patients complained or described lack of concentration, decreased alertness, and it was found in nine patients at the higher dose.

It was also, as you saw, described also in some of the placebo patients.

DR. CRITCHLOW: Nine out of how many?

DR. SANDAGE: Eighty patients I believe, let me see what the --

CHAIRMAN BONE: I think if you look at table -- in your combined data you had on Table 20 you actually had, I think, 13 subjects that were listed with that.

DR. SANDAGE: The one that I was looking at is page 32.

CHAIRMAN BONE: Yes.

DR. CRITCHLOW: Page 32?

DR. SANDAGE: Yes.

CHAIRMAN BONE: Right. That is at the higher dose, you are correct. So that 10.3 percent represents 9 subjects.

Is that right, in the table on page 32?

DR. SANDAGE: I think that is correct.

CHAIRMAN BONE: I see, thank you. Do you think the instruments that were just described or maybe Dr. Noble would answer this.

Did those instruments specifically address concentration and alertness?

DR. NOBLE: Yes, indeed. A lot of the questions, of course, on the checklist was, "Can you concentrate as well," but there were a lot of things where they had to recall things that we had told them, it was the whole gamut.

CHAIRMAN BONE: But that was of lower dose, then?

DR. NOBLE: That was 50 milligrams, twice a day.

CHAIRMAN BONE: Right. Thank you. Right. Where there further questions regarding the -- Dr. Campbell had a further comment.

DR. CAMPBELL: I would just address the issue that Lou Seiden mentioned about PET scanning and also functional disability using prolactin.

In fact, this has been done, it is widely published, but an acute response to fenfluamine is a reduction in prolactin and associated hormones, ACTH.

This is normal with a serotonergic drug you see it with others. Within 3 months, in fact, after 3 months it is normal.

This occurs within a few weeks afterward, so what we are seeing is an initial response and it

going back to normal, thereby showing that there is no functional disability by that measure.

CHAIRMAN BONE: With respect to that measurement.

DR. CAMPBELL: The other suggestion that Dr. Seiden mentioned was the use of PETs in terms of brain function, and it was Dr. Borhani who said actually saw this within your handout, and it wasn't specially said by Joe Contrera.

Can I have that slide? This shows some work that we did looking at functionality of the 5H2 receptors within the brain using PET scanning to see if we could measure whether there were any long-term changes, and this was before and after three months treatment.

This shows the kinetics of radioactivity in the frontal and cerebral regions after intravenous injection or high specific marker, 45HC receptors.

Here we see before and after treatment, and here we see the frontal cortex and the cerebellum, and it is quite simple that this is three months after -- three months treatment of the drug and then follow for one month afterwards, and you don't have to be a statistician to see that there is no change whatever in 5HT receptors by the PET scanning.

Although this isn't directly what Dr. Seiden is asking for, it does show integrity in the brain in terms of 5HT receptors.

CHAIRMAN BONE: Thank you. I have a question --

DR. CAMPBELL: Sorry. There was one further thing, that was about the calcium. Calcium mineralization. Can we address that as well?

CHAIRMAN BONE: Yes. That is fine.

DR. CAMPBELL: I would like to call upon the chief pathologist at Wyeth Ayerst who might comment.

DR. BOYSON: Yes. I basically would just like to present some information. I am Byron Boyson and I am director of pathology at Wyeth Ayerst.

The comment that I want to make is that basophilic bodies, or sometimes as they were called in this study, brain calcifications, are a common lesion in laboratory animals, particularly mice and rats, that aren't carcinogenic studies.

They tend to be amorphous bodies. They are extra cellular, and therefore I emphasize they are not associated with neurons. They are not within neurons.

They are not usually associated with any

kind of neuronal injury whatsoever, and they are not associated with any clinical signs that might expect one to believe there is neurotoxicity.

I point this out also because in our study we used the B6C3F1 mouse and there is quite a strain variation regarding the incidence of this lesion among laboratory animals.

For example, recently I talked to a colleague from the MTP, and in 51 studies that they have done with the B6 mouse they had control incidence levels that ranged from 2 to 86 percent.

The highest incident that we had in our studies was 75 percent, and therefore, I just think that we should keep aware that the data in our study might represent simple, biological variation and therefore be totally unrelated, or the incidents perhaps unrelated to the compound.

Earlier Dr. Contrera made reference to some other studies that he had looked at, didn't have that incidence and I simply would point out before I sit down that the CD1 mouse is a very frequently used mouse in North America for carcinogenic studies and the incidence of this lesion in those studies or in that strain, I should say, tends to be a lot lower.

CHAIRMAN BONE: Dr. Contrera.

DR. CONTRERA: May I respond?

CHAIRMAN BONE: Yes. I think the question, particularly, if you will, please, thank you very much, the particular question here, if you would address, is I think it was a controlled study.

DR. CONTRERA: Yes. I think there are several points that were made. First of all, it was a presumption that the amphetamine studies were CD1 studies is not true.

They were all B6C3 studies of the same strain that was used in the sponsor studies.

In terms of historical background, it is irrelevant. We were comparing it to concurrent controls and that is the only real control to compare it with, and second of all, if it is non-specific, in the mouse the point was that it was associated mainly with the thalamus, which was an area that is a focus of long term depletion in these animals.

So that those were the points that I was making, and secondly and thirdly the fact is that this is what really is needed, a more extensive histopathology of these blocks with a true pattern and distribution of these if we are going to pursue it in any way.

CHAIRMAN BONE: Thank you. Did you have

anything further, Dr. Contrera?

DR. CONTRERA: That's it.

CHAIRMAN BONE: One question that I think would be helpful to the committee and I am just asking a few questions here, kind of on behalf of the committee as a whole, is just to try to at least get a junction or a point of overlap between the perspective of the sponsor on the neuropathology and the perspective of some of the earlier speakers.

Dr. Molliver talked about the axonal changes and there was the point of view of the sponsor, if I understand it basically, is that some of these were simply related to the mechanism of action of the drug and were to be expected, in fact, would be almost intended or desirable, but Dr. Molliver made a point of the tangles that were part of the regenerative process where that seemed to be let's say a point of difference.

One aspect of that is these were seen when histological studies were done time point considerably delayed after the exposure and discontinuation with the drug.

I would like to specifically ask the sponsor, have they looked in the same kind of time frame, have they seen those same lesions or those

changes.

Lesion presumes something. Let's say, has the sponsor seen those regenerative tangles?

DR. MOORE: The anatomical structure that Dr. Molliver sees, we have not seen in our material, even with the high doses and with animals that are sacrificed at one week, 13 weeks, and 26 weeks after the administration -- the compounded doses of 2, 4, 8, and 16 milligrams per kilogram.

I think it has to do with the route of administration and so on. I don't in any way doubt Dr. Molliver's data, and I think it is simply a difference in different paradigms of doing the same kind of experiment.

CHAIRMAN BONE: I see. Thank you. That is at least helpful to know that we are looking at the same slides and looking for the same thing for that particular question. Okay.

I think there will undoubtedly be a number of additional questions from members of the committee which might be addressed either to the sponsor, the consultants or the agency, and I would invite the -- maybe we should just go around the table and ask people if they would like to raise those questions.

If not, or after those questions are

answered, we can proceed to some discussion and then maybe move forward. Yes, Dr. New.

DR. NEW: Can I get clarification of something? As I understood the position from Wyeth, said that the B6 strain can have up to 86 percent spontaneous calcification of basal ganglia, and were those the same mice that you used, Dr. Contrera?

DR. CONTRERA: Those are the same --

DR. NEW: The same strain?

DR. CONTRERA: B6 is the same strain that was used by the sponsor.

CHAIRMAN BONE: Those were the sponsor's studies that Dr. Contrera was discussing, not agency studies.

DR. CONTRERA: Yes. Sponsor studies.

DR. NEW: How can you do a controlled trial if there is random calcification from 2 to 86 percent?

DR. CONTRERA: Because the primary control is the concurrent controls. Historical controls drift, they vary lab to lab and they also vary in how the animals are treated.

The only controls that matter in studies when you really get down to it, is the concurrent controls.

CHAIRMAN BONE: So these were animals that received placebo or sham injections during the course of the study.

DR. CONTRERA: You have concurrent controls that were fed the same diet as the fenfluamine treated animals and run alongside, and so they have a lower incidence than the drug treated.

That is all we are saying. That is all that the data show.

CHAIRMAN BONE: Okay. Dr. Colley, did you have questions or comments at this point? Particularly questions? Okay. Dr. Borhani?

DR. COOPER: I think there is a point of clarification on the calcification?

CHAIRMAN BONE: Okay.

DR. BOYSON: One comment about the mineralization that I didn't make clear initially, and that is I said they were spontaneous lesions, and that they are.

They are also are most heavily concentrated in thalamus. Okay. Which is the area that we are most interested in.

Another thing to keep in mind is that the primary purpose of these studies was to determine carcinogenicity, and therefore, as Dr. Contrera

pointed out earlier, several routine sections, coronal sections, were taken from brain, but they were not done with the specificity that you may want to do to look at this lesion and this location.

If you think of the mouse brain perhaps being a centimeter and a half long, and a thalamus perhaps being 2 millimeters long, and someone taking cross sections of brain and not doing it with the kind of sophistication that we might do in another type of control, and experiments specifically addressing that purpose, it is easy to see how the incidence of this lesion can greatly vary from one group to another just based on the sectioning methods.

DR. CONTRERA: I think that I have to add that it is easy to see that you can entirely miss it.

The miracle was that they didn't, and it was only in the drug treated groups in both the rate and the mouse, and that was the only reason it got our attention.

CHAIRMAN BONE: Dr. Borhani has a question.

DR. BORHANI: Yes. It may not be answerable or you might think it is a silly question, but I have a question to you, your colleagues at FDA.

You said something about -- I can't even

remember, whatever, the company that made the previously approved drug and this has been in the market since 1973 or 1974 and if I heard you correctly you said that perhaps only during the last year the sale has been picked up and there was not really that much sale of it.

I can think of three reasons for that and I wonder if you think that any of these reasons are anywhere near the ballpark that we should consider.

Number one is that perhaps because this drug was put on the restrictive list and has to be signed off by the doctors who are tired of duplicate prescriptions and et cetera, and therefore they didn't pay attention or it was a lousy salesmanship on the part of the company that made it.

The drug reps were perhaps not allowed in the doctor's office and they didn't bother or they had a better drug to sell so they didn't want to waste their time, and thirdly, most importantly is perhaps people took it and they got all kind of subtle side effects and they didn't like it, and the company decided the drug is not going to sell, because this is an important -- it might be silly, but is there any guess you can make on this?

DR. LUTWAK: Well, the company that made

it, and distributed it, is the same company that makes dexfenfluamine, and since they are here, perhaps they have the answer.

MR. DEITCHER: Can I answer that? I am Mark Deitcher, I am the medical director at Wyeth Ayerst. Wyeth Ayerst became the successor to market the product.

It was marketed by A.H. Robbins. Dr. Borhani, you are very astute. Number one, one of the major reasons why the product was not popular in the United States was in fact because it was scheduled on the restricted list.

Number two, I won't get into discussions about whether it was promoted well or not by the sales force, but when you have a product that is on a restricted list, generally it is not heavily promoted.

What you see is the effect of the results of a study that was done by Dr. Michael Weintraub at University of Rochester in about 1990, 1991.

It was before he came here to FDA, which received a very, very large amount of press, women's magazines and so on, because of that women went to their physicians with the article and asked whether or not this was a drug that could be used.

That was a good impetus for physicians to

start prescribing the drug.

That paper that he published, as well as the information on that has now become kind of legend in literature and in the press and that is one of the major reasons why we have seen this increase in prescribing.

CHAIRMAN BONE: Thank you. Okay.

DR. TROENDLE: I don't think we should think of this just as related to fenfluamine.

All weight control drugs were not used very much.

It was not popular to prescribe drugs for obesity.

CHAIRMAN BONE: Potentially for much the same reason.

DR. TROENDLE: Yes.

CHAIRMAN BONE: Thank you. Dr. Sherwin.

DR. SHERWIN: I just want to make one -- get one point clear.

You mentioned that there was some neuropsych testing done in some of these trials?

CHAIRMAN BONE: Just the one, I think.

DR. SHERWIN: Was it just Dr. Noble's small study?

DR. BOYSON: Just Dr. Noble's study.

CHAIRMAN BONE: So not in the pivotal study and not in a study that was submitted to the NDA, if I understand correctly.

DR. SHERWIN: That is what I needed to know. Thank you.

CHAIRMAN BONE: Dr. Colley, did you have questions at this point?

DR. COLLEY: No.

CHAIRMAN BONE: Excuse me, Dr. Critchlow. I am sorry.

DR. CRITCHLOW: I am not finding it here, but I am sure it is here, is what, given the high dropout rate in the control studies, and given the fact also that this dropout rate, even in the face of some loss in weight, what are the reasons for this high drop out in these studies?

DR. SANDAGE: In the one slide I presented in the control trials we looked at the drop out rate across all.

For the dexfenfluamine, for example, it is 6.9 percent adverse events versus 5.2 percent.

Ineffective medication was 5 versus 9, intercurrent event was 6.6 versus 6.2, loss to follow-up, 8-1/2 percent in both groups, non-compliance was 2-1/2 percent in the dexfenfluamine group and almost

4 percent in the placebo group, and the patient request was 1-1/2 percent for the dexfenfluamine group and 2-1/2 percent for placebo.

DR. CRITCHLOW: So do you think in actual practice what would the compliance issues be in your mind or what would be significant compliance issues?

DR. SANDAGE: In the FM trials, which is our best, it is the open-label, long term, in clinical practice.

We have got about 60 percent, 60 to 70 percent completers at the end of that study, and about 75 percent of those people, just like in the index trial, lost at least 5 percent of their body weight.

So they -- the patients that are going to respond, continue to take the drug and it is an expectation phenomena.

They get response and they stay on it, and those that don't drop out or drop out for other reasons.

CHAIRMAN BONE: Dr. Kreisberg.

DR. KREISBERG: I would like a brief answer to this. There is this trial that Dr. Noble described, and he said there was no clinical difference.

I wonder if the data was subjected to

statistical analysis or whether we were just getting his impression. That can be yes or no or something like that.

DR. NOBLE: It is my clinical impression because I talk to every single patient.

DR. KREISBERG: Right, that doesn't count, though.

DR. NOBLE: I think the data has been analyzed very, very recently, and I trust will be submitted.

DR. KREISBERG: So we really don't know if there is a difference between the treatment group and the placebo group.

DR. NOBLE: I wouldn't have known.

DR. KREISBERG: No, you wouldn't have. I am sorry.

DR. NOBLE: When you examine the patients I think you can tell.

DR. KREISBERG: I examine patients every day too, doctor.

DR. NOBLE: Not with psychiatric tests.

CHAIRMAN BONE: Thank you very much. We are moving along here. I think we have three or four issues that obviously the committees is going to have to discuss to try to get to closure before we answer

the questions, and one where it strikes me there is still a gap, and I am going to ask, in the most concise possible way, and I really wanted to ask people to focus on this in a very, very narrow way and not editorialize at all.

Can we try to clarify the points of agreement and difference in perspective with respect to neurotoxicology.

I am talking about the brain histology issue. I am going to ask the sponsor to just comment briefly on this, extremely briefly and ask then our consultants to comment with at least equal brevity, this is probably not going to be settled by these comments, it is only going to be a question of making it very clear to the committee what the differences in agreements are.

DR. MOORE: Let me respond by taking on the points that Dr. Contrera made at the end. He first said that the ancillary measures of neurotoxicity that is gliosis and silver staining are not sufficiently sensitive to show changes in seroton and neurons.

I submit that this is incorrect. That these have been shown to be positive with the other neurotoxins that Dr. Molliver has talked about,

chlorine amphetamine and MDMA, both of those things are positive, so clearly it is possible to do this, dexfenfluamine does not do so.

He spoke about the retrograde transport study being equivocal. There is a retrograde transport study that is a part of the NDA that was done by Dr. Collia, it is in no way equivocal.

There is no difference at any dose between the animals treated with dexfenfluamine and the controls.

He also raised the issue of whether there was meaningfulness in the long term mouse study with perhaps the animals didn't get the drug or whatever, or they didn't have good blood levels, but I remind you that the brain levels at the end of the study were 51 micromolar, that is not a brain level that can be obtained by simply giving the animal a dose on the last day, it is a brain level that means the animal was getting it for some time, and I think we have to presume it was getting it the whole time, and that the brain levels were very high and sufficiently high to reduce serotonin if that was going to happen.

I think that really deals with most of the issues.

CHAIRMAN BONE: Thank you. Any further

comment from Dr. Molliver or Seiden with -- and I thank the sponsor for the commendable conciseness.

PROFESSOR SEIDEN: I would like to reiterate that we, in animal studies, we get long lasting changes in the update cites and in the labels that are hard to explain on the basis of pharmacodynamics and there are the morphological changes and I don't know how these can be explained except by assuming that some type of toxic response takes place, and after all, with a relatively low dose in the monkeys that I presented, and it was done orally, the monkeys were still depleted 14 months after the drug was discontinued. That is astounding.

CHAIRMAN BONE: Thank you. Anything to add, Dr. Molliver, please?

DR. MOLLIVER: I would like to address briefly one or two of those points. The sensitivity with which people obtain tissue, fix it, and process it varies enormously from laboratory to laboratory.

My laboratory prides itself on having one of the highest levels of sensitivity in the world for presuming a set of chemical markers, and we often have people coming to us with material, saying, "We can't see it," and we process, reprocess the material for them or refix the tissue and it can be seen. Negative

findings of that sort are not meaningful.

It is a matter of applying a maximum sensitivity in state of the art changes. Several other points need to be addressed.

Glial reactions do respond primarily to loss of cell bodies and they are very sluggish or minimal with response to the loss of these extremely minute, fine, unmyelinated axons so it is very, very subtle and very easy to miss glial responses.

The other issue, I think the most important issue that comes us has to do with the retrograde transport.

I've puzzled how logical people looking at the same material might get different results, and I think it is clear how that can happen.

The axons, if this is a diagram of a cerebral cortex, the axons come into the cortex from the brain stem and branch out with their very fine branches within the cortex.

The toxicity of this drug is remarkable in its selectivity for axon terminals. The minute parts of the axon at the very end of the terminal.

Those are the things that are killed off. When a dye is injected or labeled into the cerebral cortex and then one looks for transport back to the

cell body the stumps of those axons are still there, the damaged stumps, with the terminals cut off are present and open and in fact, it has been shown in other studies to have an enhanced ability to take up these dyes and transport them back to the cells so that I think that can explain why some people might not have seen a loss of transport one needs to use an extremely small microinjection that is carefully analyzed and documented that it doesn't spread more than 25 or 30 microns from the injection site down into the stumps.

If, as the sponsor claims, they are going to do further studies on that, we are not particularly interested ourselves in doing that but I would say that it should be specified that the size of the injections be made as small as possible and have those subject to serial section analysis to demonstrate that the injection did not spread to the stumps of those axons which are sitting there waiting to take up the dye.

For my comment further on the prolactin tests, it is -- no?

CHAIRMAN BONE: I think we are all endocrinologists and I don't know that we need to go into that much further.

DR. MOLLIVER: There is a point about that, though, and that is that the prolactin release is mediated by serotonin terminals in the arturite nuclei, and those are the terminals that are resistant to these drugs.

So it would not be expected that that would be affected by the toxicity.

CHAIRMAN BONE: I see what you mean. Thank you. Dr. Contrera, there was a specific comment about your comment about the equivocation about this study, and if you could just address that specifically.

DR. CONTRERA: I think I still stand behind the fact that there is controversy in literature about the sensitivity of the glial GFAP method for serontonergic neurotoxins.

It doesn't say that there aren't papers in which that has been identified, serontonergic neurotoxins.

MDMA in particular, that was just used as an example. You get a glial reaction, but there is also evidence that MDMA also depletes dopamine, and dopamine neurotoxin too and dopaminergic neurotoxins are highly detected by glial GFAP.

So with that there is a confounding effect

in that case. We can argue it back and forth about those things.

In terms of the equivocal nature of the retrograde study, they are difficult studies, as Dr. Molliver said, and they warrant validation and repeat because of all of the technical problems involved in it and I am certain, and the firm is repeating it.

It was so conclusive that they were repeating the study, but the fact remains that that is a good thing to do, and in terms of the 50 micromolar concentration in the mouse.

It sounds like a lot but the fact remains it is only 10 times the human brian concentration. The mouse is well known to have AD50.

It is higher than the rat so that it is less responsive to begin with so I mean, my comments there were that I didn't say that depletion could not have occurred, depletion could have occurred in high dose and followed by recovery or depletion never occurred. I said that in my talk.

I acknowledged those two. But neither case, if depletion did not occur then we still have got the calcification to deal with, and in fact, I think it then becomes even more significant, you don't need depletion to get other sequel.

CHAIRMAN BONE: Thank you very much. Now I am sure that there are questions. It seems to me that the main question that would come back to the sponsor at this point in response, and this would be the final unless someone else on the committee has a question, had to do with the precision of the injection in the area.

Were those questions addressed in your study? The question of whether the stumps were doing the uptake instead of the terminals.

DR. MOORE: Yes. I would certainly debate with Dr. Molliver on that. You can get axonal uptake. The stumps, by the way, seal themselves off.

That is irrelevant. You can get axonal uptake but it is very small in comparison to terminal uptake and what you see is almost surely terminal uptake and little tiny injections would not get you anywhere, and I must say I am offended.

My histochemistry is just as good as Dr. Molliver's.

CHAIRMAN BONE: I am sure we are all very good histochemists. Thank you. I think, unless there are other questions to be asked by the committee -- Dr. New?

DR. NEW: Is there any reason to discuss

what will happen tomorrow in view of the presentation that we had?

CHAIRMAN BONE: Dr. New is referring to this issue about scheduling tomorrow. I think we should focus ourselves on the NDA and not concern ourselves with that today.

DR. BORHANI: I agree, because these are to me two separate issues.

CHAIRMAN BONE: Fair enough. Let's then -- I think we have now a little time of discussion amongst the committee or points that people would want to raise for consideration by the other committee members and perhaps Dr. New would be willing to start.

DR. NEW: I am very acutely aware of the risk of obesity --

CHAIRMAN BONE: Dr. New, could you pull the microphone a little closer, please.

DR. NEW: Oh, I am sorry. I said I am very aware of the risk of obesity and how intractable it is once it begins in childhood, so that I see it as a very high risk disorder, and I don't know of any way to treat it unless the pharmacology of these drugs really is effective, and it is a very discouraging disease to treat, almost as discouraging as anorexia nervosa, but I have still some very unclear ideas,

maybe it is prohibitive to say this, but I don't understand why we are discussing disregulation or deregulation of another compound which has not, as far as I can tell, been tested in the same way that this one has been tested to date.

So I won't raise that, but, anyway --

CHAIRMAN BONE: We didn't hear that.

DR. NEW: Anyway, I am saying that the risk of the disease is very high and I am trying to weigh the risk of the medication against that risk of the disease and I still haven't come to terms with that.

CHAIRMAN BONE: Are there comments? Dr. Critchlow.

DR. NEW: I am very concerned about the lack of cognition and behavior studies in view of the preclinical neurotoxicity.

CHAIRMAN BONE: Dr. Kreisberg.

DR. KREISBERG: Well, I would like to make sort of a similar comment. I am very sympathetic to the company and what they are trying to do.

I think it is important to find drugs to treat obesity and it is a signal, I think, for the pharmaceutical industry that this is an area that they should become involved in.

My guess is they are already, it is potentially a big growth area, but I am a little bit ambivalent about it as a result of the fact that the experts cannot agree and so how should I be expected to know about whether there is or is not significant neurotoxicity, and I think it makes it very difficult in the face of the small incremental change that one gets with this drugs versus the unknowns related to the potential neurological or neuropathological complications, very difficult for me to be able to vote positively for the drug.

CHAIRMAN BONE: Dr. Colley.

DR. COLLEY: I guess I would add to those concerns as well with the neuropsychological effects and so much being unknown.

We have had evidence presented that it is suggested that there may be problems but we don't know enough to determine that for certain.

There was an overhead that Dr. Lutwak had shown where world wide reports of neuropsychological effects in '93 were like five or six and then went to 20 in 1994, and I think just with the indefinite nature and lack of agreement among the sponsor and the experts, that is also an area where I am ambivalent.

CHAIRMAN BONE: Dr. Critchlow. Comments?

DR. CRITCHLOW: I basically have the same comments. I can see where there are a sufficiently large pool of people who would respond to the drug and who would benefit and on the basis of efficacy alone I can see a positive effect there.

On the other hand, not being an expert in the field, I too, am disturbed at the lack of concordance and continued debate in the significance of the neurologic findings and in the absence of knowing how to interpret that on my own I would still say that I have significant safety -- residual concerns about safety.

CHAIRMAN BONE: Dr. Borhani, did you have a further comment at this point?

DR. BORHANI: Well, yes. I am sorry that Bob is leaving, but if he can stay two more minutes he can hear me because I would like to have you hear me.

DR. KREISBERG: I will stay. It will cost you though.

DR. BORHANI: That's all right. The discussion on this neurological toxicity and neurotoxicity we heard today is very interesting and it is very informative, and for me it was very educational, but unfortunately for me, I feel that I am facing another deja vu state in my career that just

happened recently.

We are talking about the cutting edge of research, the way I understand it, of neurosciences and I just came across beaten up almost to death by another cutting edge of science research in arteriosclerosis using ultra sound and measuring the internal intermediate thickness of carotid artery and carotid artery disease.

So I am a wounded soldier in this field. I feel this is all fine and good for discussion and for pursuance of science and hopefully for the good of mankind, but I don't think that it doesn't have no place in our discussion and consideration in my opinion of this NDA because we are dealing with a very severe epidemic in this country, epidemic of obesity that is killing many, many thousands every year, and unfortunately, I don't know whose fault it is, but for lack of better suspect, I blame the pharmaceutical industries.

They have not come up with any drug that is absolutely 100 percent false proof, and obviously they have put their efforts in another area or other areas.

So I think that there are ways that we can hopefully, as a group of concerned citizens, I hope

that my colleagues in the community will consider that and FDA will consider seriously that we can find a nice, compromise that will save the people in this country and will also protect them against all of the problems that we envision in this kind of discussion that this new drug may have.

I see no reason why we can conditionally, unless Dr. Sobel tells me I am totally out of order we can recommend to Dr. Sobel and his colleagues that we can conditionally approve this NDA, commit the company that makes it to a nicely designed phase IV study, and giving the FDA the authority that investigations that will ensue they can withdraw approval if they can do it I think there is a precedent for all of this I just said.

I hope we can make a compromise and I hope that we can hopefully get a message that in this country we have to deal with the problem of obesity as an epidemic and try to see how we can help it.

There is no drug on the horizon and the one that we have that has been approved since '73, nobody has used it, and that is a different story and I don't want to get into that but that is my feeling at this time.

I am very disturbed to see that somehow we

are worried about some very, very, limited information and I respect both sides, and I know that they are experts in the world in this field, but that is the cutting edge of neuroscience and has nothing to do at this time to the important public health issue.

We can safeguard the safety of the public if that is the concern with methods we have at our disposal and I hope that we can do it.

That is my comment. Thank you.

CHAIRMAN BONE: Thank you. Dr. Sherwin, did you have comments to add?

DR. SHERWIN: Not many, really. This is a real close one and I recognize the problem of obesity and have not solved it myself.

I think that this drug has efficacy and I think that the company has provided evidence for that.

I think that the problem we face is just as we have discussed, the toxicities and the fact that we as a committee had not even had a chance to think about this issue before we got here because we had no information about the controversies that existed prior to that.

I know I would feel a lot more comfortable if there had been some limited neuropsych data, and my guess is that the company could provide that with a

focus study over a relatively short period of time.

I think it might be unfair to expect a very extensive, drawn out kind of study, but at the same time it would be nice to have a little bit more refined assessment by people who are really experts in this specific area, that would be my gut feeling.

CHAIRMAN BONE: All right. Well, it seems to me that we have --

DR. COOPER: Dr. Bone, I am sorry to interrupt, but I have been made aware that in fact there were two or three relatively small neuropsychiatric studies in controlled clinical trials done and submitted in the NDA and we can give you a very brief presentation of that if it is of relevance to the committee.

CHAIRMAN BONE: Well, it's late in the day.

DR. COOPER: That's right. Literally, a few words. Dr. Richard Gammans is our director of clinical research.

CHAIRMAN BONE: I think it is -- if he will be precise, I think it -- we did ask about this a little earlier but I don't think we want to --

DR. COOPER: I just wasn't aware of the data. I am sorry.

CHAIRMAN BONE: I understand. I don't think we want to deprive the committee of the information.

MR. GAMMANS: I apologize for not being able to reach you from up here, but in fact, there were four occasions where neuropsychological testing was conducted.

Two studies at MIT involving 15 placebo and 15 dexfenfluamine patients included the pons and the reaction time testing.

Those were statistically tested and not found to be significantly different. Those are included in the NDA and are published.

In addition to Dr. Noble's study we in fact, were able to test the data. We just simply were not able to get it to him since he was blinded.

He included the Stanford sleepiness scale, and the mini-mental status scale, and again, those were tested placebo versus dexfenfluamine and they were found not to be statistically, significantly different.

Finally, the Hamilton depression rating scale was included in two of the pivotal trials that were discussed today for the expressed purposes at the request of the agency, baseline assessments, week 12,

assessments and 4 weeks following treatment were included.

The baseline scores averaged four, the in point scores also averaged four and the post follow up scores averaged four.

There were no significant differences, and there were no changes on any significant neurocognitive item assessed including the core symptoms of depression, anxiety and suicidality.

CHAIRMAN BONE: Let me see if I understand, in summary then, in the pivotal studies that have been reviewed, the larger studies, you had the Hamilton depression score?

MR. GAMMANS: The 003 and 005, specifically.

CHAIRMAN BONE: And Dr. Noble's results, which were not submitted to the NDA, you have just described, and how many patients were involved in that?

MR. GAMMANS: Those I have data on 12 placebo and 18 dexfenfluamine.

CHAIRMAN BONE: And the other study was 15 in each group. Right?

MR. GAMMANS: Right, but the 003 and 005 studies, the total 30 milligram per day exposure

versus placebo exceeded 170 per treatment.

So that is the large and the longer of the data, three months of treatment and one month follow up.

CHAIRMAN BONE: The largest study looked only at the depression score, but did look at that.

MR. GAMMANS: Right.

CHAIRMAN BONE: It was in 170 subjects over three months.

MR. GAMMANS: One hundred and seventy in each treatment.

CHAIRMAN BONE: Correct. Exposed for three months.

MR. GAMMANS: For three months and one month following the three months.

CHAIRMAN BONE: Are those summarized in the briefing document?

MR. GAMMANS: I am not aware that they are. They are included in the study reports, but I don't know for sure that they are in this briefing document.

CHAIRMAN BONE: Okay. Thank you. Dr. Lutwak, were those reviewed?

DR. LUTWAK: No. They weren't.

CHAIRMAN BONE: Okay. Thank you.

DR. LUTWAK: You mentioned one other study with 15 subjects. How long was that one?

MR. GAMMANS: Three months.

CHAIRMAN BONE: All right.

DR. COOPER: I have got 5 weeks as the duration.

CHAIRMAN BONE: Okay. So it does sound as though there is a small amount of information on this point.

It seems to me that we are not simply at a crossroads, but at a confluence of several considerations, one is the enormous concern with the public health implications of obesity, which have been very well outlined by both the sponsor and the agency and the committee are all very sensitive to this, and each of us in our practices or in our academic disciplines have been concerned with this problem in a significant way. I am sure.

It seems to me that on the efficacy side we are reviewing studies which were completed prior to the formulation of the recent guidelines so naturally they are not perfect aligned with those guidelines as there would have had to have been prescience on the part of the sponsor in order to do that, but those guidelines suggested that the first criterion would be

a five percent difference in the average weight loss between the placebo group and the treatment group as the sort of, first line efficacy end point with the provision for prospectively planning to identify responders versus non-responders or looking at categorical analysis, and it turns out that, obviously this couldn't have been done prospectively in this case --

DR. COOPER: It was. The index was prospective.

CHAIRMAN BONE: I see. All right. Fair enough, and there was a significant difference in subjects.

There was about a 50 percent increase in patients reaching the 5 or 10 percent weight loss goal over the placebo group, about 50 versus 75 percent, if I recall.

So, in effect, it seems like the second line efficacy criteria have been addressed, and there certainly was a high degree of statistical significance even though the margin of difference was somewhat smaller on the mean.

The duration of study was a year's observation, and we did not have the opportunity to have the year follow up or year-on open label

treatment that was suggested in the guidelines, but again, these are the data we have to review.

It seems that with respect to the safety question there seem to be two concerns which have emerged.

One is the relatively rare but frequently fatal or usually fatal complication of pulmonary hypertension, which is more common in patients who have been taking this drug, and we have heard discussion about the comparative number of lives saved versus lives lost based on this.

Also, it seems that there is a major concern about neurotoxicity. We have been told that clinical concerns about neurotoxicity have not arisen from the spontaneous reporting information around the world, but we also saw that a dose only twice as high as the proposed dose there was significant increase in the risk of patients having trouble with concentration, primarily.

The numbers were not enormous, but then the studies were not enormous so that has to be taken into context.

The discussion on the histopathology here has been one that I am sure has been a little frustrating for members of the committee as well as

members of the sponsoring organizations and the consultants because it is clear that there still remain some controversies about this and we have had a spirited discussion of methodologies.

One of the important considerations, it seems to me here is the discussion of co-morbidities and the discussion of clinical effects on neurological and psychological function.

We have data presented in the briefing document by the sponsor indicating a favorable effect on co-morbidities, but if I understand correctly these are not data for which the FDA has received as part of the ND application and so they have not been reviewed yet.

DR. COOPER: All of that data was included in the NDA.

CHAIRMAN BONE: Is that correct?

DR. LUTWAK: Yes, but --

CHAIRMAN BONE: That is an important point.

DR. COOPER: Every piece of data shown was in the NDA.

DR. LUTWAK: Yes, but those were not statistically significant.

DR. COOPER: It was highly significant.

DR. LUTWAK: They were not statistically significant.

DR. COOPER: I beg to differ, sir.

CHAIRMAN BONE: Thank you. The committee members may wish to take a moment then to review the briefing document and have a look at that before we go on to answer the questions, and the functional consequences of a possible neurotoxicity as to say some alteration in brain function we have a limited amount of data that has just been described.

I think that naturally the committee members would like to see long term data and large numbers of patients because that would reflect the clinical circumstances that are likely to occur here, but the information that we have is what we have.

I think we are just going to take a moment here. The page number for the --

DR. COOPER: Forty-five.

CHAIRMAN BONE: Page 45. Maybe we could just take a moment while people review that.

DR. COOPER: Chairman Bone?

CHAIRMAN BONE: Yes.

DR. COOPER: Forty-five to 47.

CHAIRMAN BONE: Thank you.

DR. LUTWAK: I apologize. You have data

on a co-morbidity in one study of blood pressure.

You talked about effect on diabetes, but the diabetes data is published data, the data themselves have not been submitted to the NDA.

DR. COOPER: The published studies were submitted to the NDA.

DR. LUTWAK: Yes, the articles were, but the data was not, the articles were.

CHAIRMAN BONE: I see.

DR. LUTWAK: The articles were.

DR. COOPER: In two of the studies the primary data was submitted, the rest were published articles.

DR. LUTWAK: There were three studies submitted to the NDA. The index study and the 24 week studies. This study on diabetes was not.

CHAIRMAN BONE: It doesn't sound like we are going to get --

DR. COOPER: We submitted all 19 placebo controlled, double-blind trials to the NDA as well as about 22 other clinical pharmacology studies, studies in co-morbidities and I believe the record will show that all of those studies are, in fact, concluded in the NDA.

CHAIRMAN BONE: Do I understand correctly

that the hypertension data were from the pivotal study and the other data on co-morbidities were from some smaller, independent studies?

DR. COOPER: That is correct.

CHAIRMAN BONE: Thank you. So we do not have the co-morbidity data from the index study, for example, except for hypertension.

The diabetes data and lipid data are --

DR. COOPER: We did show one data set this morning of index patients who are hypocholesterolemic showing a significant change at 6 months and 12 months in total cholesterol levels, which was the only measurement given in that study.

CHAIRMAN BONE: Right. Thank you, and the index study was it the index study that included the depression scale or no?

Was that a different study?

DR. COOPER: That was the three month study.

CHAIRMAN BONE: That was the three months study only. So the long term study was you have some biochemical measurement and blood pressure.

Thank you. All right. What, then, I think, each member of the committee I think, will have to bear in mind is the relative weight to give to

these additional pieces of clinical information when trying to evaluate our concerns about efficacy and toxicity.

Certainly it may be productive to have further review at some time of some of these pieces of information, in a more formal way.

Is it agreeable to the committee now to go ahead and start answering the questions? Dr. New, did you have a --

DR. NEW: I just wanted to ask, what exactly are the options to the questions? Is it just yes or no?

CHAIRMAN BONE: Well, I think the tradition in this committee has been to give a yes or no answer and then a very brief comment can be appended for the record, if you like. Okay.

All right. I think we have all of those sort of summary points I made. Everybody is clear about now, at least, so we know what we have got as well as we are going to.

The first question for the committee is the efficacy question, and that is: Is the evidence of efficacy sufficient to warrant approval of dexfenfluamine for long term or indefinite use as proposed?

We have received comments or answers from two of the committee members who stayed until very recently and then left their notes, and we will read those after the rest of the committee has voted.

Dr. Critchlow.

DR. CRITCHLOW: On question one I think there is sufficient evidence of efficacy.

DR. SHERWIN: Yes.

CHAIRMAN BONE: Dr. New.

DR. NEW: Yes.

CHAIRMAN BONE: Dr. Colley.

DR. COLLEY: Yes.

CHAIRMAN BONE: Yes. The Chairman would say yes with some reservation as to the co-morbidity information being much less than we would like to see.

I see nodding that other members of the committee would agree with that point.

MS. REEDY: Dr. Illingworth responds yes provided the indications for use are sufficiently stringent, body mass index greater than 30, and I would favor a lower body mass index in the concurrent incidence of type II diabetes, hypertension, hypolipidemia and sleep apnea.

Dr. Kreisberg says no. I endorse the concept of incremental reductions in weight loss

produced by monotherapy with anti-obesity drugs or use of drugs in combination.

The incremental change produced by dexfenfluamine is small in light of uncertainly about neuropathological changes and the absence of clinical data regarding neuropsychiatric or personality changes. My answer is no.

CHAIRMAN BONE: I think obviously some of the comments made by the absent members would bear on questions 2 and 4 as much as they would on question 1.

The second question is: Is the evidence of safety sufficient to warrant approval for long term use as proposed? Dr. New, would you care to start.

DR. NEW: My answer is no and my reason for it is the absence or rather, not the absence because we have just heard some small report, but I am concerned about the paucity of data regarding psychiatric and cognition outcomes which I think may be in the offing but still need to be analyzed and reported and although we have heard that there is good study on hypertension.

I think that the co-morbidity studies for the other co-morbidities of obesity would benefit from a greater in depth study.

I also put down that I thought that the

efficacy was proven but that I would use it with caution with a BMI over 30, and I do not know if that is within my right, but I also thought there should be interyal visits at three months where there is a report and that the drug would be stopped if it is infective, of course, and that if the committee finally decided to approve this and with respect to the safety studies I also thought that there should be three month interval visits with reports.

CHAIRMAN BONE: Thank you. I think those comments would apply very well in question 4 about labeling of issues. That would be fine. Thank you.

Dr. Colley.

DR. COLLEY: My answer is no, and again, for the limitations on the data we have on the neuropsych toxic effects.

DR. BORHANI: My answer is yes because I am not convinced of the argument on the neuroscience debate.

CHAIRMAN BONE: Dr. Critchlow.

DR. CRITCHLOW: I would say no at least until the FDA has had a chance to review some of the neuropsychological data, which would be the closest in my mind to clinical significance of potential neurotoxicity.

CHAIRMAN BONE: Dr. Sherwin.

DR. SHERWIN: No. I am not convinced that there really are toxic effects, but I think there is enough of a question and I think the company could -- I am particularly concerned with the long term aspects of the question.

I don't believe we have proved safety long term. Short term, perhaps.

CHAIRMAN BONE: The Chairman would also answer in the negative. I think this is where I would balance the lack of favorable co-morbidity information on a large scale, long term kind of basis as being weighed against the concerns about toxicity, particularly I think there was -- it is too bad in a way that opportunities to collect more information of the kind that Dr. Sherwin has just mentioned weren't taken in the past.

These might be addressable issues, and again, from my standpoint would be balanced against the first question.

There were two additional comments I think.

MS. REEDY: Dr. Kreisberg, no. There is insufficient data to resolve the discrepancies concerning the sponsor's position and those of the

experts.

They are important differences that should be resolved before these are answered.

He would be willing to accept the idiosyncratic complication of PPH.

Dr. Illingworth responds yes at the proposed dose and with a two year study to look at phase IV trial to gather more data. I would vote the safety data is adequate.

DR. BORHANI: Mr. Chairman, can I ask you a procedural question. I don't like to be the minority. I can't speak for Roger. He is gone, but knowing him I have the feeling he might agree with me.

I have a feeling the reason there is that kind of dichotomy among the members of the committee is because that we are mixing up our concerns when they belong to the issue number three and four and my dear friends at the FDA, can I ask you again, Dr. Sobel, a question?

Is it appropriate for us to make a stringent recommendation for a well-designed phase IV study or recommendation that if some of the concerns are not answered by the sponsor FDA could indeed withdraw?

I realize our recommendation is not going

to tell FDA what to do, what not to do.

We are just advising but these two administrative and politically potential questions, can you answer?

DR. SOBEL: Yes. The idea of conditional approval. That isn't the word that we like to use since it doesn't have any real regulatory strength, but there are routes of expedited approval with such studies with provisions of retraction.

The issue here, though, may not fall within the realm of the so-called accelerated approval.

It is something we could consider, but my original reading is that this would not be the type of situation in which we would apply that,but certainly your question is a legitimate question given these ideas would we move to some sort of a situation where we would have an expedited approval with understanding that the approval could be readily withdrawn but, frankly I don't think that this situation would warrant that particular paragraph in our rules to be applied and I don't want to go into all of the shadings of that, but my reading would be that it would not apply here.

CHAIRMAN BONE: Dr. Sobel has in the past

come out about difficulties involved in enforcement of this kind of thing. Dr. New, please.

DR. NEW: I guess I need also some advice. If the phase IV study is very stringent with reporting and with discontinuation of the approval, if the reporting is unfavorable, then I don't know why we are voting on 2 as a yea or nay.

I mean, it is confusing to me, because you see, I am in favor of the phase IV trial, I am strongly in favor of it, but if my voting no on two means that I vitiate that opportunity then I am going to vote yes.

CHAIRMAN BONE: Well, I think --

DR. BORHANI: That is exactly the question because I have discussed this with some of my friends and that is exactly the sentiment I heard from them, that if they cannot have a phase IV to answer all of these important questions, they are going to vote yes.

CHAIRMAN BONE: I think at this point what we have to -- just a moment please. Go ahead Dr. Troendle.

DR. TROENDLE: I was just going to say that I think you have the option of saying that this study should be done prior to an approval or whatever you feel is appropriate.

CHAIRMAN BONE: That was certainly suggested earlier in Dr. Stadel's comments about whether that -- it is a question about whether such a study would, in effect be a phase II study required for approval or a phase IV study for follow up.

I think the question we are being asked is, is the safety information sufficient to warrant approval for long term use as proposed, and I think, then the, if I understand what the agency is asking us in the third question is the -- if you did approve the drug, if the drug were approved should such a phase IV study then be added on.

If the drug were not approved then presumably additional data would be required by the agency before approval.

The question III would only apply in the event of approval. It wouldn't mean that the study wouldn't be done. It would only mean it wouldn't be done after approval.

Is that a correct understanding of the agency's question to the committee?

DR. SOBEL: Yes, the agency questions that if we had voted yes to one and two then we would get your input as far as the phase IV study, but as it stands now, I think what Dr. Troendle was saying,

there is no reason why, in the process of gaining approval, that this so-called phase IV study be done now as a preapproval step.

Is that your --

DR. TROENDLE: Yes. I think this would be a way to get approval because it would show the people the actual benefits, perhaps.

DR. NEW: Henry, I think that the sadness of this would be because there are no, practically no other agents to deal with a chronic disease like this, that if it means that approval isn't given that phase IV would not be done because it wouldn't become a phase III, then you would never get the drug evaluated.

CHAIRMAN BONE: No. I don't think that is what Dr. Troendle and Dr. Sobel are saying.

DR. BORHANI: No? What did they say.

CHAIRMAN BONE: Let me see if I can just rephrase here. I think the question is the following: If the drug is not approved in the immediate future, than obviously additional studies would be required by the agency for approval.

If the drug is approved now then would additional studies be required after approval? Okay.

It is not saying -- I don't think the

agency is suggesting that this information would not be obtained. It is just a question of whether it would be obtained after approval if approval had been recommended or before approval if approval were not recommended.

Does that correctly state the case here?

DR. SOBEL: That is correct.

CHAIRMAN BONE: Thank you. Okay. Then I guess the next question to go on to then perhaps should be modified slightly, and that is to ask each of the committee members in the first place do you think a study of this kind should be done, irrespective of the phase in which it is done, and would you make some additional comments about important end points that might be looked at.

Perhaps you would like to address that, Dr. New.

DR. NEW: I would really like very much to endorse that the phase IV study be done and I am feeling sufficiently unsure about my no vote on 2 that I am prepared to change it to a yes, with the idea that safety has been evaluated and insofar as it has been evaluated it seems to be adequate, but I think the phase IV study must be done emphasizing particularly neuropsychiatric disorders, co-

morbidities, and very careful reporting at three monthly intervals.

CHAIRMAN BONE: All right. We will let you think another minute about whether you are actually changing your vote or just thinking about it.

Dr. Colley. The question now is the majority of the committee having voted in the negative on question 2 and in the positive on question 1, I think that we should put aside for the moment the question of what phase this study is done in and do you favor doing such a study.

Do you think this would be -- and what particular comments would you have to make about it?

DR. COLLEY: I would encourage such a study and in addition, the co-morbidities of glycemia, lipemia, blood pressure control and responders, also would want to look at the toxicities.

CHAIRMAN BONE: What do you mean by toxicity?

DR. COLLEY: Excuse me, to be a little more specific, neurotoxicity

CHAIRMAN BONE: Do you mean in subjects or in animals?

DR. COLLEY: In subjects.

CHAIRMAN BONE: In other words you would

want to do what kind of studies to evaluate neurotoxicity?

You are talking about psychological and functioning?

DR. COLLEY: Psychological, yes. Clinical.

CHAIRMAN BONE: Okay. Thank you. Dr. Borhani.

DR. BORHANI: I am sorry to prolong this, but this conversation reminds me of the zen and the art of motorcycle maintenance, and we are sitting on a whole other dilemma.

I hate to see that this phase IV type of study we are talking about, and I have a feeling there is unanimous agreement among the committee.

I hate to see that FDA people will end up not having it or this country will be deprived of the results of it.

In my experience and my reading of whatever I see, I am a very naive person but I can guarantee and bet on it right now that if we talk about approval of phase IV kind of study, that conducting the phase IV kind of study before approval given you will never see this kind of study done.

I hate to say that. I don't know this

company, but I know other companies, and I would like to emphasize that the industry and the government and the people owe it to the people of this country to do something to prevent this epidemic of obesity.

CHAIRMAN BONE: I am aware that the sponsor would like to make a comment, but we are in the middle of voting. I am sorry.

DR. BORHANI: I am sorry. The answer is yes.

CHAIRMAN BONE: Dr. Sherwin.

DR. SHERWIN: Obviously the committee is having difficulties today because we are torn, and clearly the sentiment of this committee is enthusiastic and supportive of efforts to deal with obesity.

I feel most comfortable with getting more data. I want to encourage the company to come back to us, and we would all be very disappointed if you didn't.

CHAIRMAN BONE: Dr. Critchlow.

DR. CRITCHLOW: I think I am becoming lost in terms of what --

CHAIRMAN BONE: I think we are talking about now, irrespective of the phase in which this kind of study is done, do you think it should be done?

Is it necessary, and what specific suggestions would you make?

DR. CRITCHLOW: I think a study should be done. I am not convinced that it is necessary in terms of approval.

I think I am relatively convinced by the epidemiology data that significant weight reduction will result in reduction in co-morbidities.

CHAIRMAN BONE: Do you think it is necessary for evaluation of safety of the drug?

DR. CRITCHLOW: Safety is another issue. I think I would be more inclined to say that some additional data on safety need to be made available.

The issue is, it is unclear to me how much additional data is perhaps out there that has not been adequately reviewed.

CHAIRMAN BONE: From the standpoint of the Chair, I think that clearly the sense of the committee has been some frustration in that the package, although many studies done for various reasons over the years have been included, is not quite as solid as we would have liked to have seen with respect to a number of these issues including co-morbidities, clinical neurological and psychological effects, closure on some of the pathology and toxicology issues

and so on.

So it seems to me that a very well designed additional clinical trial would go a long way toward resolving some of these questions.

Whether these can be completely resolved without really reaching closure on the neurotoxicology it is another question.

I think that is an area in which the agency and the company and probably independent consultants from various concerned fields would do well to try to come together on a way of resolving that issue.

We are disturbed by finding that doses which are not remarkably high, we saw this clear difference between treatment and placebo treated animals with respect to calcifications.

MS. REEDY: Dr. Kreisberg supports a phase IV study adequately designed. He likes longer than two years.

Dr. Illingworth responds: strongly endorse a well-controlled two year that compares dexfenfluamine and lifestyle modification versus lifestyle only, and the trial should include stringent follow up, assessment for morbidity and mortality, use any available means to assemble evidence for serotonin

depletion long term.

DR. BORHANI: So, Mr. Chairman --

CHAIRMAN BONE: Please.

DR. BORHANI: I have to ask a question.

CHAIRMAN BONE: What is it?

DR. BORHANI: The answer is unanimous, therefore.

CHAIRMAN BONE: No. I think what we said was that irrespective of the phase in which the study was done, a study along the lines described was regarded as very important by the committee.

I notice Dr. Bilstad has a comment or a question.

DR. BILSTAD: I just wanted to put into perspective the first two questions. There was some discussion after those questions that led me to believe that perhaps there was some misunderstanding of the intent of the agency in asking those questions.

Whenever a drug is presented to a committee those two questions are asked. It is an efficacy question and a safety question, and sometimes those questions are combined into one question.

For example: Is there sufficient evidence of safety and effectiveness to approve the drug?

Sometimes they are split up as they are

here. Sometimes a third question is added: Do you recommend that the drug be approved?

The intent here, dealing with efficacy first, the safety question becomes relative. There is no absolute safety.

It is always relative compared to the indication of the drug and how effective it really is.

The intent here is that it was sort of in the safety question that the benefit/risk part of it would be included.

If the committee voted in favor or no to a majority to either one of those, then we would view that as a vote not to approve the drug.

The question about the phase IV study, phase IV by definition is after the drug has been approved. So, if you vote not to approve the drug, then in one sense the phase IV question becomes moot.

I have some impression from some of the discussion, particularly from Dr. New, that she did not view question number 2 as necessarily being a vote against approval.

DR. NEW: I wasn't clear on that. If I could phrase what I want to have happen is I would like to approve the drug, but not approve it unless the phase IV study is absolutely agreed upon.

Approval should be contingent upon the phase IV study.

CHAIRMAN BONE: Dr. Bilstad any further comment?

DR. BILSTAD: I would just like to make one further comment on phase IV and commitments. Dr. Sobel had mentioned accelerated approval.

That is a formal process that is reserved for certain situations and probably doesn't apply here.

However, we certainly raise the issue of phase IV studies with companies and we can ask for a commitment from the company to do the phase IV.

DR. BORHANI: That is exactly the question I posed to Dr. Sobel. You just rephrased it and I appreciate that.

I think that is an important issue. If we can recommend to FDA that we would like you to consider what you just said. That makes me happy. That makes her happy.

CHAIRMAN BONE: Thank you. The final question will be having to do with the issues the committee recommends be addressed in labeling.

This will presuppose that the drug were approved, obviously the drug is not approved. This

will be issues for later on.

So irrespective if you are in favor of approval at this time or not, do you have specific comments about directions, prescribing directions, warnings, precautions, evidence, whatever.

Dr. New.

DR. NEW: Yes. I have two. It should be prohibited in pregnant women.

There should be something that says this drug should not be taken if you are already taking X, Y, Z, or other drugs that we saw might be in any way additive or conflicting.

There seemed to be some drug interactions, and perhaps the label should include information on the drug interactions.

CHAIRMAN BONE: What would you say about to the extent that drug interactions had not been investigated as well?

In other words, if there is an absence of information about certain classes of drugs, should that be included?

DR. NEW: I really don't know enough to answer you.

CHAIRMAN BONE: Okay. Thank you. Dr. Critchlow, do you have labeling comments?

DR. CRITCHLOW: I felt the contra-indications section should be expanded, and the other was again depending on how the data eventually looked, perhaps a slight expansion of the animal data.

There is one sentence in here on the relationship, again, potentially to the neurotoxicity, and again, in the warning section perhaps some type of alter to potential signs of neuropsychiatric issues as well.

CHAIRMAN BONE: Dr. Sherwin.

DR. SHERWIN: My only point is anoretic agents that shouldn't be combined, not to mix anoretic agents.

CHAIRMAN BONE: Dr. Borhani. Any additional comments?

DR. BORHANI: No, I suppose.

CHAIRMAN BONE: What were the comments of the other two members?

MS. REEDY: Dr. Kreisberg had none, and Dr. Illingworth's was: Do not use with one of the drugs in the same class, and mentioned the need for ongoing follow up and continued lifestyle changes in support of that, used as an adjunct to, not as a substitute for caloric restriction and exercise.

CHAIRMAN BONE: Dr. Bilstad.

DR. BILSTAD: I have just a little residual concern. I want to make sure that the agency understands what the committee is recommending.

In view of the comments that I made before, would it be worth while for the committee to consider the question: "Should the drug be approved on the basis of the information presented at this time?"

The reason I ask that is I am still struck with what appears to be different signals in the response to question number 2 and the response to question number 3.

What is your perception on that, Dr. Bone?

CHAIRMAN BONE: Certainly our principal function here is to act to advise the agency on questions which the agency would like advice about.

I think I put a preposition at the end of a sentence. I am sorry.

I think we have a problem in that some of the committee members were obviously not asked about this.

Perhaps a way of handling that would be to poll the remaining committee members but not regard this as a formal vote of the committee. Would that be acceptable to you?

DR. BILSTAD: On whether or not they recommend that the drug be approved on the basis of the information?

CHAIRMAN BONE: Right. It is, in effect, adding an additional question.

DR. BILSTAD: I would like to add the additional question: In evaluating the benefit risk, the benefits and the risks of this drug, would the committee recommend approval based on the data presented.

In other words, it is a benefit/risk assessment, based on the data presented does the committee recommend approval.

CHAIRMAN BONE: We have five members of the committee remaining. That is a point to consider. It doesn't constitute a quorum.

DR. BILSTAD: I understand that.

CHAIRMAN BONE: Thank you. Dr. New.

DR. NEW: I would evaluate the benefit/risk ration meriting approval.

DR. BORHANI: I agree with her.

CHAIRMAN BONE: Dr. Critchlow.

DR. CRITCHLOW: I think the agency should consider approval.

DR. SHERWIN: I don't have enough

information to fully evaluate that issue. I would have to say no, even though I suspect it would be yes in a few months.

CHAIRMAN BONE: I would have to say that the questions that remain open, based on the information presented here today, would prevent me from favoring approval at this time.

After closure of those questions it is a different story. So that is a no.

DR. BILSTAD: One possibility would be for us to poll the other members of the committee who have left, since they did not have the opportunity to answer that question. Would that be appropriate?

CHAIRMAN BONE: You can do that. You have heard their comments, which I think were quite -- did address that fairly well.

I think that would be reasonable and we will ask the executive secretary of the committee to do that with this question in mind.

I won't speak for the other members of the committee. So we won't have a resolution on that question today. Okay.

It is clear that there will not be an majority answer to Dr. Bilstad's question today.

We won't have a final answer on that

because the committee is divided 3 to 2 and several members are not here.

Have we finished on labeling? The Chairman would just endorse the labeling comments made by the others, I think.

Well, it has been a long day and it is 5:36. So I think we will adjourn this meeting and thanks very much to everyone who was involved.

(Whereupon, the proceedings were adjourned at 5:38 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Endocrinologic and Metabolic Drugs Advisory Cimmittee

Before: Food and Drug Administration

Date: September 28, 1995

Place: Rockville, Maryland

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