we had seen after ablation of these other compounds.

This shows the pattern from front to back with the axons growing in, heading back, and then sprouting into the cerebral cortex. And this is a very slow, gradual process. It takes from one to six months where there's this sprouting of these normal fine axons, it takes a couple of months to start. And then it's this rostral to caudal gradient that I've mentioned with this progressive re-innervation gradually reaching the posterior regions of cortex between six and nine months.

However, then we come to another bit of bad news. The re-innervation isn't complete. It never quite reaches the most posterior regions of cortex. And between 8 months and 18 months -- and this has been shown with both PCA and MDA. We have not studied this with fenfluramine, but we think that it's likely to be very similar. There is a significant problem that occurs.

There is a subsequent accelerated decrease in the density of serotonin axons throughout the cortex with the appearance of abnormal, tortuous, slow axon tangles that are present throughout the cortex, seen with antibodies to serotonin and the serotonin uptake carrier, somewhat similar to the tangles that

can be seen in other degenerative disorders, like Alzheimer's disease.

Let me show you some examples of those. Here are these swollen tangles. These are from a MDA-treated rat essentially from a group that had recovered and now at slightly over a year has these tangles.

The next slide shows another example of that, these odd tangles. Here's another example of that. That's a pattern that we never seen in the adult. And appearance and incidence of these gradually increases as the overall density decreases of the serotonin axons.

And here's a computer graphic image. This is actually a video photograph that was intensified to show what these tangles look like in the cerebral cortex.

Similar tangles have been reported in much older rats, three to four years of age by this time. But we suggest that the amphetamine-induced injury may lead to, while there may be recovery, progressive and precocious aging and degeneration of the sprouted serotonin axons. So that there's accelerated aging in second phase of degeneration that occurs much later.

Let me stop and summarize, then. Evidence

for 5-HT axon degeneration associated with the amphetamines, the 5-HT axon terminals are not detected after treatment for months. There's a loss of immunoreactivity to serotonin.

There are swollen axons more proximal to that. So the pre-terminal axons remain, but by showing signs of other degeneration and subsequently an attempt at sprouting, where the serotonin may dam up in the stumps of these axons.

The cell bodies, however, are completely spared and make abundant serotonin, indicating that the synthesis of the serotonin and the enzymes for serotonin synthesis as well as the uptake carrier, are intact in the cell bodies. And we have seen that the cell bodies retain the ability to synthesize enough proteins to make new axons so that axon transport in these cells up to the terminals remains intact.

Now, further evidence is that we have observed with PCA and MDA an almost complete loss of retrograde axonal transport in the RAPHE neurons following treatment with these other amphetamine derivatives.

Now, it was mentioned earlier today that there were no effects on axon transport. I presume that Dr. Moore meant that that had not been seen with

fenfluramine. And we have not studied it with fenfluramine, but since fenfluramine is so similar to these other compounds and all the other phenomena are essentially identical, we would expect that the same thing would occur. And that is we have seen an almost complete loss of retrograde axonal transport from the cortex back to the dorsal RAPHE nucleus.

And, in contrast, the median RAPHE nucleus, whose axons are spared, shows completely normal retrograde transport. So the toxicity of these amphetamine derivatives is focused on the dorsal RAPHE nucleus. There's positive evidence of toxicity, such as acute structural damage. You saw all those pictures of fragmented, swollen axons.

And then, further, the regenerator process itself I think is one of the strongest pieces of evidence in the process. And that is these axons are seen to grow in and gradually move and extend back from frontal back to occipital cortex over a period of months and months and months, eight months or so, further evidence.

And then after we made this slide, we have the additional rather strong evidence that serotonin uptake carrier itself using an antibody to dye also shows that the serotonin axons are swollen and

ablated. It's not that serotonin itself as a marker is gone.

So we think that, in fact, when you look at the serotonin axons in the cortex several months, two months, after treatment, that virtually all properties of axon viability of the terminals are gone.

There's no transmitter storage. The serotonin isn't present. There's a loss of re-uptake in the carrier sites as well as a loss of the carrier protein. So the plasma membrane of the terminals appears to be gone.

There's a loss of synthesis in the serotonin in the terminals in the cerebral cortex. So the synthetic enzyme of cytoplasmic protein is gone. And, in fact, there's a loss of axon transport. So the cytoskeletal elements must be gone. In fact, so this latter point we've seen we've not observed.

We haven't looked at dexfenfluramine, but, again, with MDA and PCA, it's a striking loss. And we presume that the same thing would be true for dexfenfluramine. It's a rather tedious long-term study that needs to be done quite carefully on that.

So what we have here is a diagram showing what we think is a similar effect. Here are RAPHE

neurons with the serotonin axons, heading up to cortex with fenfluramine, MDA, PCA, and other amphetamines that bind to the serotonin uptake carrier attacking the axon terminals leading to release depletion and terminal degeneration.

Degeneration is shown here as these terminals shrink back and swell. And then there is this they swell and shrink back here. Then there is abundant regeneration.

And then we project based on this data with MDA that there may be, despite the regeneration, a delayed phase, year to year and a half later, of accelerated aging and degeneration of serotonin axon terminals that remains to be verified for dexfenfluramine but is certainly most likely and should be done by a group that has a particular interest in this product. Well, we don't. And it's a very labor-intensive study to proceed with.

Well, thank you very much.

CHAIRMAN BONE: Thank you very much. And, Dr. Molliver, if you'd like to take your seat, I think what we'll do is have questions and discussion by the Committee.

And then I think there clearly would be benefit for us to have some discussion between the

neuroscientists representing the sponsor and those who have been invited by the FDA regarding some of the questions that undoubtedly will arise about suitability of models and interpretation of some of these results because obviously some of the comments made earlier by the sponsor anticipated some of the discussion. I think we'd like to at least clarify the differences and see if there's any overlap there.

But now if panel members would like to ask questions of either of the two speakers? Dr. New and then Dr. Illingworth?

DR. NEW: Have any of the experiments been conducted with doses that are similar to those proposed in the human trials? That is, Professor Molliver, you said five milligrams per kilo. And I calculate that the human dose is somewhere in the range of .3 to .4 milligrams.

DR. MOLLIVER: Right. We had used a much higher dose. We were at that time not trying to develop this drug for commercial use but looking at the mechanism of toxicity until we picked a dose that was quite toxic. And I'm quite sure that lower doses have similar toxicity.

The toxicity appears to be dose-related. Dr. Ricaurte, as Dr. Seiden pointed out, showed that

the dose of one and a half milligrams per kilogram had very similar toxic effects.

In addition, as Dr. Seiden also pointed out, in the rat the ED_{50} for an anorexic effect is the same as the five-milligram per kilogram dose that produced the toxicity.

DR. SEIDEN: If I could just add a few words to that? I think when you're comparing between species due to the differences in metabolism and drug, the rate of excretion, the smaller the animal gets, the more drug you give to achieve effect in rats and mice, dose goes up.

The point that's crucial is the effective dose and toxic dose are very close together. I would suspect the same thing might be true in humans.

CHAIRMAN BONE: Dr. Illingworth was the next person to have a question.

DR. ILLINGWORTH: I'm just thankful for my colleague's comments. I think the data on MDA -- you haven't studied fenfluramine or dexfenfluramine. So to include that is irrelevant to this discussion on fenfluramine in my opinion at the dose used.

The second question I think is the studies in monkeys using 10 milligrams per kilogram per day, by my calculations, the rat data is similar, 10

milligrams per kilogram per day. That's 20 to 30 times greater than the human dose. I again question the relevance of this to the use in humans.

DR. SEIDEN: Well, I really --

DR. ILLINGWORTH: Steady the dose that's being used in humans and show comparable data, and you'll convince me that's there's neurotoxicity.

DR. SEIDEN: Well, look, you have to have a benchmark, it seems to me, of an effective dose. And you have to have a ratio between effective dose, the toxic dose.

Very frankly, in some of the studies that were included in the handout, they were using 60 milligrams of d-fenfluramine twice daily. Now, in my view, that does get up into the range of what might be a toxic dose even in a monkey.

DR. ILLINGWORTH: But the information that we've heard this morning, the dose that's being asked for is 15 milligrams twice a day.

DR. SEIDEN: Yes.

DR. ILLINGWORTH: So to consider higher doses, which the company isn't asking for, is irrelevant.

DR. SEIDEN: I don't think it is quite irrelevant. I think the point is that people may

decide to use higher doses. You can't necessarily control that.

And, secondly, in my view the smaller doses that were presented in the handout weren't efficacious at all.

CHAIRMAN BONE: Maybe we could just have one comment here. It's typical in toxicology studies to look for toxic effects at multiples of the projected administered dose in order to provide some margin of safety.

Perhaps Dr. Troendle or one of the other people from the agency would comment on what a typical safety margin you would look for in relationship between dose and toxicology studies versus expected clinical dosage.

DR. SOBEL: We have pharmacologists here, but usually we try to push a dose in preclinical toxicology to a dose where there is an effect. The exact ratio of multiples becomes one of judgment and risk-benefit.

Whether there's a threshold effect is really the issue, in other words. If it's a continuum, then in a large population, even a fairly large ratio will manifest itself. If there is a threshold effect, then we're out of the woods. But we

don't know that.

Then I think perhaps you would like to comment on that. We have a person, Dr. Contrera, who works with neurotoxicity.

DR. CONTRERA: Yes. I'll be speaking later this afternoon for the agency in this regard.

We have been attempting to do a comparison of systemic exposure and, even more important, in other words, blood levels in experimental animals, both rats and the squirrel monkey, -- those are the two main species -- and also brain concentrations, micromoles of drug in brain of rat, squirrel monkey, and the human at clinical steady state levels. This information has just become available due to the application of magnetic resonance spectroscopy studies that the sponsor graciously contributed to try to address these issues.

And so from that basis, I think the sponsor and the agency probably agree that the brain concentration of drug -- and that drug includes the dex and the nordexfenfluramine -- is the pivotal factor in assessing the potential for neurotoxicity.

And right now the estimates for -- and this is based on the most recent study that the sponsor did, a 13-week dosing study in rats. We

estimate that for 8 milligrams per kilogram oral, probably the brain margin of safety is only about 10 -- it may be slightly less than that -- for the lowest toxic effect. For a nontoxic effect, it's probably four.

CHAIRMAN BONE: Thank you.

Are there questions, further questions, from the Committee members? Dr. Kreisberg?

DR. KREISBERG: I hope that the two experts will be patient with me. I'm way in over my head here. But two questions come up. One is: Do you have any experience with other drugs that are currently used that have similar properties, such as peroxetine or fluoxetine? And do we know whether they have similar effects?

And the second question is: If we use PET scanning and demonstrate the achievement of a brain steady state concentration of the drug, would you predict in the face of degeneration of neurons that we would not have a steady state, that, in fact, the level would go up and then come back down as the nerve endings degenerated?

DR. MOLLIVER: Let me start, and then I'll let Dr. Seiden take over from there.

We have looked at interactions and

comparisons with serotonin uptake inhibitors, such as citalopram, peroxetine and fluoxetine. These drugs are remarkable in that they bind to the same site on the serotonin axon terminal, as does dexfenfluramine.

But they protect the serotonin axons against toxicity. So that, for example, if you co-administer any of these compounds with dexfenfluramine, you completely abolish the toxicity.

In fact, we have actually gone so far as to propose, not in writing, that fluoxetine might be useful as an antidote for an overdose of dexfenfluramine since it affords essentially complete and extensive protection, even if it is given 24 to 36 hours after the fenfluramine, which we have done.

DR. SEIDEN: Our experience has been very similar. We have pushed doses of the compounds that solely block re-uptake that do not cause release, as does fenfluramine, to very high levels and never have seen any neurotoxicity from these compounds. And, again, we think that it has something to do with the fact that fenfluramine and MDMA-like compounds block release but promote release as well as block re-uptake.

And that's the difference. The circuline, fluoxetine just block the transporter and don't

promote release. That's a crucial difference between the drugs.

Now, your second question was?

DR. KREISBERG: Steady state levels in the brain in the face of degenerating neurons. Would you expect there to be achievement of a steady state and maintenance of that steady state as the neurons degenerated?

I mean, if, in fact, they have a specific site of action in these neurons, then you would think that there would not be any localization and, therefore, no retention of the drug or is that not fair?

DR. SEIDEN: Well, it's fair, but I just don't know. My offhand opinion is that there are relatively few serotonin neurons in the brain, relative to the other types of neurons. Maybe one to two percent of the neurons in the brain contain serotonin.

I think when fenfluramine crosses the blood brain barrier or when its metabolite crosses the blood brain barrier, it's not looking for serotonin neuron. It happens that it can act on a serotonin neuron.

So my offhand guess, there wouldn't be any

significant changes in the concentration between the drug or its metabolite, but I have no evidence one way or the other about this.

DR. ILLINGWORTH: Thank you.

CHAIRMAN BONE: Are there other questions from the Committee?

(No response.)

CHAIRMAN BONE: I think what would be useful at this point is to have a very concise summary from the company regarding their obvious difference of opinion about some of these models. And then perhaps there might be one or two very brief questions. And Dr. Molliver perhaps would have a further discussion, if he has one, to the discussion of the models. And then we'll have a lunch break, which will probably do everybody some good.

DR. COOPER: Thank you. Mindful of the lateness of the hour, we will be brief, but we appreciate the Chairman's giving us some time to respond to a very complex set of data that you have seen.

I think we don't want to respond to the questions that were raised with respect to efficacy that the first speaker raised because the data that was presented to my mind bears very similarity, I

think, relationship to the efficacy database that was presented to the Committee this morning. And we certainly haven't used doses of 60 milligrams twice a day of dexfenfluramine. I'm not sure where that's come from.

But in commenting specifically on the neurotoxicity issue, there really are three very brief points I'd like to make and then allow the real neuroscientists to make a few specific points.

First of all is the issue of clinical exposure. This drug has been used by over 40 million patients in the form of fenfluramine, the racemic drug, and dexfenfluramine, the isomeric drug.

We have seen the power of post-marketing surveillance to detect possibly very rare signals, such as primary pulmonary hypertension. And there has been absolutely no evidence in clinical trials or in post-marketing surveillance of a neurological syndrome, clusters of events, that seem to talk to an issue of a neurotoxic potential of this highly used and highly studied drug.

The second issue relates to the scientific interpretation, scientific validity of some of the data that was presented. That's not really for me to comment on. I'll leave that to Dr. Moore and Dr.

Wurtman.

But I will say that it's going to be almost impossible in a period of three or five minutes or the half an hour that's been allotted for the Committee I think to feel completely comfortable with the nuances of neurochemistry and the special techniques that are used.

Although we will make specific comments, I think the third part is the most important. it's the margin of exposure issue. And I think that, as Dr. Contrera has alluded to, we have made great efforts to try and define margins of exposure and show that, in fact, there is a very large margin of exposure if one accepts serotonin depletion to be a marker of neurotoxicity.

If one doesn't accept that, -- and I think some of the scientists do not accept that -- then the margin of exposure is infinite because there is no other objective evidence for neurotoxicity of this drug.

So let me just ask Dr. Moore to make some comments.

DR. MOORE: Thank you.

As my old friend Dr. Seiden said, I will also try to disagree but not be disagreeable. He

pointed out there is a long history of changes in serotonin neurons that have been related to the use of fenfluramine.

Indeed there was an FDA hearing in 1978 that I participated in that went over some of the early studies that reported changes in serotonin cell bodies. And these were I think at that point clearly demonstrated to be artifact and things that had nothing to do with the drug.

I don't mean that to imply that any of this is, but, rather, that this has a very long history. Essentially it has been a series of demonstrations of decreases in serotonin content. Those are the major things that are found.

I want to point out to you that these effects depend upon a lot of different things. They depend very much upon the dose of drug that is used. They depend very much upon the route of administration. And they depend very much on the schedule of administration. It is much more difficult to obtain effects with oral dosing than it is with parenteral dosing. If the dosing is given over time and particularly if there is a buildup in dosing, then it's very difficult to get effects.

Dr. Contrera pointed out a very important

observation that has come from the continued efforts to try to understand the relationship between the drug and changes in serotonin content. And the one thing that is clear is that the concentration of the dexfenfluramine and dexnorfenfluramine taken together are a predictor of changes in brain serotonin content independent of species. That is that the species does not make a difference if you look at the concentration of the drug and its metabolite.

And this allows you then to have some predictive statements to be made. And we have tried to do this with respect to the brain concentrations and relate that to the human.

Let me now go over a couple of other issues. Dr. Molliver made the point that fenfluramine should be like the MDMA and PCA. That is not what has been found in our study. As I pointed out to you in my earlier presentation, PCA, MDMA, and 5-7 didroxy-tryptamine produce hydrophilium. They produce glioses. And, as he said, they produce changes in retrograde transport.

The very careful studies of Dr. Kalia that are included in the NDA show quite substantially that dexfenfluramine does not produce changes in retrograde transport in doses up to 16 milligrams per kilogram.

We are now in the process of repeating those studies over a long term, but in the initial part of the studies it's clear that the same is true, that dexfenfluramine does not alter retrograde transport, which indicates that the terminal plexus must be there because axons cannot take up very substantial amounts of a retrograde tracer. It must be the axon terminals that take it up.

I would also emphasize for you the long-term mouse study that I reported. Mice were given 27 milligrams per kilogram per day of dexfenfluramine for 2 years. In those animals, there was no change in either serotonin content or in the content of the transporter, as shown by the fluoxetine finding. Thus, over a very long time in a mouse's life, this drug has not produced any significant changes in this system.

CHAIRMAN BONE: For about 30 seconds.

DR. WURTMAN: It can't be done. Look, calling something neurotoxicity does not make itself. All the changes that have been described are changes in serotonin neurons themselves.

It is certainly true that if you give a rat or a monkey a dose of the drug which will raise brain levels to 10 times or more the dose of the

levels you see in people, you will indeed deplete serotonin. Therefore, you can't save the cell.

You will indeed suppress the synthesis of macromolecules. And we have shown this in the cell body. You stop making tryptophan hydroxylase. You stop making the transporter. These are proteins that are characteristic of the cell.

The reason that fluoxetine works, by the way, is that the dexnorfenfluramine has to get into the nerve terminal. And it gets in via the serotonin transporter. So, of course, any drug that blocks the transporter is going to block the entrance and, therefore, the release of serotonin.

Last statement, I would point out three laboratories have now shown that if you give rats high enough doses of fluoxetine or fluvoximine or any of the SRIS drugs, you also will deplete serotonin. But you don't do it as much, and it won't last as long. It will last a couple of weeks, not a couple of months. And the reason, again, is that you don't also release serotonin from the nerve terminal. And so you don't have the mega activation of the presynaptic receptors.

Last word, you can call something neurotoxicity until you're blue in the face. But, in

fact, there's a community out there of neurotoxicologists. And what they look at is glioses. And they look at silver staining. And they look at loss of cell bodies. They don't look at pharmacologic changes in transmitter levels.

CHAIRMAN BONE: Thank you.

I think perhaps if Dr. Molliver at this point might want to do -- would you want to comment on some of these questions about validity and interpretation of models? Because I think it addresses particularly the material you presented. And then there might be one or two further questions or comments from the Committee before we have our intermission.

DR. MOLLIVER: Sure. Be happy to briefly comment on that.

The lack of data that was presented here in the initial rebuttal showing evidence of clinical syndromes resulting from loss of serotonin axons is probably something that is uninterpretable since, first of all, it's not clear exactly what serotonin depletion does except for we know causing, leading to clinical depression with in some cases suicides. And I understand that there have been anecdotal reports of patients, but I don't know of anything in the

literature about depression.

Again, the problem in assessing clinical syndromes is two things. First, the effects of serotonin are extremely so and are related to mood, vigilance, and alertness. And I don't know if anyone has actually gone about attempting to characterize changes in those factors. So, therefore, it's hard to know what that would mean.

With regard to the comments by Dr. Moore regarding the neurotoxicity studies, first, it is true that in 1958 there was such a meeting here, at which Dr. Harvey showed that there was a loss of serotonin and serotonin axons. And he thought that there was a change, not a loss, in some of the serotonin cell bodies.

It turns out that there wasn't a loss, but, in fact, he was probably right since we have now seen not yet published data showing a change in mRNA for the serotonin uptake carriers in the cell bodies. And the change that he saw was a subtle change in the cell bodies, which might very -- it was an increase in the Nissl staining, which stains ribosomal RNA. And it's probably that.

And that was probably a real response to the loss of the axon terminals and not, as we now

know, degeneration of the cell bodies since they don't, they clearly do not, degenerate.

Let's see. It's also been emphasized by all of the speakers here that changes in serotonin levels are the sign of neurotoxicity. Again, I would contest that and would never rely upon the changes of levels of any transmitter or, in fact, any single parameter as a sign of neurotoxicity.

The important issue here is that all of the parameters of viability of these axon terminals are gone, not just one, all. So that, indeed, these are somewhat ghastly. If they're alive, they're rather ghastly terminals.

But they're probably not there since there's no evidence using any markers at all that the axon terminals remain present after treatment. It is not just loss of serotonin, the loss of the enzyme, the loss of the uptake carrier in 24 to 48 hours, which is much too soon to result from an effect on the cell body when, in fact, we have seen that the cell body is then making an increased amount of mRNA for the uptake carrier for several days following the treatment.

CHAIRMAN BONE: Lew, would you like to, just a word or two?

DR. SEIDEN: A short comment. My comment on the efficacy was 60 milligrams come from Table 7.

CHAIRMAN BONE: Okay. Well, let's focus on the specific questions of neurotoxicity. I think --

DR. SEIDEN: I just wanted to note that I didn't make that number up.

CHAIRMAN BONE: Fair enough. Thank you for bringing that out.

DR. MOLLIVER: Another piece of data that may be important is that the emphasis that was given to the mouse data is of interest and that that seems not to be neurotoxic.

There are two points about that. First, it's been known for many years, for 15 years now, that mice are extremely resistant to the effects of any of the amphetamine derivatives and do not show toxicity to MDA, MDMA, PCA, or fenfluramine. So there's something completely different. And, therefore, I think the mouse is not an acceptable animal model for use in these studies.

The other results that Dr. Moore alluded to was that someone had given 16 milligrams per kilogram of fenfluramine over a long period of time and found no changes in axon transport. It seems to

me to be close to unbelievable or -- I shouldn't say that -- most extraordinary.

If that's true, then the protocol and regimen should be very carefully examined because that laboratory has probably come up with a remarkable new neuroprotective agent that was somehow added inadvertently and unknowingly to this system since it's so unequivocal in our minds that the toxicity is there.

I do not doubt that there is a low dose at which the toxicity would not be found. I think, as rational people, we ought to look at this comfortably and easy. As you accelerate the dose to these large doses, I would not call them mega doses, but 5 or 10 times the dose that humans take as a reasonable toxicological dose.

I think that any reasonable person would agree with all of the data that at those doses, there is toxicity. So the issue becomes then: At the lower dose, is there not toxicity?

The evidence, presenting evidence, that there's no toxicity at high doses I think is not very meaningful.

CHAIRMAN BONE: Thank you very much.

Are there further questions that we need

to go into? Dr. Kreisberg?

DR. KREISBERG: Yes. I hate to prolong this, and I know it's late, but I'm going to have to vote and I want to be absolutely certain on this very serious issue that I've got as much as I can possibly get out of it.

What I heard Dr. Wurtman say is something that I seem to understand very well. And that is as an endocrinologist, if you increase the concentration of something, you get a lot of negative feedback and suppression or decreased expression of various enzymes and proteins. And I actually find that coinciding with some of the early structural data.

But what worries me is what appears to be irreconcilable. And that is I would think that the animals would recover because that's a functional suppression ot activity. And, yet, we still see prolonged structural abnormalities. So the question is: How can we reconcile that?

CHAIRMAN BONE: All right. I think we're going to get into this probably further in the discussion. If Dr. Wurtman would want to take 30 seconds or so and --

DR. BORHANI: I have a procedural question.

CHAIRMAN BONE: Okay.

DR. BORHANI: It's very important.

CHAIRMAN BONE: Well, wait a second.

DR. WURTMAN: The brain is a strange and wondrous place. Some of the feedback loop has taken an enormous amount of time. This is not an answer, but just to throw out. Consider tardive dyskinesia, which I guess we've all seen, to which you can administer dopamine receptor blocking agents to a patient for months and months and months. And the suddenly wham. You start seeing changes.

Again, there is the example of depression. The answer is I don't know, but I think that the kinds of studies that we and others are now doing on the time course for genetic expression will probably lead to an answer.

DR. BORHANI: I have an important question.

CHAIRMAN BONE: Yes, Dr. Borhani?

DR. BORHANI: Like Bob, I am concerned because if you want to ask me to vote, I'm very disturbed now, to put it mildly, because I received volumes of documents. And I faithfully read and went to the library and reviewed practically every reference that every one of these documents had given

me. And I have not received any document on the argument that was just presented by two distinguished neuroscientists.

And my question is: Why? Why did we not receive a written document that we would have studied this issue, we could have checked the reference?

I would like to know the methodology. I would like to know the exact studies that these structural changes were observed. To me this is very disturbing. And the amount of the time you're allowing for this kind of a discussion is not going to give me any answer.

And to put either of these two gentlemen or the sponsors on the spot to come up with the answer to me is at best unfair. And I want to know why we did not receive these documents in advance.

CHAIRMAN BONE: Thank you for pointing out that problem, Dr. Borhani. I think probably we won't be able to answer that question during this discussion. But it's a point worth noting.

I think we are going to spend quite a bit more time on this issue during the discussion period this afternoon. So probably it's a fair time to take our lunch break. It's now 1:25. The scheduled resumption time is 2:00 o'clock, and we're going to

try to stick to that.

(Whereupon, a luncheon recess was taken at 1:26 p.m.)

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

(2:13 p.m.)

CHAIRMAN BONE: Dr. Reedy read the conflict of interest statement at the beginning, which covers the current and ongoing activities of the members of the panel as well as the invited guest speakers. A question arose concerning the fact that we had information about prior activities of the speakers on pulmonary hypertension, but a question arose about those dealing with neurotoxicity.

And if I can just ask Drs. Molliver and Seiden to make a quick statement to that, certainly addressing that question. Dr. Molliver?

DR. MOLLIVER: I have screened a number of drugs derived from a number of different drug companies at various times in my career. I have never received financial support from any drug company for which we have screened drugs. In fact, that is expressly prohibited by Johns Hopkins University.

CHAIRMAN BONE: Thank you.

And, Dr. Seiden?

DR. SEIDEN: I have never done any neurotoxicity work for drug companies, but I have screened antidepressant drugs on screening models that I have in my lab for drug companies, for which they

paid the expenses for the rent and the labor to screen them.

CHAIRMAN BONE: Are you aware of any of those projects being involved in this indication?

DR. SEIDEN: Absolutely not.

CHAIRMAN BONE: We'll proceed now with the FDA presentations. First will be the medical review, which will be presented by Dr. Leo Lutwak of the Division of Metabolism and Endocrine Drug Products.

DR. LUTWAK: Thank you, Dr. Bone.

This morning we heard very apt and apropos discussions from public representatives and from Interneuron's consultant group, Dr. Bray and Dr. Lasagna and Dr. VanItallie and Dr. Manson, about the severity of the problem that we are considering today, the provision of drugs for weight loss. And we heard a great deal about the severity of the problem of weight loss, of weight gain and obesity in terms of its impact on total health care, total costs of health care, total morbidity, relationship to other diseases.

From the point of view of the FDA, we have to consider the balance between the benefits of a drug or an indication and the potential risks that the drug may carry. Obviously if we're going to expect certain benefits, we want to make sure that these are not at

the cost of producing disease that might be worse than the disease we're trying to control.

The drug under consideration today, dexfenfluramine, which is part of a molecule of -- part of the compound that's been approved, last approved anti-obesity drug in the United States, fenfluramine, which was approved in June of 1973, I believe. Dexfenfluramine is half of that capsule. And this is the next one that we're considering.

I agree with the early speakers this morning that I wish we had a larger armamentarium to present to the public and to physicians for the treatment of this very severe disorder.

Now, for dexfenfluramine, we have to consider the potential benefits, which should include: first of all, a significant weight loss; secondly, and equally important, decreased co-morbidity, as we heard of the serious co-morbidities that one sees with obesity; and a long-term effect, which obviously we can't demand as part of the validation procedure for approval of a drug, prolongation of life. On the other side of the coin, we want to evaluate today the risks that taking this drug might produce to the individuals who will be taking it.

We've had a discussion of the

neurotoxicity, hypertension that's been associated with the use of other drugs that have been advocated for appetite suppression. Stroke has been listed as a potential risk factor; pulmonary hypertension, of which we heard a good deal this morning; and possibly unpredicted risks that may not have become apparent, despite the fact that 40 million people -- and 40 million people, whether Frenchmen or not, can be wrong sometimes, and Americans.

(Laughter.)

DR. LUTWAK: And we should add to these 40 million all the millions who have taken fenfluramine as well over the years.

Now, you have in your kits the questions that we're asking you to help us with. I'm going to go over these four questions. I think we feel very strongly that one cannot ask these questions too frequently to keep your mind on what we're after, what we want help with.

Question Number 1, is the evidence of efficacy sufficient to warrant the approval of dexfenfluramine for long-term; that is, in definite, use, as has been proposed?

Remember, all of the drugs that we have approved to date, including fenfluramine itself, have

been approved for short term, which has generally been interpreted as three to four months' use. So today we're asking whether the efficacy is sufficient to warrant approval for indefinite use.

And we saw the results. Dr. Sandage presented the efficacy data for dexfenfluramine. I'm going to concentrate just on the one index study since that was the only one, really, that looked at long-term usage. The others were relatively short.

And we see that with dexfenfluramine the weight change with the drug, the solid bars, exceeded the weight change, the weight loss, since these lines are going down, seen with placebo at each of the points that were examined in the 48 weeks of study. And then at eight weeks after the drug was discontinued, there still was a difference, although much less.

What I was interested in is that the placebo loss remained about the same eight weeks later, as it had been at the end of the study. But the loss with the drug was somewhat less. People had started gaining weight, which answered in part one of the questions that the Advisory Committee asked earlier today.

And if we look at the categorical

response, we see the same thing that Dr. Sandage showed this morning -- and I'm emphasizing the 48-week study particularly -- that with the drug, it was a greater number of subjects who lost between 10 and 20 percent of initial body weight than did with placebo alone. It's not much of a difference, but this was statistically significant.

But in lower weight loss, zero to 10 percent, and weight gain, the placebo actually showed greater numbers of subjects. This suggests that in the 48 weeks a somewhat larger number of subjects showed weight loss in response to drug.

If we look at the actual numbers, we begin to question the clinical significance of this statistically significant difference. Again just looking at the 48-week data, on drug an average of 9.64 plus or minus the standard deviation of 7.71 kilos was lost compared to 6.91 plus or minus 8.0 kilograms with the placebo group. In other words, use of the drug provided approximately three-kilogram greater weight loss than the placebo alone.

And the reason I'm bringing this up is, as I threatened the last time we met with this Committee, coming back to you again and again with the same issues and the same questions, and we raised that last

time.

What also is interesting is the dropout rate at 48 weeks was about the same in both groups. There was a slightly higher dropout rate in the placebo group than in the drug group, but, at least superficially, this suggested that the drug didn't produce any greater causes for dropout.

Now, the important issue is that little line on the bottom: effects on mortality and related morbidity. Now, we heard a great deal about the strong epidemiologic evidence associating increased obesity with increases in cardiovascular disease, coronary artery disease, Type II diabetes, possibly in cancer.

There have been one or two rather fascinating epidemiologic studies recently reported indicating that voluntary weight loss; in other words, weight loss not associated with disease, may provide improvements in some of these conditions, particularly non-insulin-dependent diabetes.

We heard quoted some studies that have not been submitted to the NDA with dexfenfluramine indicating improvement in glucose tolerance, blood pressure. These are data that we haven't had an opportunity to examine. We don't know how many of

these were short-term, how many were long-term, how many subjects were involved, whether these were placebo-controlled.

As I say, we haven't had an opportunity to examine them. But, if true, these are interesting and attractive concepts to bear in mind in considering this drug because the effect of a drug on these diseases is not quite the same as an effect of weight loss carried out by means of exercise and other hygienic controls, such as diet.

The drug is always suspect until proven otherwise of producing increase in co-morbidity. And this has to be clearly shown that the drug does contribute to the decrease in co-morbidity. And these are data that we do not have at present for dexfenfluramine.

Now, the second question that we're asking you is probably more significant. Is the evidence of safety sufficient to warrant approval for long-term use, as proposed?

Now, for proof of efficacy, we demand very strict criteria: placebo-controlled, double-blind studies conducted under very careful conditions for long periods of time.

Safety data generally are much softer. If

evidence of lack of safety, suspicion is often enough to raise questions. And the reason for that, of course, is the way safety data are collected.

Obvious deaths are easily measured. But other data are generally reported in anecdotal form. Other data except for those that are derived directly from the controlled studies, the studies that are submitted as part of the NDA, the other data are obtained by spontaneous reporting. And these generally are quite soft.

I have assembled here the data that I've managed to pull out of the most recent submission, about a month ago, from the sponsor, which contained post-marketing safety data, the use of dexfenfluramine from August 1984 through December 1994. Events are classified by the reporters as either serious events or non-serious events.

The obvious drawback to this type of data from both the point of view of the sponsor and the point of view of those trying to evaluate it, the regulatory agency, is that we do not have a denominator. The denominator is a very guessed-at number.

Now, serious events, there are a total of 162 events reported that could conceivably be

considered related to CNS. These included things such as stroke. They included events such as serious enough sleep disturbances, suicide -- no. I'm sorry. Suicides were kept out of it. No. That includes. Suicides were included with overdose, memory losses, other events that caused the patient to either be hospitalized or drop out from the study.

The non-serious events, of which there were many more, were generally not accompanied by any anecdotal information or any hysterical information, included: 227 sleep disturbances, which were primarily problems with nightmares and daytime somnolence; 115 reports of dependency, which was not spelled out more, in greater detail; and 39 cases of amnesia or short-term memory loss.

The most significant event that appeared in the serious events was primary pulmonary hypertension. And there were 101 reported reports included in this post-marketing safety database that was submitted to the agency this month.

I heard somebody make a statement that there were only 30 cases known with dexfenfluramine, but there were 101 in this particular report. Now, I parallel that with 27 cases of non-serious events that appeared to be related to the pulmonary system, such

as shortness of breath that was unexplained, and other vague symptoms that at least raise suspicion of possible early pulmonary hypertension.

There were 79 instances of serious overdose or suicide that led to discontinuation of use of medication and/or hospitalization, 61 GI events that were sufficiently severe to require discontinuation or hospitalization, and 377 that included primarily diarrhea that were not considered serious.

There were 50 cardiac events in this group and 78 in the other group. And this ranged all the way from peripheral edema to cardiac arrhythmias, which is probably not to be unexpected in this type of population.

There are 15 that were labeled as severe withdrawal symptoms; 44 in this, in the non-serious ones; 16 instances of hypertension, sufficiently severe to require discontinuation; 41 that were not that severe; 12 instances of musculoskeletal events, such as muscle pain, myositis; and 34 that were not considered severe; and 32 instances of syncope, which was somewhat alarming. Now, remember, though, these are anecdotal spontaneous reports.

Primary pulmonary hypertension, which

we've heard a good deal about this morning, is deserving of a little bit more emphasis. In 40 years of medical practice, I've seen only one case. And it was frightening. It is a bad disease. And when I came across approximately 100 cases of primary pulmonary hypertension in association with the drug, this was frightening.

These 100 cases were primarily women, as Dr. Abenhaim pointed out and Dr. Rich. There were 14 deaths reported in the case reports that we received, 6 lung transplants.

The average age was 49, with a range of 18 to 78, very similar to the cases that were reported in the case-controlled study of Dr. Abenhaim's. BMI in this group was generally higher than the average of the patients that were reported in some of the other studies, about 31 plus or minus 5.8, with a range of about 19 to 44.

And this was a skewed group. In this population of 100 that was randomly assembled through spontaneous reports, we see demographic data very similar to those in the better controlled, case-controlled, study of Dr. Abenhaim that there is an association with excess body weight, with obesity.

And what is particularly interesting is

that 18 percent, about one-fifth, had BMIs that generally would be considered not warranting treatment with potent drugs. And about 20 percent had very high BMIs of 35, the population that Dr. Bray treats, the population that I would treat, population we considered at high risk.

Also of interest are some other parallelisms with the findings in the case-controlled study in this random group of 100 spontaneous reports. Twenty-seven percent used other anorexiates. This suggests to me that this population who develops primary pulmonary hypertension are those that are reaching out for help and are willing to take as many drugs and whatever drug is available on the market. Twenty-seven percent of them were taking other drugs.

These other drugs included fenfluramine; -- a surprising number of subjects with pulmonary hypertension were taking both fenfluramine and dexfenfluramine, simply because the two were available at the same time -- diethyl-propion, which is known in Europe as amfepramone; phentermine; and other amphetamine derivatives, many of which are not available in this country.

Approximately 30 percent of the patients had known hypertension and were on various

anti-hypertensives, which answers your question of this morning, disassociation. About 18 percent were taking some psychomometic drugs, antidepressant agents, antianxiety agents, frank antipsychotic agents.

Only six percent of these were on hypoglycemics. Only six percent of those that developed primary pulmonary hypertension were taking drugs for Type II diabetes, suggesting that they were really a population that was not at high risk to begin with for Type II diabetes. And only five percent were on drugs for dyslipaemias.

Coming back to the point that dexfenfluramine is the dextro inantimere of fenfluramine, which has been available in this country for approximately 20 years under the name of Pondimin, we have very few reports of primary pulmonary hypertension that have come to the agency in patients taking Pondimin alone. And, as I said, we have 100 cases with dexfenfluramine.

The fenfluramine population, with an n of 7, really cannot be compared statistically to the population with dexfenfluramine. But this does raise another interesting question.

Is there something about the L-inantimere

that Servier has eliminated from dexfenfluramine that might be protective against other side effects? Because we do not have any data on L-fenfluramine or any studies comparing the dL-fenfluramine with the d-fenfluramine, which leads us to the third question.

Would a large simple at least two-year randomized trial be required to provide us with additional information on weight, mortality, serious morbidity, such as heart disease, diabetes, and stroke? And if the Committee feels that such a study would be of value, should this trial be a commitment in Phase IV or should this be a requirement for initial approval?

And, the last question, are there any other issues or are there any specific issues that are coming up today in our discussions that would make the Committee think there should be specific comments in the labeling as protection, as a safety factor, or for other factor?

I think we'd like to at this point also get a little bit out of the order of the schedules you have there. Dr. Nevis has some evaluations of the data that led to the efficacy statements from the point of view of the agency. He has some additional evaluation of this that may be of some help in

considering the data presented.

CHAIRMAN BONE: Are there any questions?

(No response.)

CHAIRMAN BONE: Dr. Lutwak has suggested that the questions for the agency presentation be pooled if the Committee is agreeable.

DR. NEVIS: Thank you.

The sponsor did a good job presenting the primary results this morning. I don't want to repeat anything, but I do have a couple of overheads, slightly different ways of looking at the data.

The Advisory Committee originally in talking about guidelines had suggested that a five percent difference in placebo was a clinically meaningful change. Dr. Taneja at the last meeting in July suggested several alternative ways of looking at the data: responder analyses and categorical analyses. and those were presented this morning.

The Committee may still want to see how the data looks in terms of differences in percent change from baseline. I don't believe this has been presented yet today.

The Committee has copies of this in the handout that was given to them early this morning. So you can follow along. This is the INDEX study. At

the top of the table is completers, people who completed the whole 48 weeks of treatment.

And at the bottom is the LOCF, carrying forward the last data available, to include every patient. And the numbers that would be pertinent for the Committee would be the differences between drug and placebo. And we see this range between 3.11 up to the median of the completers is 5.43 percent.

The Noble study, I have presented similar results here. Again, the differences between drug and placebo at the end of the study -- this is a 24-week study -- ranged from 3.20 to 5.44 depending on whether you're using people who have completed or carrying forward the valleys.

And finally the similar results for study IP92003. This is only a 12-week study. And the differences were as marked on the transparency, which the Committee has a copy of.

One other thing that came up this morning was the idea of carrying forward last valleys. Now, you know, Dr. Taneja at our meeting in July mentioned some of the pitfalls of analyzing clinical trials where you have a lot of dropouts. and he suggested obtaining data from dropouts as protocols specified into the study. Of course, these studies were done

before that advice was available.

So we have to make do with what we have. Now, carrying forward last valleys, which is a question this morning, is one way of having some data to analyze for every patient under the general idea of an intent to treat analysis, but it does rest on some assumptions which might not always hold. So we always try to look at various methods of handling dropouts, including the LOCF and looking at completers, and look for consistency.

Now, one thing that was, one graph that was shown this morning, the Committee has a copy of this. This has a little more on it than the one shown by the sponsor this morning. But this does give some way of seeing what happened to every patient that was randomized in the trial.

Theoretically every patient should be in one of these cohorts that are graphed over time. For example, these two lines here show what happened over time to the patients who completed the study. Those two orange lines graph over time the placebo and the drug patients who were in the study until month 10 but then were not available after that.

And, similarly, going back to each point you can for drug and placebo track over time every

patient, every group of patients, and see how those groups are doing over time.

Now, one thing that we can see from this particular -- also, by the way, in the legend you can see actually how many patients there were in each one of these cohorts. So this is the idea of intent to treat. You can actually see what happened to all the patients over time depending on what their dropout status was.

Now, one thing that this tells us about consistency is that you have the similar magnitude of drug-placebo differences for each of the various cohorts as well as a relative balance in how many people are in each one of these cohorts doing drug and placebo. So this gives us some assurance that a consistent magnitude of drug effect is seen over all the patients.

One other type of analysis was suggested in July by Dr. Taneja and alluded to by the sponsor this morning. Without getting into the details, -- I think it's getting late in the day -- I'll just mention that the longitudinal data analyses which we did perform showed that completers and incompleters had different time trends in each treatment group.

So we had to analyze completers and

incompleters separately. And in each case, however, statistically significant differences were seen in time trends favoring drug over placebo with similar differences between drug and placebo as seen in the various other analyses that you've been shown. I could show more details if anyone is interested, but I'll stop here for now.

One other question this morning had to do with what happened to patients after they were taken off drug. I did want to mention that the Committee does have some graphs which speak to this.

If you look in Tab 4 of your FDA mailing of the statistical review, it's the second part of Tab 4. There's a yellow piece of paper in between the two parts of Tab 4. If you look on Pages 17 and 27, you'll find graphs for the two studies which did follow patients after the drug was discontinued. Maybe the sponsor has a slide or can speak to that more, but you do have some information available on those two pages, 17 and 27.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Nevis.

Did Dr. Lutwak have anything further? No. The next speaker, then, will be Dr. Contrera, who will talk about the review of the neurotoxicology, which

seems to be a subject of some interest today.

DR. CONTRERA: Well, I have the decided privilege of reviewing 20 years of a very controversial area for the agency. And my review was submitted to the division and should be in your packages.

Most of the information that was presented by Dr. Molliver and Dr. Seiden, a good deal of it anyway, that was published is in the agency reviews.

First thing is the legal definition anyway of neurotoxicity. That's any adverse effect on the structure and function of the central peripheral nervous system related to a chemical exposure. And, of course, the big adverse is a tough one for pharmaceuticals, obviously. What is adverse? And what is beneficial? And how do you define those things?

We try to make a distinction between the pharmacological effects of the drug that we're all aware of. It's the neurochemical changes after treatment, many of which are associated with efficacy, and other effect. Every drug has a beneficial and a not so beneficial effect.

So the neurotoxic factors I think are really the duration of completion of 5-HT if we use

5-HT as a biomarker for neurotoxicity. And, as Dr. Molliver stated, it should not be used certainly as the only biomarker. It's the most convenient and effective, at least for preliminary screen for this kind of an effect.

And then more importantly are operations in axonal morphology, degree and quality of recovery of serotonergic neurons. And these, again, coincidentally were things that were already mentioned this morning. I want to state that Dr. Molliver and I have not discussed either one of our talks today.

The evidence as we see it, then, goes to these factors: the long-lasting, -- and you've heard about this already, and we're talking about weeks and months as the parameter for long-lasting -- depletion of 5-HT, and reduction of 5-HIAA, which is the metabolite of 5-HT, after very short exposures in animals.

We're not talking about chronic exposures here. We're talking about four-day paradigms. And, in fact, there is quite a bit of evidence of one-day exposure doing similar things in animals.

There is -- I won't dwell on this, but at roughly more than five kilograms per kilogram for four or five days in just about every species tested. So

I don't think there's any issue there.

Then the loss of the fine axonal serotonergic fibers and the appearance of these abnormal swollen, fragmented, or beaded axons that were alluded to by Dr. Molliver and then the long-lasting loss of axonal 5-HT re-uptake sites that could be linked, could be interpreted as loss of serotonergic terminal axonal degeneration. And these, already stated, are similar to what you get with other blatantly neurotoxic means.

The other issue, the other factors are one that concerned us the most was of the evidence in a squirrel monkey of a very long -- I mean, this is going now past a year -- lack of recovery in 5-HT levels after 10 milligrams per kilogram per day for 4 days and also a very high-dose study in rats. But it did show that after 31 weeks there was still a lack of recovery.

The other one point that was mentioned today was that two-year studies, you don't get any depletion with chronic exposure for two years as part of the standard carcinogenicity studies that are required for all chronically used drugs.

In other words, drugs are exposed to both rats and mice for two years as part of a

carcinogenicity study. It is not a neurotox study. But you do look at several sections of the brain and as part of a very standard simple histopathological assessment with HNE stains as part of this protocol.

And it's true that -- and the company and Servier monitored the drug levels in the rats and the mice during the two-year study and also for the mouse only looked at depletion. Depletion wasn't evaluated in the rat study, unfortunately.

And there was an absence of 5-HT depletion. When you look, though, at the concentrations that were attained in the mouse in this study, you realize that the low dose, the plasma levels of dexfenfluramine and nordexfenfluramine in the low dose are below the clinical plasma concentration. And the mid dose is at the human clinical plasma concentration. And only the highest dose is roughly 10 times the human plasma concentration.

So even though at first glance this study implies that the mice were dosed with high doses of dexfenfluramine, 27 milligrams per kilogram per day, in the feed -- and this is we don't have many feed studies with dexfenfluramine.

The systemic exposure of drug substance is

a lot less than you would have guessed. So that this is something that you have to factor into your interpretations of the lack of depletion.

One possibility, they weren't dosed enough. The second possibility, there was recovery. And the only factor, though, in looking at these studies more carefully, we saw that we did get an unusual finding in the mouse and the rat studies.

And that is of statistically significant brain calcification in all the male mice, low, mid, and high dose, and also in the rat study, including those doses that were well below the human clinical exposure. This was surprising because, as I said, this is across in a genicity study.

There are only four or five sections that are generally taking of the brain during these studies. And only HNE staining is used. So it's not a detailed analysis of a brain histopathology by any stretch of the imagination.

So with the low power of this study, for this kind of an effect to be identified makes one thing that if we did step sectioning of these animals, this would be an underestimate of the calcification effect. The calcification effects that were these, if we looked in the mouse studies, again the 3, 9, and

the 27.

Now, the three is about a quarter to a half of the human plasma level. Nine is about at the human plasma level. And this is about 10 times.

Females we didn't see it. It was just in the male. And in rats it was a different pattern. So we don't know what to make of those.

We went back and looked at amphetamine and looked at ephedrine. Both of these have carcinogenicity studies in the same strains of animals that were done by the NTP of NIHS NTP studies. And none of these showed calcification findings for these amphetamines.

So the only thing we could say about this is that calcification is associated with aging, especially in mice. And it sort of rings a bell with what Dr. Molliver said, that perhaps this is a manifestation of enhanced aging, CNS aging, a drug-related CNS aging effect that we're seeing. The other thing is that these calcifications could be micro emboli, micro infarcts. But at this point we cannot tell from this study.

So, moving on, I think in terms of relative margin of safety, clinical margin of safety, I think the sponsor has stated and I think we agree

that the concentration of drug and drug metabolite, dexfenfluramine and nordex, in the brain is a determining factor for neurotoxicity in all species.

And this is just a threshold brain concentration of dexfenfluramine and nordexfenfluramine where neurotoxicity may exist. This is my hypothesis, has yet to be really looked at more carefully, but it's possible based on what we know.

The brain concentration of dexfenfluramine plus nordexfenfluramine in rats at the highest dose not associated with long-term depletion. And that's the four milligrams per kilogram per day in the most recent, the rat study that the sponsor has applied, is only about four times the human brain concentration at the maximum recommended daily clinical dose that we now have because of the MRS study.

The brain concentration for dexfenfluramine and nordexfenfluramine at the lowest dose in rats associated with long-term depletion -- and, again, this is from the doses used in the sponsor's most recent study, which were 4, 8, and 16 -- using 8 and 16 as roughly the effect dose give us approximately 10 to 15 times. That's for the toxic dose, the lowest toxic dose estimate.

Some estimates of AUCs based on lots of data from different sources is difficult to estimate, but these are rough estimates. Plasma AUCs for the rat at neurotoxic doses would range from one to four times the human steady state AUC levels roughly by our estimate.

Now, Dr. Moore went over the reassuring qualities in terms of the standard paradigm for assessing neurotoxicity that are used. And these are the GFAP in gliosis, the lack of gliosis in GFAP, cell death as measured by silver staining, axonal degeneration by retrograde transport study.

Well, there is a controversy about whether GFAP in gliosis is really intimately associated with neurotoxic agents in the literature, that the serotonergic nervous system may not be the best place to get gliosis in GFAP. Even though there are some studies that show that they can measure it, there are others that show that they can't. And so this is a controversial area.

In terms of silver staining, it's a good classical method, but it's not very sensitive, especially for the fine fibers and the fact that the fine fibers are associated with the axonal degeneration that we're talking about here and the

very small population of serotonergic nerves in the brain to begin with.

And also timing is everything, you know, just like in the stock market. When these studies were done, when the animals were sampled are critical. If, as Dr. Molliver states, it takes six-eight months to get degeneration and the silver staining is done at two weeks, you don't expect it to be positive. But at the time the silver staining studies were done, no one knew that. So it's no one's fault. It's just that we learn more in this area as we move along.

And it looks like the issues never end. They never end because every experiment leads to other experiments. And in this area the knowledge is just exploding. So you wind up going back again and again. But the fact remains that that may not be a clusive piece of evidence right now. These are all equivocal kinds of findings.

The retrograde studies are being redone by the sponsor. And right now we would characterize them as equivocal. And then, of course, the lack of depletion in the two-year mouse I already dealt with.

Trying to sum up here, then, the questions that remain to be answered or that are pivotal -- maybe they have been answered in some people's minds,

but these are pivotal questions from the animal neurotoxic point of view. And that is the reversibility and slow retrograde neuronal degeneration.

These are the phenomena we're most concerned about. and if long-term depletion of 5-HT is a result of axonal degeneration, can this lead to an eventual irreversible degeneration? In other words, there may be an incomplete regrowth of these axons.

Again -- and we have referred to the observation these effects really last a long time. I don't know of any drugs in which one dose gives you an effect or four doses give you an effect a year or two from now.

If this was associated with weight loss, this would be something. That would be good. But it's not, unfortunately. Then we would have a one-treatment effect for appetite suppression. And I think the benefit-risk would be totally different.

There is a one-year study, as I said, going on right now to address these issues, exact time course, dose-response. The sponsor gave a little of the preliminary data on the six-month. We have to go out to a year.

We have to look at the retrograde transport and all the other biomarkers, in addition to the depletion parameter, and finally the quality of recovery. And, again, Drs. Molliver and Seiden alluded to this.

If the 5-HT content goes back to normal, does this really mean that this is recovery? Is the normal axonal morphology an innervation reestablished or are these mainly the beaded fibers which some people say are non-junctional? In other words, these are not synaptic fibers. So now you have lots of serotonin in fibers that don't make connections with anything.

And then, finally, -- and this is a concern I have -- more widespread use of this, fenfluramine, with other appetite suppression means. Potential adverse consequences of a combination of dexfenfluramine with other marketed appetite-suppressing drugs, which are likely to be used to enhance appetite suppression, are unknown.

And such combinations may potentiate neurotoxicity and reduce the margin of safety of dexfenfluramine because if we have a 10 or a 15 margin of safety and a concomitant drug shifts the dose-response curve to the left, then you have a

different story with a clinical margin of safety. And, in fact, if I'm not mistaken, Dr. Seiden has studies underway that show that very potentiation of phentermine with fenfluramine 5-HT depletion.

So that is the end of my remarks in this area, and I'll entertain questions.

CHAIRMAN BONE: Shall we do that after the completion of the FDA comments altogether or should we proceed with that now? We had decided we would go. I think we're going to take your questions after we get the rest of the FDA --

DR. CONTRERA: Very good.

CHAIRMAN BONE: -- because there is some overlap between the substance there.

The next speaker scheduled is Dr. Stadel from the Division of Metabolism and Endocrine Drug Products, who will discuss epidemiology and considerations or aspects of a Phase IV study.

DR. STADEL: I only have one transparency. So I'll speak primarily initially. I think it's worthwhile maybe to touch on a couple of key issues that are involved in looking at the epidemiologic data. That is, we do use stronger criteria for evaluating drug benefits than risks, but we do use criteria for evaluating risks.

I think it's important to mention Dr. Lutwak showed you the list of spontaneous reported events that have come in. And it's very important for us to go through those kinds of things, to screen them to look for things that look like they ought to be pursued further.

However, those lists themselves may well represent simply the background occurrence of events in the population treated. And I think he meant to convey that, and I just wanted to emphasize as we look through, screen through reported associations, adverse events during use, we've got to look for what merits further investigation, how should it be investigated, and so on.

There's been fairly extensive use of dexfenfluramine in France primarily. And the one thing that has come out clearly that needed to be investigated was primary pulmonary hypertension.

In my opinion the risk data there haven't met criteria for causality that are appropriate to a safety issue. I sort of don't want to debate that. That's my opinion.

I think the findings of specificity with regard to recency of use and duration of use and apparent synergy, some synergy with the independent

effect of obesity fit together in a way that outweighs the likelihood that the findings are simply a function of one of the various forms of bias that you can speculate as a possible explanation.

That's on the one hand. On the other hand, I think it's important to recognize that the absolute risk of this is quite small. Now, I've obtained some data from Dr. Abenhaim and have looked at: If you consider the data themselves, what is the absolute annual incidence of primary pulmonary hypertension that you would attribute to use of dexfenfluramine for longer than three months within the past year?

And during that computation, now, that there takes all durations that are longer than three months lumped together. And it averages effects in heavier and lighter women. But it's a starting place. And I came out with one in 45,000.

Now, that's a point estimate. There's no way I can compute a confidence interval around that. But it gives you an illustration that we are talking about something that does appear to be in my opinion definitely precipitated by the drug in certain individuals. But the absolute risk in the experience in those countries thus far has been rare.

Now, there does appear to be some synergy with the effects of obesity. So that overall average might represent one in 20,000 at the heavier end of the phrase and a lower figure at the smaller end.

The more difficult topic I think is the degree to which that may increase with increasing duration or use. Whether it does or not is a suggestion. I don't think there's enough data to evaluate that in depth. And I think that's an issue for long-term consideration.

I'd like to ask if Dr. Abenhaim agrees with the figures I'm saying since I'm talking about his.

DR. ABENHAIM: Yes, I completely agree. Yes.

DR. STADEL: Thank you very much.

So I think that I would say that on the risk side. This is the one thing that has come up. The neurotoxicity questions, I listened with great interest to material I don't know a great deal about. All I can say epidemiologically is that based on the international experience with the drug thus far, which has been reasonably extensive, that issues have not been brought up for investigation the way that pulmonary hypertension has.

As epidemiologists, that's the way we function. Leads lead to case series, and case series lead to debates. And those lead to studies and so on.

This has happened for pulmonary hypertension. There just haven't been issued raised about neurological abnormalities or behavioral abnormalities that have appeared to warrant this kind of inquiry. And that's my comment on that.

With regard to benefits, I would like to just make the comment that I think that the American Cancer Society study, which was the only one that I know of that looks specifically at intentional weight loss and separates it, does provide some substantial reason to believe that intentional weight loss will bring with it a reduction in mortality and morbidity.

And that kind of reduction if this is causal between how the weight loss is accomplished would greatly outweigh the risk of primary pulmonary hypertension. They were talking 20 percent net reduction in total mortality for the group with obesity-related health conditions.

So, clearly, then the question comes, though: Okay. There is evidence showing that weight loss is being caused by this drug in a responding group of people. There is no direct evidence,

however, that that itself will lead to weight loss-associated reductions in mortality and morbidity.

That's plausible, but it's not proven. And there is a difference. Just as there is a difference in speculating about bias and emphasis, likewise on this side, I would emphasize in your deliberations that that has not been established. It seems plausible.

I would like to make one other comment before talking about a possible Phase IV study. And that is simply to note that fenfluramine is available in the United States and that it has grown from about 60,000 prescriptions in 1992 to a projected estimate of one million this year. So we need to understand that this drug, at least the resuming form of it, is already being used in a geometrically growing rate.

That usage in 1994 was 89 percent by women, spread fairly evenly across the age range of 20 to 59. So I think that as a sort of context for understanding what you're evaluating, the drug is available. It is being increasingly used. And it is predominantly used by women in the United States, as is clearly the case from the control series and other data in France and Belgium, that this data is a drug almost exclusively used by women thus far.

So, with that as background, I would like to just comment briefly on if you decide to recommend approval of the drug, one of the questions you have been asked is: What are the possibilities by way of a Phase IV study?

A somewhat related issue came up in the sense of: What are possible needs for a Phase IV study with the approval of Metformin for Type II diabetes?

And at the advisory committee discussion there, it was recommended that a Phase IV trial be considered. We have since been actively developing and are in the process of employing that trial.

The thoughts here are based upon the general considerations that gave rise to that trial. And that is the concept that what you get in small studies that you can do before approval and what you get in the real world of medical practice are not always identical.

So that a compromise between the extreme precision of the double-blind, fully controlled smaller study, placebo control, versus the desirability of getting data that are referable to a larger population -- I'm talking a little bit about the bridge between those two.

The way this bridge has been evolving in the thinking of a lot of people is that if you use fairly tangible outcome variables, like death, that you don't have to have double-blinding in these kind of phase studies and that when your primary concern is with an outcome that is not misinterpretable, that your need for that is less, and that what you get from open label, active control, randomization is that you can do it in the context of medical practice. It is much easier to deploy.

The care itself of different approved care rests within the medical care system and the payment structure that supports it. So it's much easier to do these studies. One can I think get quite a lot out of them.

So the concept would be one of a very large simple trial, large numbers of physicians chosen to be reasonably representative of physicians who treat this type of patient, so that you get data that tell you what's actually happening in the country for regulating from a federal level, that you randomize, that you get a large number of these physicians, that you get patients numbered in the levels that make randomization sure to control confounding so that you do not have to debate the distribution of baseline

characteristics of the n.

It's pretty well demonstrable statistically that in studies that have hundreds of people in the groups you can run into problems with imbalances. When you add tenfold increase to that and have thousands in the groups, it's a simple matter of averages. Baselines work out. So one sacrifices some complexity of study for size.

Open label randomization. In this case I just put this up as illustrating what would have to be a negotiated protocol. I want to emphasize the first part of this, very, very simple design. Either you add this to how you manage the patients or you don't. And you randomly do that. And you say, "What happens if the physician goes down this pathway of adding this to management of the patient or does not?"

Now, in this case there would have to be some restrictions on that. You couldn't have fenfluramine mixed in with it, for example. It's not quite so simple as this, but the basic principle is a very simple bifurcation: What happens if we go down this road versus that one?

I think given the length of time in the approval studies that one would want something on the order of two years or more. One gets again into

what's negotiable and what's feasible and so on, but I think one would want longer than has been done.

The outcomes need to be very simple in large trials of this type. Obviously we could get compliance with the recommended regimen, which is important in terms of assessing how people are responding to what's being marketed.

You get continuation rates. You get weight loss. And you get as the bottom line in the main issue mortality and serious morbidity. Mortality, the most important outcome, obviously, and all-cause mortality is the most important outcome from the oversight point of view. Is there or is there not an impact on mortality?

So this clearly can be done. One doesn't even have to sort out clearly the cause of death if one sees clear differences. One would like to, but it is secondary.

The way we have evaluated proposals in this way is that I have begun this process with Metformin of formally soliciting a proposal through a written communication to the sponsor that sets forth categorical criteria; that is, that the study be reasonably representative of the intended marketed population, that they describe the procedures that

would be used to detect and control confounding, go through the powered calculations, procedures for validation of data reporting, discuss the timeliness of the proposed study mobilization in relation to the marketing plan, the feasibility.

One very important issue that comes up as the drug is approved for marketing, will you be able to get people to enroll patients in the trial or will the docs do it? That has to be dealt with up front as a feasibility issue; and, finally, investigator qualification.

So if you choose to recommend approval of this drug, I clearly am very much asking support for the idea that we work with the sponsor to negotiate a plan for a large-scale Phase IV trial, which would gather much more data on basic outcomes, continuation plans for treatment. That's my first point.

I thought to put up as a second point that I think it is an issue as: Well, okay. What do we do if it goes to market about surveillance for primary pulmonary hypertension?

Obviously we're going to look at the spontaneous reports that come in. Sometimes that creates for me as many problems as it does answers. They're very difficult to quantitatively interpret

spontaneous reports.

Publicity about an issue will raise the reporting rate. Then it will fall off. And you really have quite a bit of difficulty once you have identified an issue.

So mortality surveillance, we trying to work with CDC to work out a national mortality statistics in the national death index, some way of following mortality in the categories that would cover primary pulmonary hypertension to see if one would detect a large rise only after a lag time. It is, however, very nice in terms of its being national and a fairly definite endpoint.

And the last possibility that would I think need to be discussed with the sponsor and ourselves that's really kind of come to me recently was: Would there be value to try to look within the U.S. in case control comparisons, especially if one could identify co-factors that would sort out the people who get this? Is there any practical point to get out of it? And I haven't given much thought to that other than to put it on the list.

Thank you.

CHAIRMAN BONE: Final comments from the agency before we discuss and ask questions about the

various agency presentations will be from Dr. Gloria Troendle, Deputy Director of the division.

DR. TROENDLE: In the face of an increasing incidence of obesity in this country, we are anxious to have new therapies, including new weight control drugs. So far all approved weight control drugs act by decreasing appetite, as does dexfenfluramine.

Dexfenfluramine is the active inantimere of a racemate that has been marketed in this country for 23 years. It is not known to differ from fenfluramine. Dexfenfluramine is not known to differ from fenfluramine, the racemate. And it is not a unique addition to our armamentarium for weight control.

What is unique about this drug is the proposal to label it for long-term use. So benefits and risks must be evaluated with a long-term drug administration in mind.

First I'll discuss benefits a little bit. At our July Advisory Committee meeting on statistical methods to evaluate efficacy of weight control drugs, Dr. Marcus described a display that he had found impressive. I have prepared displays similar to what he described using dexfenfluramine data.

At the top is the completers, and at the bottom is the LOCF, last observation carried forward. There were some questions asked about that last observation carried forward. It does seem that the patients who drop out may be dropping out because they're beginning to regain weight or lose their effectiveness. So I think that there is some bias, but I think there's bias in any way that we look at the data because of the dropouts.

This shows that the patients who gain weight: the total number, percent of patients who respond by weight gain; then the ones who have less than a 5 percent gain; then the 5 to 10 percent gain; and, lastly, the 10 percent gain. So on the right we have the most responders. And that is where we have the most effectiveness.

In an obese population, dexfenfluramine produces a small mean weight loss; that is, less than five percent between drug and placebo at one year, less than four percent difference.

However, in controlled trials, a subgroup of the treated population sustains a more substantial weight loss. If we define responders as those who lose at least 5 percent of initial body weight, the responders are -- 77 percent of drug-treated

completers were responders. In the placebo group, 50 percent of the subjects were responders.

The difference between drug and placebo was 27 percent. And that is the effect that can be attributed to drug, at least a five percent weight loss for one-quarter of the treated patients.

When we use, to the right, the right side of the slide, the last observation carried forward population, one-fifth of the subjects lose at least five percent. And, surprisingly to me, the results are just about the same if we define responders as those with a 10 percent weight loss.

The differences are not very great. Those with a 10 percent weight loss have a drug-attributable 10 percent weight loss of 25 percent in the completers, 19 percent in the LOCF.

The responders cannot be identified prospectively, but it might be possible to discontinue. And it was proposed that they discontinue treatment in those patients who are not responding after two or three months.

However, the responders are 77 percent of the treated patients. So drug would be continued in three times the number of patients who require drug for a response.

Adverse effects. Adverse effects are not very impressive. They are relatively benign. The drug can always be discontinued if the side effects are bothersome.

The brain serotonin depletion seen in animals has no identified clinical correlates. And I wanted to ask Dr. Molliver if he could suggest any if he is aware of any effects that might be expected from the disturbance of the RAPHE that he was pointing out to us.

We have a few reports of neurological findings, such as the short-term memory loss. And there are no studies that are adequate to detect a relationship to drug so far done.

The anorectic drugs taken for a period of at least 90 days appear to produce pulmonary hypertension, but rarely. Dr. Stadel mentioned that.

We do not know whether patients treated for 12 to 24 months or longer will have a substantially greater risk. It will be of interest to observe whether the great increase in use of anorectic drugs in recent years will be associated with any increase in the overall incidence of pulmonary hypertension.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Troendle. We're, as everyone can see, a little behind our original schedule. But I think that it's essential that we have the time here to discuss the FDA presentations while they're fresh in our minds. And then we'll take our break and start the discussion and question period.

If it's necessary to go a little past 5:30 to complete this, we will, but I'm hopeful that the fact that we've had a very good discussion of a number of points during the course of the day will permit that allotted time to be used sufficiently.

I'm going to ask the members of the Committee if they have questions for the FDA presenters. And maybe we could start with the medical review by Dr. Lutwak in particular. Dr. New?

DR. NEW: Dr. Lutwak, this may seem very naive, but you said that fenfluramine, the racemic mixture, has been in use since 1973. And I don't know how many people. You said a million prescriptions were written in --

DR. LUTWAK: No, no.

DR. NEW: I'm sorry.

DR. LUTWAK: It almost hasn't been used at all.

DR. NEW: Fenfluramine has hardly been used?

DR. LUTWAK: Right, until a few months ago, until the past year. There are no available figures in the database before 1990 because the numbers were too small, the prescriptions written.

DR. NEW: So you mean this drug was on the market and nobody used it?

DR. LUTWAK: Nobody used it until '94, 364,000 prescriptions written. And the projected estimated number for this year is 1,100,000.

Now, if we do a little bit of speculation using Dr. Abenhaim's numbers and Dr. Stadel's numbers of an incidence of one in 20,000 and the fact that it takes a duration of use before pulmonary hypertension is seen, we can predict approximately 100 cases of pulmonary hypertension as a result of this year's prescriptions.

DR. ABENHAIM: I'm sorry. Just a comment on this last thing. Are you talking about prescriptions or individuals? Because the one in 20,000 that Dr. Stadel proposed was per patients, not --

DR. LUTWAK: Per patient. I'm sorry.

DR. ABENHAIM: Oh, this is prescription?

DR. LUTWAK: This is prescriptions, but then you figure one prescription for three months.

CHAIRMAN BONE: All right.

DR. NEW: I guess I'm not getting my right answer headway. So I want to just pursue this a minute. Okay. So do you agree that it's been used for five years?

DR. LUTWAK: Yes.

DR. NEW: Okay. Do we know what the reporting has been in terms of neurological, cognitive, other brain damage, suicide, pulmonary hypertension? What's the story on fenfluramine? And why is it not applicable to what we're hearing now on dexfenfluramine?

DR. LUTWAK: Well, part of the problems is I think that there were very, very few prescriptions written for it until this year. We're talking about a very low denominator. We're talking pulmonary hypertension is a relatively rare disease and requires a large denominator to be able to see it.

DR. NEW: Was this not used in Europe either?

DR. LUTWAK: We have very few reports. There are very few reports that have come to the agency on fenfluramine.

DR. NEW: Okay. So, then, your response to my question is the experience with fenfluramine cannot be used to evaluate the toxicity or the efficacy reports of dexfenfluramine?

DR. LUTWAK: Yes because the pattern of use has been different than the pattern of use that's projected for this, for dexfenfluramine.

DR. NEW: Thank you.

CHAIRMAN BONE: Other questions that would be directed particularly to Dr. Lutwak? Yes, Dr. Sherwin?

DR. SHERWIN: Just to remind me, there was one slide that you showed us about pulmonary hypertension. And there were 100 cases in a post-drug phase. Which drug was that? I just want to be sure I get this straight.

CHAIRMAN BONE: Wasn't that from the sponsor's most recent safety report?

DR. LUTWAK: Yes, the sponsor's report for dexfenfluramine.

DR. SHERWIN: Okay. Now, how were those 100 cases? How many patients are we talking about? And how is it documented? That was the thing that struck me as being kind of high, and I didn't understand that.

DR. LUTWAK: These were 100 cases that were reported to the agency by the --

DR. SHERWIN: U.S. treated patients?

DR. LUTWAK: No. These are worldwide.

DR. SHERWIN: Worldwide treated patients?

DR. LUTWAK: Yes.

DR. SHERWIN: But we don't --

DR. LUTWAK: But we don't know what the denominator was.

DR. SHERWIN: But it can't be that much; right? I mean, in other words --

DR. LUTWAK: These are 100 case reports.

DR. TROENDLE: Something that happens with reporting of adverse effects is that something will become public knowledge. And people begin looking for cases. And they may even report some that happened a few years ago. I'm not sure what is accounting for this, but I know there are some factors.

DR. SHERWIN: There's a clinical diagnosis not based on anything specific to make the diagnosis. Is that right?

CHAIRMAN BONE: I think the sponsor evaluates the quality of information. Those are the sponsor's cases that they have recognized. Perhaps the sponsor could help us by answering the following

specific question: In any year how many patients worldwide that would be the way the denominator's for that take this drug for more than three months? How many people, in effect, that are on dexfenfluramine?

DR. SHERWIN: That's what we've been talking about.

DR. COOPER: Well, with spontaneous post-marketing experience, there's no way to track the duration of usage. So we don't know for a patient population or for given individuals how long the drug is being used.

The number of 101 cases of primary pulmonary hypertension represents a 10-year post-marketing experience involving approximately 10 million or 10 million plus patients who have treated with dexfenfluramine.

Those cases have been evaluated carefully. There's quite a bit of clinical data that has been captured because of the fact that most of these diagnoses require cardiac cauterization.

So data is captured. We have done an extensive analysis of these cases. And I think if I can ask Dr. Thompson to make a very brief comment about these cases because I think it's --

CHAIRMAN BONE: We're really discussing

the FDA's presentations here. I absolutely insist on one sentence. I mean, just be limited to one sentence.

DR. COOPER: Well, Dr. Faich stood up. So I'll let him give the one sentence.

DR. FAICH: Okay. One sentence. The 101 cases consisted of 63 who had exposure prior to dysthymia.

That is, there were a number of these cases that may well have had onset of primary pulmonary hypertension before they got the drug.

That is, this is protopathic. This is an obese individual, develops shortness of breath, and then gets treated for the obesity.

Of those 63, 43 were known not to have underlying cardiac or collagen disease. So it is 43 that look like they are unconfounded.

CHAIRMAN BONE: Dr. Abenheim had a comment.

DR. ABENHEIM: I might maybe give you some information on your question about the percentage which I -- more than treatments.

CHAIRMAN BONE: Please.

DR. ABENHEIM: From our study, and from other data that I have seen, you can count around 10

to 15 percent of the users of the prescription for dexfenfluamine in Europe, to be more than three months total durations. I mean, over one year.

So I think if you would apply this to the denominator, I think it would count about 10 or 15 percent of the total prescriptions.

CHAIRMAN BONE: It sounds like more than the 2 million people exposed for that length of time then, and that would be a fair estimate of the denominator, which wouldn't be too far off on the ratio from the other discussions.

I think Dr. Rich had a comment about that. The medical impact of this? In terms of the cases, also on this same subject, and then we will move on.

DR. RICH: If the issue is the risk, I really think there has been a lot of confusion about risk versus benefit.

I think the only person who gave an estimate of lives saved was Dr. Faich. Didn't you have a table that had if you have a 5 percent weight reduction, lives saved per million per year equal 10 percent.

Do you recall what the number was for the 5 percent?

DR. FAICH: Well, the total, it is 280 for

the package. You don't just get 5 percent.

DR. RICH: I understand, but I am just asking for the 5 percent. Do you recall what that was, because the point is, when you say that there will be a reduction in heart disease of 10 or 15 percent, you are talking about over an indefinite period of time.

If we talk about lives saved, per million, per year, and deaths per million, per year, getting PPH is a death sentence in this country, and I think you have to project that there will be a minimum of 20 cases of PPH per million, per year in this country, and I am not sure that there is compelling evidence that there will be more than 20 lives saved per million, per year, and I think that needs to be put in perspective.

CHAIRMAN BONE: All right. We have had quite a bit of discussion on that. Thank you very much.

Let's return to discussion of the FDA presentations. Dr. Borhani had a question for --

DR. BORHANI: I have a question about neurotoxicology for whoever would like to answer. I was under the impression that some PET and MRS study was done in man by sponsor.

Am I correct on this? Can you give me your feelings or results or what opinion you have on the results of those two types of studies?

DR. CONTRERA: All of our concentrations, in other words, all of the estimates that I made on the basis of -- in humans, the brain concentrations of the drug that I made in humans used for our estimates of relative effectiveness and exposure came from the clinical MRS study because I think with fenfluamine we just were lucky in that the structure is a trifluromethyl structure.

So you could do MRS and estimate the concentration in the brain. If we didn't have that structure we couldn't have done it.

So, yes, that was used.

DR. BORHANI: Are you comfortable with the methodology and the conduct, just generally speaking of those two --

DR. CONTRERA: Well, the company did a -- I think -- a good job. They ran concurrent and alongside the human study a Rhesus, no, a baboon, no, a Rhesus monkey study in which they did the MRS, and did sacrifice and chemical analysis, so that you had a validation of the concentrations and error limits of the MRS estimates in humans based on a parallel

primate, you know.

So that seemed fair to me.

CHAIRMAN BONE: All right, other questions or comments from the committee?

I should say specifically questions that would relate to the clinical review, Dr. Lutwak's review, what about in relation to the neurotoxicology review.

Any further questions about that? Dr. Illingworth has a question.

DR. ILLINGWORTH: Just one question. Are there any good means of assessing long term clinical users?

Let's say there is a two year trial, what would be the best methods of assessing clinically, methods for serotonergic depletion of neurons or depletion of serotonin in patients who have been on this drug long term?

DR. CONTRERA: That is a problem I think we are all struggling with, coming up with a protocol which is reasonable.

Even though it has been proposed, for example, spinal 5HD and 5HIAA could tell you, but that is not something you do lightly, and maybe perhaps, and this is just off the top of my head, if people

that were on it for many years have similar kinds of effects, like the calcification, those, there are clinical ways of assessing that clinically, in literature for neurotoxins you do see some clinical data on using PET or some other imaging, but perhaps Professor Seiden, I think has a --

PROFESSOR SEIDEN: There is a couple of views. If you stimulate certain nerves in the brain with a serotonergic you get a proactive release and the kind of proactive release you get will be proportional to the seroton available to be released in the hyperthalmus.

So that is one indirect measurement of whether or not all of the serotonergic neurons are intact.

The second method is she has, as you mentioned, looking at metabolized, and the third method which is under development would be as right as the PET scan if you can find a reliable ligan that binds specifically to the seroton transporter molecule, you should be able to see in a quantitative way how many transporters there are in the brain of a person who has been exposed to fenfluamine.

There is three different methods that all have some promise. They all have some problems, but

it is a thing that is doable and in my view, should be done.

CHAIRMAN BONE: All right. I have a question for doctor -- oh, excuse me, Dr. Sherwin, please go ahead.

DR. SHERWIN: I am struck by the fact that I haven't heard anything about performance on neuropsyche testing, for example.

There must be some information perhaps. Have you seen any information provided with respect to performance in some way?

DR. CONTRERA: No. I have seen information in animal studies, like I haven't focused on the clinical data.

I know in the animal studies, even in the rodent studies, there was enhanced aggression and problems in dealing with that affected animal.

I do not know with the --

DR. SHERWIN: However, there are studies in humans for MDMA that Dr. Brigan has provided. It would be applicable if it has to do with fenfluamine, I am not saying that they have been done, and it is surprising to me again that no neuropsychological tests have been applied to these individuals, given the amount of time that this has been an issue and we

don't have the data on hand.

DR. COOPER: It has been done. There has been some neuropsychological testing done like you are describing.

CHAIRMAN BONE: How about if we get into that at the discussion period. I would like to get through discussion of the FDA presentation at this point, and then we have substantial amount of time set aside for discussion, and there will be some questions, obviously, that we will go back to the company with, and additional questions may come up as we go along.

I had a question for Dr. Stadel, and that had actually, it was prompted by one comment that he made, which was that he felt that if you could randomize his patients in a phase IV study who were seeking treatment for obesity to treatment versus no treatment without placebo control or blinding, if I understood correctly, and it strikes me as a clinician and clinical investigator that there would be a very major problem with the subjects or patients in this case who would be assigned to no drug, removing themselves from the participation or seeking alternative medications from other physicians.

DR. STADEL: I think yes. There are two

issues raised. One is placebo, and the intent of a phase IV study -- if a drug is approved is to see how it racks up against what is currently being done, not how it racks up against doing nothing.

So the randomization would be to adding dexfenfluamine versus the other ways that the people manage obese patients.

CHAIRMAN BONE: So you would just compare them with whatever other treatments?

It wouldn't be -- the way you rephrased it at one point it was a question of adding on to whatever else they were taking as opposed to just using that as an alternative to other treatments.

DR. STADEL: No. Let's see, let me try to put it in a language that is best -- language that is specific to how we have written the protocol otherwise is randomization to adding dexfenfluamine to the treatment of the patient versus "usual care" of that physician or those patients.

DR. BORHANI: Excuse me.

CHAIRMAN BONE: Yes, Dr. Borhani.

DR. STADEL: We take an individual physician's patients and bifurcate them, either they manage them as they have been managing them, you would have to exclude here fenfluamine or they add

dexfenfluamine.

It is as simple as that.

CHAIRMAN BONE: Well, the point is that it isn't just a question of adding it or not adding it because the patients who don't have it added will feel that they are missing something.

DR. STADEL: That is an issue of validation. I did address that one of the things one has to do in developing a protocol for such a study is address the issue of validation of protocol analysis and feasibility.

Those have to be addressed and I think there is a question that arises in these kind of things and those are legitimate issues to be concerned about.

DR. BORHANI: There is a precedent that easily, relatively easily, can be repeated and the precedent is in the clinical trials in the secondary prevention of coronary heart disease, with approved "methods and drugs" for lowering serum cholesterol and patients can be randomized and they are indeed being conducted now in this country.

They are randomized into the routine treatment accepted medically using the drugs even if they have to, that are approved by the FDA, and then

randomizing the participants into cases and controls; controls will receive placebo, and the cases will receive, in his case, DF.

I think that kind of randomized clinical trial can be conducted, there is a precedent for it, and if we talk about phase IV or whatever.

I hope that is what you have in mind. That is what we can do.

CHAIRMAN BONE: Thank you. Dr. Troendle and then Dr. Kreisberg.

DR. TROENDLE: Okay. I was going to comment on this. It seems to me that we should find out what interneuron did exactly with their patients, because 50 percent of their placebo patients were 5 percent of body weight loss responders, and if you have that high maybe you will have enough patients left on the regimen to compare even if it is an open study. They are effective.

CHAIRMAN BONE: Thank you. Dr. Kreisberg.

DR. KREISBERG: Dr. Bone, I assumed that Dr. Stadel's presentation was simply an example, and that the specifics in it were not specific.

CHAIRMAN BONE: Fair enough.

DR. KREISBERG: Because I think there is a lot that could be argued about over the trial that

he has proposed.

CHAIRMAN BONE: I was just trying to make a general comment to the effect that that was one of the sorts of things.

I think it is probably not fruitful to pursue the details.

DR. STADEL: May I just make one sentence that is true?

CHAIRMAN BONE: Yes, please.

DR. STADEL: The specific is a procedure of solicitation and review. I simply described, very briefly, what we have done with another problem.

It might no apply exactly. The procedure is to solicit a written proposal, have it address certain criteria, establish an ad hoc written peer review panel, put the feedback back and forth, and that is the procedure that we have followed and I had meant to have a line on there for procedure.

CHAIRMAN BONE: All right. So you were really trying to use that as an illustration of an approach rather than a specific design. Thank you.

Are there other questions that are directly related to the presentations by the agency staff from the committee.

Thank you, what we will do then is I have

3:47, we are really going to reconvene at 3:55 and start talking at that time.

(Whereupon, a 10 minute break was taken at 3:57 p.m.)

CHAIRMAN BONE: The committee is back in session or will be in a couple of seconds here, just to let these people sit down.

Shortly I will give you the company a moment to be thinking about how they would like to respond to this.

In connection with a couple of questions that came up in earlier discussions, and a comment that we wanted to hear from the company, this all relates to this whole neurotoxicity business.

Two questions, sort of asked on behalf of the committee, I think. They will be one, the clinical information we have from the clinical trials, and particularly the long term clinical trial, the one year clinical trial, so far does not address neuropsychological testing.

I understood from a comment a moment ago that the company has some information on this subject. I would like to ask them to describe, concisely, we are really short of time, and it is not -- just the facts, please -- their findings, and I want them to

indicate which of those findings have been submitted to the NDA.

The second question which I would like to have addressed second will have to do with the toxicology and the brain anatomy, the brain structural changes, long term follow up and looking at the tangles questions and wither they have found a zero-effect dose in studies done along those lines.

The first question has to do with please describe the information that you have, if you have it, about neuropsychology testing, under what circumstances and, first of all, please state whether this has been submitted to the NDA.

DR. COOPER: Okay. There have been two levels of studies done that I think address some of the questions that the committee raised.

One, specifically, neuropsychological testing, a battery of neuropsychological testing was performed in one of our double-blind, placebo control trials, a six month study of the so-called Noble trial, and I will hand over to Dr. Rudy Noble who performed that study, that data has not yet been submitted because it is a relatively recent analysis that has just been completed.

The other data relates to, I think a

comment that perhaps Professor Seiden made about using surrogate measures, prolactin levels, ACTH, that data has been published.

It has been submitted in the NDA, and Dr. Bruce Campbell will say a very brief comment about that.

DR. NOBLE: Hello, I am Dr. Noble. I will make this very short because my voice is giving out and it is late in the day.

Anyway, I am the director of the obesity clinic in San Francisco, have been so for the past 30 years, and have personally treated 10,000 overweight patients, and done about 100 different studies testing various anorectic agents.

A lot of these studies have turned out negative, but let me tell you about a study I just finished, which is very pertinent to what Dr. Sherwin asked, and perhaps this will answer your question.

We took 80 obese patients. We treated half of them with dexfenfluamine, 15 milligram, twice a day, and the other half, matching placebo.

We followed them for six months. They were either treated or not, and then a one year follow up where everybody got placebo.

So six months of treatment, one year

follow up, eighteen month's study. Along the way we did a whole battery of psychiatric tests.

We consulted with all sorts of psychiatrists to see what will tell us is there any neuronal damage. What would be a good marker here?

So are we to test like the MMS where we asked them to spell the word "world" backwards, something I don't think I could do at this point, along with a whole host of other questions.

Sixty-five little questions about mood. Twenty-one other questions about mood. Different mood scales, Stanford sleepiness scale, and to make it very brief, as I said, we did this while they were treated for six months, then we followed them for a year later and as a clinician, not a neuroanatomist.

Let me assure you all, we saw absolutely no evidence of any impairment of any cognitive function.

The scores stayed pretty much the same, same as placebo, and I am just speaking as a clinician, I don't know anything about neuroanatomy.

We saw no evidence of any loss of cognitive function.

CHAIRMAN BONE: Right. Now is this the study that was, if I understand correctly, the weight

data from this --

DR. NOBLE: No. That was another study.

CHAIRMAN BONE: In other words, no part of this study has been submitted to the FDA?

DR. NOBLE: No, not at all, no. We just finished it.

CHAIRMAN BONE: Okay. So there had been no agency review at that point?

DR. NOBLE: Absolutely.

CHAIRMAN BONE: Thank you. Maybe I should ask one follow up question just to that. In the 30 milligram b.i.d., it will be to Dr. Cooper, probably, in the 30 milligram b.i.d. dosage there was a significant excess.

I realize that is not the dosage you are making a claim for. There was a significant excess of patients with abnormal thinking described in your results.

Can you characterize what that means and would that not be an appropriate agenda, let us say, for doing neuropsychological testing in the future to look for more subtle examples of the same sort of problem.

DR. SANDAGE: The coating convention we used was code starts, codes is abnormal thinking. The