the diastolic and that the patient was seated for five minutes. I think that's a better description than I read in most adult literature but -- and because I work in hypertension all the time, these factors are extremely important.

Secondly, when I addressed Dr. Colman -- and I seem to have lost my mind because I wanted something in sleep -- the fact of the matter is that the way I would plot this data if I were doing this study is I would plot the blood pressure and the several blood pressures at every monthly period or visit to show the variability and the tracking of that blood pressure. I don't know, for instance, whether the blood pressure was lower at ten months than at 12 months. You really have to check every individual in the blood pressure and to show the centiles that he's in, and whether the centile comes up. Only then can

you tell if you have a blood pressure effect of this drug which is consistent.

I said it before. I think we need some sort of indication of the standard deviation of the measurement and I don't see that.

CHAIRMAN BONE: Dr. Illingsworth?

DR. ILLINGSWORTH: I just echo the comments made concerning the proposed Phase IV trial, that I would also have reservations about a comparison with another drug, particularly if morbidity is going to be one of the endpoints. Because I don't think in two years in a patient without coronary artery disease, you'll get any difference in morbidity or mortality. I think although you could make a case for doing it with an active control, I think I would certainly endorse the need to do a placebo controlled trial and to see what happens long-term. That's the only way we'll find out what's the incidence of hypertension going up substantially in subsets of patients or provide this kind of a study.

CHAIRMAN BONE: Thank you, Dr. Illingsworth.

Dr. Colley?

DR. COLLEY: I would echo Dr. Marcus' comments as well in obtaining data with patients using

other substances that would increase blood pressure, capping, smoking, other risk factors like smoking that will increase the rate of hypertension that we don't have data on. Again, although the subset may be proportionately small that people who have significant increases in blood pressure, it's clearly a definite subset that does. This is a drug that's likely to be used in much larger population than simply the BMI greater than 27 as is indicated. For that reason, I think the need to be vigilant as to the adverse effects is especially important.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: I think one of the comments earlier I liked because it really is -- I think it was Bob who said it's a paradox that the people who this drug probably would be best for, the people have the least problems. The people with the most comorbidity perhaps, are the poorest risk for this drug.

One of the problems with the people who have very few problems and have obesity is -- and the reason we think that they have higher risks of hypertension and diabetes and dyslipidemia relates to resistance. This is the underlying factor, we believe, that contributes to all these other complications. I haven't heard anything yet about

insulin resistance, insulin action except for one study in some ob/ob mice which clearly don't relate to human problems. So, this is a unique animal model of obesity which probably doesn't relate to human disease at all, which is a disease of leptin deficiency.

So, my feeling is, number one, I was struck by that absence of information for me to assess people who were healthy and looking at long-term problems. With respect to people who do have problems currently, so far I haven't heard anything that diabetes has benefitted and I'm not sure that hypertension is benefitted. It seems to be equivocal about lipids, although I'm impressed that my gut feeling is that there may be some tendency in that direction. Those are just rambling comments.

The final point I'd like to make is if we're going to have a long-term trial, I do believe you need a control group.

CHAIRMAN BONE: What kind of control group?

DR. SHERWIN: I mean a control group with placebo.

CHAIRMAN BONE: Thank you.

DR. SPIGELMAN: Dr. Bone, if you do want, we do have some glucose insulin data that addresses

the issue. Obviously, we can't present everything within the time allotted.

CHAIRMAN BONE: Is this human data?

DR. SPIGELMAN: Yes, this is from the clinical trial in the study submitted in the NDA.

CHAIRMAN BONE: Okay, why don't you get that up very quickly while I'm making some additional comments --

DR. SPIGELMAN: Yes, okay.

CHAIRMAN BONE: -- and we can then respond to Dr. Sherwin's question or comment.

I have, I think, the same concern as everyone else about balancing risk and benefit here. Clearly, the drug does have a sufficient anorectic effect to result in a reduction in body weight. But I think we have uncertainties about the magnitude of the risk and the magnitude of the potential benefits. I think the model system that was presented on behalf of the sponsor took the most optimistic case on both sides.

It looks to me as though the magnitude of the risk, just based on the blood pressure measurements from the trials, is at least two to three millimeters of mercury and I don't think this has been systematically analyzed. But when one looks at the

largest trial and the longest term experience, it appears that for the doses likely to be used clinically, the magnitude of blood pressure increased maybe as much as twice as that used in the assumptions which would substantially increase their risk from hypertension.

One worrisome aspect of this is, it's extremely difficult in the clinic to make much out of a five millimeter increase in blood pressure measurement when we know you've got a ten millimeter or so variability on an individual measurement. This is the sort of thing that you can't detect easily in an individual patient unless the magnitude is really larger than that. At the same time, the evidence is that changes of this magnitude do influence risk over time.

The other question has to do with the assumed favorable effect on comorbidities. I think the problem here is that there was no sufficient attention to the effect on these comorbid conditions as defined endpoints in the clinical trials. That data were not collected in a prospective and rigorous way and that may be part of the explanation for the fact that there's some considerable variability and uncertainty about that. Because we'd like to think

that weight loss would consistently improve some of these things, although the data are not consistent.

The assumption that was made in the model that was presented was that the reduction in the total cholesterol would be about ten milligrams per deciliter. Whereas, in the studies, actually, that is a little higher than what I read from the sponsor's studies. Even small differences may be important here. All of the comments that were made earlier about the extrapolation limitations from intentional weight loss -- and I would also say that we might very well see a different kind of extrapolation from weight loss induced by altered dietary practices and increased exercise and weight loss that was as a result of an anorectic agent -- to me make the calculation that the benefits would more than offset the risk of the increased hypertension no more were certain than a calculation showing that this would be a wash, or conceivably even going the other direction. It would depend on an equally tenable set of assumptions to support either case. So, those are the areas I have of residual concern here.

Is the sponsor ready with their data on glucose and insulin?

DR. WEINSTEIN: Yes.

Dr. Steven Weinstein, Knoll Pharmaceutical.

Dr. Mendel already mentioned this morning that in diabetic patients on sibutramine who lose weight, their fasting plasma glucose decreases. This slide shows mean fasting insulin parameters in sibutramine treated patients who lose greater than or equal to five percent of their initial body weight. These are in patients who are not taking insulin. I need to remind you that there were no patients in the placebo group who lost this amount of weight. Fasting insulin in the sibutramine treated patients who lost this amount of body weight decreased from a baseline value of 21.5 milliunits per liter at baseline to 13.5 at week 12. This is a decrease of eight units.

The fasting glucose, the fasting insulin ratio which may be viewed as an index of insulin sensitivity -- and an increase in this ratio would indicate an increase in insulin sensitivity -- this parameter increased from baseline to week 12 by 5.2 units. In contrast, in the all placebo group, fasting insulin as well as this glucose insulin ratio showed only a modest increase. These data suggest an increase in insulin sensitivity.

Can I have the next and last slide,

please?

This slide shows mean glucose and insulin kinetic parameters during a test meal in subjects for this study. These are basically in the same subjects, sibutramine treated subjects not taking insulin who have lost this amount of weight. The insulin area under the curve was about 31,000 at baseline. This decreased to 24,000 at week 12. This is a change of about 7,000, a decrease of 7,000. The area under the curve for glucose remained about the same, actually with a modest decrease by week 12. The area under the curve for glucose divided by the area under the curve for insulin, which is, again, another measure of insulin sensitivity, actually increased from .18 to .23 at week 12, an increase of .05.

There were very modest changes in the all placebo group in this same time period so we believe that this does suggest an increase in insulin sensitivity in the sibutramine treated patients who lose weight.

DR. SHERWIN: Do you have data in non-diabetic individuals?

DR. WEINSTEIN: No.

CHAIRMAN BONE: I notice that you have groups of five and six --

DR. SHERWIN: Yes, we're dealing, obviously, with small numbers of patients in a selected population who had -- the weight loss itself presumably would have this kind of effect. You might have seen a greater effect, for example, if they hadn't been on the drug and lost that same amount of weight.

DR. WEINSTEIN: Right. I think the point is though, if the patients are not on the drug, they don't lose the weight. There were no patients in the study who lost that amount of body weight.

DR. SHERWIN: Well, I think that's fair.

DR. WEINSTEIN: And indeed, the effect of the drug on the comorbidities is due to weight loss, not due to the drug itself.

DR. SHERWIN: I think when you look at that data on balance, it's really up in the air at this point.

CHAIRMAN BONE: Did you look at insulin levels in the isocaloric patients in the other study, where you've maintained weight on drug?

DR. WEINSTEIN: No, not to my knowledge.

CHAIRMAN BONE: Okay, thank you.

Dr. Molitch?

DR. MOLITCH: Yes, can we go back to this

last set of data? Did you try to stratify the placebo patients for the same amount of weight loss as the diabetes patients to see if there was any particular beneficial effect of drug or detrimental effect of the drug for the same amount of weight loss?

DR. WEINSTEIN: I'm sorry. Can you repeat that again?

DR. MOLITCH: To stratify the placebo patients for the same amount of weight loss, so that you have equal weight loss for placebo versus drug.

DR. WEINSTEIN: In this study?

DR. MOLITCH: Yes, in these last two slides you just showed us.

DR. WEINSTEIN: Right. There were no placebo patients who lost that amount of body weight. Twenty percent of the patients on sibutramine lost five percent of body weight by week 12. There were no patients in the placebo group who --

DR. MOLITCH: But you only had six insulin treated patients here -- six diabetic patients.

DR. WEINSTEIN: That group was the number of patients treated on sibutramine who lost that amount of body weight, approximately 20 percent of the entire sibutramine treated group.

CHAIRMAN BONE: Did you match groups with

equivalent but lesser degrees of weight loss and do the same analysis?

DR. WEINSTEIN: We have not done that analysis.

CHAIRMAN BONE: All right.

Dr. Kreisberg and then Dr. Flack.

DR. KREISBERG: Well, I think if I'm hearing all of this right, what you've compared here in these slides is patients who lost weight with patients who did not lose weight. I don't think that gets to the question at all.

CHAIRMAN BONE: Dr. Flack?

DR. FLACK: On the ambulatory blood pressure side -- I'd like to shift gears a little bit -- I would like to re-echo the comment that was made earlier today about looking at blood pressures during exercise. Because if you think about it, these are patients who were talking about losing weight and they'll probably be enrolled in comprehensive programs, or at least they should be. Exercise will be a valid part of that. Many of them -- more than a handful may elect to even go do resistance training, or may not be cautioned not to do it at the health clubs and stuff. So, I would certainly want to echo that.

Dr. Kreisberg made a comment earlier and he started me to thinking. In the higher risk patients, particularly higher risk people with multiple risk factors for ischemia, it might be worthwhile in some of the future studies that are done to look at ambulatory ischemia along with ambulatory blood pressure because actually, there are monitors now that do both of those simultaneously. One of the major concerns about some of these patients with multiple risk factors, or even people with coronary disease, is that the blood pressure burden and the sympathetic nervous system activity may increase the risk of ischemia. You're probably not going to study enough people to actually count events.

So, ambulatory ischemia, along with the ambulatory pressure where you can actually even relate the ischemia occurrence to the change in pressure, whether it's followed or not, I think would be a consideration in the design of future studies.

CHAIRMAN BONE: Other members of the Committee?

Dr. Zawadzki?

DR. ZAWADZKI: I would just like a point of clarification. The guidelines that we have, granted, were written after submission of this IND,

but there are two points raised here that I would just like to clarify to what extent we have the data.

One point is the demonstration that the weight loss is actually fat loss in humans. Number two, that we have data going beyond 12 months.

CHAIRMAN BONE: I think the sponsor did one study with dual energy x-ray absorptiometry, is that correct? And also, had a number of studies in which circumference or girth was measured.

DR. SPIGELMAN: That's correct. I think the waist/hip ratio data was presented. There is a DEXA study that is in the briefing packet that also showed reduction in fat. Again, we can show that data if you would like. I believe it is in the briefing document. Therefore, the weight does come off from the appropriate areas.

CHAIRMAN BONE: Actually, I think you showed a reduction in mean body mass but it was not as great as the reduction in fat mass, isn't that correct?

DR. SPIGELMAN: Yes, I --

CHAIRMAN BONE: Okay.

DR. SPIGELMAN: No. No, I'm sorry.

DR. SEATON: One specific measurement in one group showed that in the gynoid region, there was

a slight reduction in lean body mass. Overall, there's really no reduction in lean body mass.

CHAIRMAN BONE: Thank you.

Dr. Zawadzki, you had another part to your question. What was that?

DR. ZAWADZKI: The other point was extension of the data beyond 12 months.

CHAIRMAN BONE: Is there just the one 852 extension that goes longer?

DR. SPIGELMAN: That's right. And that 852 extension -- we have not discussed in detail. I think there were some misassumptions though that were made in the earlier discussions about that, however.

Specifically, that the doses that were used in 30 percent of those patients was 30 milligrams. Over 100 patients were at 25 milligrams and that really has an impact on the interpretation of the vital signs of those patients. I'm not sure that was clear from some of the discussion earlier.

CHAIRMAN BONE: Yes, I actually was looking at it by dose in the table that was provided.

DR. SPIGELMAN: And also, there were breaks in therapy. Practically all patients stopped because of just the design of the trial. Those were pure safety trials. Or that was purely a safety

trial. This is not continuous data in terms of even beginning to try to interpret what was one of seven centers.

CHAIRMAN BONE: All right, thank you.

Dr. Kreisberg?

DR. KREISBERG: I wonder if somebody could clarify for me whether the Committee is asked to consider this drug for more than 12 months' therapy, or are we only considering it for 12 months' therapy?

CHAIRMAN BONE: Dr. Troendle, would you care to comment on the question of the duration of exposure?

DR. TROENDLE: Well, we would like to have longer studies but we don't have them to deal with. We'd like you to tell us what you think would be suitable.

CHAIRMAN BONE: I guess Dr. Kreisberg's question had to do with the proposed length of duration of use. As it stands, would it be indefinite?

DR. TROENDLE: No, I don't think so.

DR. SPIGELMAN: Our studies clearly have only been done out to 12 months in a randomized manner, and that's the data that we have at this point.

CHAIRMAN BONE: What claim do you plan to ask for?

DR. TROENDLE: And there's only one study that went to 12 months.

DR. SPIGELMAN: Two, the SB 1049 and the 1047.

CHAIRMAN BONE: The question I have is, are you pursuing a claim for a year's treatment or for indefinite long-term treatment?

DR. SPIGELMAN: Again, similar to -- we believe that the data that was there on the drug dexfenfluramine, there was one study only for one year. The data obviously can only speak to one year as far as in labeling where there has been shown efficacy. That would clearly have to be reflected in the labeling, in my opinion.

CHAIRMAN BONE: Obviously, there's no practical control over the duration of treatment beyond the advice that's given in the labeling. A physician is free to prescribe for any term.

DR. MARCUS: Mr. Chairman, I'd like to move that we go on to voting. I don't want you to lose your quorum.

CHAIRMAN BONE: Yes, thank you.

I think we're ready, unless there are

further comments or observations from the Committee members, to go through the questions. I certainly appreciate Dr. Marcus' concern.

We'll just go around the table in different directions and I'll vote last, I guess, each time. Perhaps we'll start with Dr. Zawadzki on -- excuse me, Dr. Zawadzki is a participant but not a voter today. So, we can start with Dr. Kreisberg. As I mentioned earlier, I'm going to ask the Committee members to vote yes or no based on the data in hand. Then to make additional comments briefly if they think it is necessary to do so.

DR. KREISBERG: Yes.

DR. CRITCHLOW: Yes, based on the responder analysis but not by the other criteria of greater than five percent difference between placebo and drug.

CHAIRMAN BONE: Yes, Dr. Critchlow.

This is Dr. Marcus.

DR. MARCUS: Yes.

DR. NEW: Yes.

CHAIRMAN BONE: That was Dr. New and then this is Dr. Illingsworth.

DR. ILLINGSWORTH: Yes.

CHAIRMAN BONE: Dr. Colley?

DR. COLLEY: Yes.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: Yes.

CHAIRMAN BONE: Dr. Molitch?

DR. MOLITCH: Yes.

CHAIRMAN BONE: The Chair votes yes.

The second question is, is the pressor effect of sibutramine clinically important?

Perhaps we'll start with Dr. Marcus for that.

DR. MARCUS: Well, I don't know the answer but I think I have to give it the benefit of the doubt and say yes.

CHAIRMAN BONE: Dr. New?

DR. NEW: I can not answer because I don't think I have sufficient data.

CHAIRMAN BONE: Dr. New abstains.

Dr. Illingsworth?

DR. ILLINGSWORTH: Potentially yes in a subset of patients.

CHAIRMAN BONE: Okay, that's a yes?

DR. ILLINGSWORTH: Yes.

CHAIRMAN BONE: Thank you.

Yes, go ahead Dr. Colley?

DR. COLLEY: Yes.

DR. SHERWIN: Potentially yes in a subset of patients. Therefore, yes.

CHAIRMAN BONE: Okay.

Dr. Molitch?

DR. MOLITCH: Yes.

CHAIRMAN BONE: Chair says yes based on the data at hand, just as we were talking about.

The third question is --

DR. CRITCHLOW: I vote yes.

CHAIRMAN BONE: Oh, excuse me, Dr. Kreisberg. I am very sorry.

DR. KREISBERG: That's okay. It doesn't make any difference what I vote, actually. But it's yes.

CHAIRMAN BONE: Dr. Critchlow, I'm sorry. I confused myself with my innovative order of voting. It just goes to show you.

Okay, I'm sorry. So, that's a unanimous yes except for one abstention.

The third question is do the benefits of sibutramine outweigh the risks? We'll start with Dr. Molitch answering this question.

DR. MOLITCH: I would have to say yes, barely.

CHAIRMAN BONE: Okay.

Dr. Sherwin?

DR. SHERWIN: Yes and no, because -- it has on the patients. I would say no. I don't have the data -- can I just comment because I'm not happy about saying that.

My gut feeling is that we've not been dealt a full card and that's making it very hard. You would like, if nothing else, better data on the ambulatory blood pressure. If I hadn't seen that ambulatory blood pressure readings, I might have weighed the other way. Because I think we could screen out more effectively, the individuals who might have a subtle change and I'm not sure that's so significant.

CHAIRMAN BONE: But unfortunately, we have to speculate about that, I think. It's a question of what we have.

Yes, Colleen?

DR. COLLEY: I'd say no based on the data that we have currently.

CHAIRMAN BONE: Dr. Illingsworth?

DR. ILLINGSWORTH: I'd say yes, given to appropriate patients with comorbid conditions. In other words, the patients need to be accepted appropriately.

CHAIRMAN BONE: Do you have a basis for that selection at this point?

DR. ILLINGSWORTH: I would say the criteria that we have discussed originally, a BMI of 27 with diabetes or hyperlipidemia who are at risk --

CHAIRMAN BONE: Okay, but -- okay.

I guess we have a question here because that's not the indication that's being sought.

DR. ILLINGSWORTH: Correct.

I still would favor yes.

CHAIRMAN BONE: Okay.

Dr. New?

DR. NEW: Yes, barely.

CHAIRMAN BONE: Dr. Marcus?

DR. MARCUS: Barely yes.

CHAIRMAN BONE: Dr. Critchlow?

DR. CRITCHLOW: I'm going to have to be conservative and say no based on the pressor effect, the inconsistency in findings with respect to lipid reduction and weight loss, and the modest weight loss.

CHAIRMAN BONE: Dr. Kreisberg?

DR. KREISBERG: Dr. Bone, I would like to tell you that I have never enjoyed these questions and I still don't enjoy these questions.

CHAIRMAN BONE: I don't either.

DR. KREISBERG: I don't think they're right. I don't think these questions are framed properly. We're always stuck at this meeting with these types of issues about yes and no for the same question. I think we need to work better on the questions.

I'll have to vote no.

CHAIRMAN BONE: Have to vote no.

I take your point. The questions are -- we're sort of to advise the Agency and these are the questions that the Agency has asked us. Perhaps we could have some further discussion with the Agency about the questions perhaps in the future.

On question number three, based on the available data, I would have to say no.

The fourth question is if sibutramine were to be approved for marketing -- now, this supposes at some point that the drug were approved.

I'm going to add one comment since other people made comments to my vote on number three. I would say that more information directly on the subject of comorbidities would be extremely helpful and might result in a different answer if the data were available.

Number four -- if sibutramine were to be

approved for marketing, should there be a Phase IV study? And the implicit question is then, very briefly, what would be your major comments on the character of that study?

Perhaps we'll start with Dr. New.

DR. NEW: I think there should be a Phase IV study and I would like more precise data on the variability of blood pressure, the comorbidities, and some idea of compliance.

CHAIRMAN BONE: One of the design issues that came up earlier had to do with whether this could be an open label study comparing with dexfenfluramine. There's been some discussion of different perspectives on that. Would you favor, oppose, or have no opinion on that particular question?

DR. NEW: I don't think a comparison is necessary. I think it should stand on its own.

CHAIRMAN BONE: Thank you.

Dr. Marcus?

DR. MARCUS: I agree that the appropriate comparitor arm would be a true placebo arm. If the company wanted to go to the expense and have all three arms, that would certainly be acceptable to me. But I think the major comparison needs to be the placebo.

In addition to the things that Dr. New

asked for, I just reiterate a rigorous attempt to evaluate blood pressure.

CHAIRMAN BONE: Dr. Critchlow?

DR. REEDY: That's a yes?

CHAIRMAN BONE: That's a yes.

DR. MARCUS: Oh, yes.

CHAIRMAN BONE: Yes, with editorial comments.

Yes, Dr. Critchlow?

DR. CRITCHLOW: Yes, definitely. I just wanted to reiterate previous comments on increasing the ethnic diversity in the group, making some attempt to increase the people who stay on the drug for whatever period of time because it's very difficult to evaluate these data, or the validity of these data, given the approximate 50 percent completion rate.

The other concern is -- and I don't know if this is even possible -- given that probably at least half, if not more, of the patients taking the drug will be ones for whom are not according to the label. I don't know if it's possible to get safety data, for example, in young women who are not necessarily obese but on contraceptives, but there's certainly a large population of people who will be on it for whom we will have no other way to get data.

CHAIRMAN BONE: Thank you.

Dr. Kreisberg?

DR. KREISBERG: Well, I've previously spoken to this point and yes, I think a Phase IV study should be done. I think it should be a placebo control study. I would certainly accept Dr. Marcus' suggestion that the company could add another arm if they wanted to compare it to dexfenfluramine.

I'm a little bit concerned, based upon the issues that Dr. Flack discussed, as to whether or not the projections that the company has already made on the numbers of patients is likely to give important differences at two years, particularly if patients that are at high risk for events are going to be excluded because they are, in fact, risky patients. It would seem to me that their projections are wrong.

CHAIRMAN BONE: Let's see, Dr. Molitch?

DR. MOLITCH: Yes, I certainly agree with the Phase IV study or more than one Phase IV study that will get at some of these issues, especially the comorbidity issues. Because the drug, if it does get approved will, in fact, be used in patients who do have comorbidities. I think we need to find out that information sooner rather than later.

CHAIRMAN BONE: Let's see, Dr.

Illingsworth?

DR. ILLINGSWORTH: I would endorse a Phase IV study, ideally placebo controlled, so you can assess the efficacy, safety and comorbidity. I'd also suggest inclusion of patients with significant hypertriglyceridemia who have most to benefit from treatment of dyslipidemia. Triglycerides are a risk factor in women and in diabetics particularly, quite strongly. The population who have been studied with dyslipidemia didn't have significantly high triglycerides. So, it's not surprising that the lipid changes are not very profound because a weight loss doesn't really dramatically change LDL cholesterol.

CHAIRMAN BONE: Thank you.

Dr. Colley?

DR. COLLEY: Yes, and I would agree with the comments made previously that it should be placebo controlled whether or not it has dexfenfluramine as a comparison as well. And that it include the groups that have a higher rate of hypertension in Native Americans, Blacks, Hispanics, as well as older patients.

CHAIRMAN BONE: I think the need for Phase IV studies is manifest. It may well be, as Dr. Molitch has suggested, that the large simple trial may

not be the answer to all of the outstanding questions, some of which are vague by the fact that they weren't addressed in the trials done to date, specifically comorbidities. I think some of the issues that my colleagues have suggested must be addressed in placebo control trials -- could be addressed in placebo controlled trials that were more narrowly focused and smaller in size. That would not necessarily require the scope of study that was initially suggested by the sponsor in their positive control trial.

So, there might be more than one way of getting at these issues. It might be that the large simple trial, accompanied by a program of more limited and focused studies, could be satisfactory.

Just a moment, please?

Oh, Dr. Sherwin. I'm very sorry.

DR. SHERWIN: No, that's all right.

CHAIRMAN BONE: I'm very sorry. I've very sorry, Dr. Sherwin. When I try to vary the sequence, occasionally, as everyone has noted, I get out of order. I apologize.

DR. TROENDLE: I would like to ask for opinions from Dr. Flack and Dr. --

CHAIRMAN BONE: Can't hear you.

DR. TROENDLE: I'm sorry. I wanted to ask

for opinions from Dr. Zawadzki and Dr. Flack on this last question in particular, even though they're not voting members.

CHAIRMAN BONE: Certainly. Thank you very much. We'll do that.

Dr. Sherwin has voted.

DR. SHERWIN: Yes. We've heard enough comment.

CHAIRMAN BONE: Okay. Then Dr. Flack and then Dr. Zawadzki.

DR. FLACK: On the issue of the Phase IV study, yes. What should the control group be? I would number one, endorse that it be a placebo control. If the sponsor wants to spend the money to add an active control, that would be fine but at the very minimum, a two arm study. One of them needs to placebo versus sibutramine.

Again, I'd just like to reiterate that there should be sampling procedures in place, or recruiting procedures up from, to ensure adequate subgroups of patients, non-White patients in the study. An additional thing I would do is encourage them to perhaps look at no higher than 15 milligrams a day, but that's up to them.

CHAIRMAN BONE: Thank you, Dr. Flack.

Comments from Dr. Zawadzki?

DR. ZAWADZKI: I agree that a Phase IV study may provide some very useful data, I think, particularly regarding some of the issues regarding hypertension induced by the medication. I think the comments that were previously made regarding careful measurements of blood pressure during clinical use are very important.

I also agree that unless the studies are very, very carefully designed, we may not find some of the real final endpoints that we would be looking for.

CHAIRMAN BONE: Thank you.

Any additional questions from the Agency for the Committee? No?

Thank you.

All right, well, to summarize, in its 64th meeting, the Endocrinologic and Metabolic Drugs Advisory Committee has reviewed the presentation for sibutramine for the long-term treatment of obesity. The four questions were answered by the Committee with all the comments and the Agency has previously noted on a number of occasions that the comments are often more important than the vote because of the nature of that process.

On the first question, the Committee voted

nine members voting yes, that the sibutramine met the criteria for effectiveness and none voting no.

On the second question, is the pressor effect of sibutramine clinically important?, eight members voted yes and one abstained. Several of the members voting yes commented that that was based on the available information but that the clinical significance wasn't fully explored.

On the third question which was, do the benefits of sibutramine outweigh the risks?, the Committee was closely divided. Four of the Committee members voted yes, that the benefits outweighed the risks. Five voted no, that the benefits did not outweigh the risks and there were a number of comments to the effect that uncertainty about estimates of both benefits and risks made this question particularly difficult.

The fourth question was, if sibutramine were to be approved for marketing, should there be a Phase IV study? All of the Committee members, nine, voted yes with a variety of comments concerning different aspects that they felt should be considered.

I want to thank the sponsor for an outstandingly clear and cogent presentation, and for the timeliness and cooperative way in which this was

handled. We really appreciate that very much.

I would like to thank the Agency for their presentations and close the meeting at this point.

(Whereupon, the meeting was concluded at 3:18 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING #64

Before: HENRY G. BONE III, MD

Date: SEPTEMBER 26, 1996

Place: BETHESDA, MARYLAND

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

Irene Gray
IRENE GRAY