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ADVISORY COMMITTEE

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P R O C E E D I N G S

9:25 a.m.

DR. DETRE: I would like to call this meeting to order, and welcome everyone to the 28th meeting of the Psychopharmacologic Drugs Advisory Committee.

My name is Thomas Detre. I am from the University of Pittsburgh, and the chairman of this committee.

Next, I would like to introduce those people arcund the table, or more precisely, ask them to introduce themselves.

DR. HAYES: Tom Hayes.

DR. PRESKORN: Sheldon Preskorn, University of Kansas, Wichita.

DR. STANLEY: Michael Stanley, Columbia University.

DR. STEINBACH: I'm Sandra Steinbach of Dallas, Texas.

DR. KAPIT: Richard Kapit, FDA.

DR. CHI: George Chi, FDA.

DR. LEE: Hillary Lee, FDA.

DR. CHIEN: Ching-piao Chien, from the University of California, Los Angeles.

DR. KESSLER: Linda Kessler, FDA.

DR. LEBER: Paul Leber, FDA.

DR. DETRE: Ladies and gentlemen, Mr. Abramek has a few administrative announcements to make before we begin the meeting. Following him, Dr. Leber will make a brief welcoming

statement.

Mr. Abramek?

MR. ABRAMEK: Thank you, Dr. Detre.

Again, as Dr. Detre has indicated, this is the 28th meeting of the Psychopharmacologic Drugs Advisory Committee. My name is Fred Abramek, and I am the executive secretary of this committee.

In regard to administrative announcements, there are agendas, handouts, et cetera, on the front table, and I hope those of you -- everyone in the audience does have a handout, and if you would be kind enough to sign our roster, that would be very much appreciated.

The acoustics in this room are rather bad, and for that reason we ask that all speakers, whether they be members sitting around the table, or speakers from the audience who have been recognized by the chair, to be sure to speak into a microphone. It will make our transcriptionist's and recorder's jobs a lot easier.

In addition, this room is, as the day wears on, will become increasingly hotter, so please make yourselves comfortable.

If anyone desires to make comments in the open public session, which will immediately follow Dr. Leber, we ask that you not speak until you have been recognized by the chair, come forward to the microphone, and identify yourself

and your affiliation.

Statements made must relate to the issues being considered at this meeting, or be of general interest to the committee at large.

Smoking is not permitted in this room, and for those of you who do smoke, smoking is permitted outside this room elsewhere in the building. There is a cafeteria on this floor for those of you who need either a drink or a refreshment. Make either a right or a left-hand turn as you go out the door, and the same for restrooms. Regarding the drink containers, newspapers, et cetera, it would be very much appreciated if those of you who brought something into this room could bring it out with you. It would certainly make my job a lot easier -- or, at the very minimum, deposit it in one of the numerous receptacles around the room.

For those of you who wish to record this meeting, recordings are allowed. Just a reminder, though, that the recordings are unofficial in nature.

A review of the agenda by Committee Management Personnel Branch indicates that no committee members require limitation on their participation at today's session. However, in the event that there might be some things we have overlooked, I now ask the committee members, is there anyone who feels that they have a conflict of interest or a potential conflict of interest which might preclude them partaking in

today's discussion?

(No response.)

MR. ABRAMEK: There have been no indications of potential conflict of interest.

I would now like to mention the fact that Dr. Hillary Lee, who is sitting to my right, is acting -- serving as a consultant to the agency, and will be presenting the efficacy review of fluoxetine hydrochloride today.

Dr. Lee is a former FDA employee, and her participation has been cleared by the Committee Management Personnel Branch also. And one last item is that fluoxetine hydrochloride will be the only issue discussed by the committee today. Haloperidol is on the docket for tomorrow.

Dr. Detre?

DR. DETRE: Dr. Preskorn would like to make a brief statement.

DR. PRESKORN: Yes. I have been approached by Lilly about doing a study with fluoxetine, although we have not entered into doing such a study at this time.

DR. DETRE: Thank you very much.

Dr. Leber now has a few remarks to make. Dr. Leber?

DR. LEBER: I just wanted to take the opportunity to welcome the committee again, officially, to thank you for coming.

I would like to welcome two new members of the committee who are here for the first time today -- Dr. Sheldon

Preskorn, who is sitting at the right front, and was kind enough to join us. He is from the University of Kansas Medical Center; and Dr. Walter Carter, who is going to serve as our biometric anchor and outside expert. Thank you two for joining the committee.

In addition, I want to offer my personal thanks in regard to Dr. Detre, who is serving as our chairman, a job that isn't always so much fun. I thank you.

With those remarks, I think we can probably get on to the open session, I hope.

DR. DETRE: Ladies and gentlemen, the open public session is now in progress. Although neither Mr. Abramek nor I have been approached by anyone requesting time to make a statement, the floor is now open for comments.

Does anybody in the audience desire to make any comment at this point? Yes?

Yes, please? Would you come forward?

DR. MYERS: I'm Dr. Myers. It's inaudible back here and it may be that that microphone is out of order.

DR. LEBER: I think it is. I thank Mr. Myers. The problem may be the microphone system, but I'm not really certain. Are people hearing me at this point?

Let me switch microphones. Are you now hearing me? (Pause.) I'll tell you what -- if you're hearing me, raise your hands.

Stand up if you don't hear me.

(Laughter.)

I'm having a hard time reading the data. I think that the -- that I will try to yell, and if I run out of steam, you can probably pick it up in the transcript, for a small fee, later, but I will do my best.

DR. DETRE: Dr. Leber would like to make some introductory comments.

DR. LEBER: Okay. I'm now really moving into the formal session on fluoxetine, a drug product which the Division has concluded is an antidepressant drug, and one which we believe, at this stage of our review, is a reasonably safe antidepressant drug.

I will make clear in the following remarks why we are not yet to make an official recommendation that the product be approved, and are not really asking the committee to address that question at this stage in the review process. We are really, because of timing of when we come to advisory committees, looking at the issue of the evidence in hand. There is still evidence to be submitted regarding the dose-response relationship and the labeling of the product, a final safety update, and other matters that are yet to be determined, but we felt that we wanted to get a reading from the committee at this time of the direction in which we are going.

And, with that understanding, let me go over some

generic issues and points that I think might be worth discussing, because, in truth, the FDA guidelines on antidepressant drug products were issued almost eight years ago, and as a result, I think the information out there about how the Division approaches the review and assessment of antidepressant drugs may be a bit stale, and I think it might be useful for the committee, in view of its two newer members, and in addition for the audience, to go over how and why we integrate what we do, with the Food, Drug, and Cosmetic Act, and with the field of antidepressant drugs.

Now, it isn't only, I suppose, with antidepressants, but in terms of tomorrow as well, what we do may be important. The Division has clearly identified some studies, and rejected others, as probative sources of evidence of efficacy bearing on the two drug products that we will discuss over the next two days. It might be useful for you to understand why we've done that.

To do that for you, I want to start with the basic issue of the law itself. Now, under the Federal Food, Drug and Cosmetic Act, a drug can't be approved, introduced into interstate commerce, and sold, unless its vendor, someone we call a sponsor, submitted to the agency, and the agency approved, a new drug application for that product.

Now, there is a bias in the Act, and the bias in the Act is to approve new drugs. And, thus, the language of the

Act says that we should go ahead and approve such applications unless we make certain negative determinations.

Now, what are those determinations? Well, there are six of them in the law. One says that we should not approve an application if we find that there are not adequate tests by all methods reasonably applicable, to show that the drug will be safe -- and I'm paraphrasing, if it is used as directed in its labeling.

The point, again, for you all to remember, is safe in view of the labeled use.

Also, if there are such adequate tests available, these should be considered, and if we find that the drug has adequate tests, we can approve it, unless these tests show that the drug is unsafe, that is, a positive finding of a lack of safety, or the tests fail to show that the drug is safe. Again, all this emphasis on safety and labeling.

We should also approve the drug, unless we find that its manufacturing processes are not adequate to insure that the drug will be what it claims to be -- that is, that it will be chemically okay, and it will be pharmaceutically correct, that it will provide what it says in its labeling, in terms of the strength, purity, identity, and so on.

We are also instructed to approve unless we find that the information we have in front of us, from all sources, is adequate. If it is inadequate, we shouldn't even make a

decision.

Now, in 1962, added to the law was the concept that we should approve a drug, unless we find -- and this, I do quote, "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have, under the conditions of use prescribed, recommended or suggested in the proposed labeling."

That's the old efficacy; and finally, of course, what has been around in the law since, probably, the progenitor of the law, in 1906, is the need that the labeling of the drug not be false or misleading in any particular, because if it is, we shouldn't approve it.

Now, again, take note of what these instructions stress. Safety is mentioned in three of the six items that we are supposed to consider for non-approval. Also note the nature of the evidence required to demonstrate efficacy. It comes from adequate and well-controlled clinical investigations, and note that all of these requirements are linked to the claim that the sponsor makes for his drug product.

In summary, the Act is very clear that a decision to approve an application is going to depend upon adequate evidence, developed in a sufficiently comprehensive testing program to permit us to make reliable judgments about the product's safety, its pharmaceutical quality, its efficacy, and its labeling accuracy.

Now, obviously, there is more than one theoretical way to carry out the instructions of the Act, and consequently, to insure its orderly and efficient enforcement, the agency has developed and promulgated regulations and policy that are designed to insure that we accomplish the aims of the Act.

Now, these regulations are a result of a process called notice and comment rulemaking, that seeks to insure that everyone who is affected by the language of the Act, and the requirements of the Act, has a role in the generat of these regulations, that is, manufacturers, sponsors, physicians, single-interest constituencies, the broad base of consumers -- all can participate in this process; and, thus, the regulations governing new drug applications pretty much reflect not only the intent of the Food, Drug and Cosmetic Act, but the collective wisdom of society, and in particular the scientific community.

Now, obviously, collective wisdom usually speaks to generic issues, so field-specific and/or drug-specific issues rarely are covered in regulations. Instead, these issues are covered by guidelines. I mentioned we have one that is somewhat stale, and policy; and policy is what I want to get.

Now, to better serve us as consultants, and you do serve the agency, I think you ought to understand about our division's specific approach to antidepressants. I think the approach, and again, I'm biased, melds requirements of law,

scientific principle, and common sense.

First, let's go back to the issue of efficacy. The Act is very clear that probative evidence of efficacy must come from adequate and well-controlled investigations, including clinical investigations.

Now, the evidence must be substantial. "Substantial," by the way, is a term of art, and I wouldn't attempt to define it without counsel, and even then I'm not sure it can be precisely defined. But I would like you to listen to the description of what substantial evidence is attached to in the law. It is evidence of such quality that experts, qualified by relevant training and experience, could rely upon it, to conclude fairly and responsibly that the drug will have the effect it purports or is claimed to have in its labeling.

Again, it's got to come from controlled clinical trials. It must be evidence that one can rely upon, and it must be linked to the labeling claim.

Now, obviously, even experts can disagree on what substantial evidence is, and they can certainly agree or disagree about what adequate and well-controlled clinical trials are, and consequently, in our regulations, we have made an effort to define what we interpret, that is, the agency interprets, adequate and well-controlled trials to be.

As a matter of fact, in the NDA rewrites, you all know that the description of such trials, at Part 314126, has

been revised slightly, so that there are now a list of five types of clinical controlled conditions that could be used in study of drug products.

I think you know these are the placebo control, the no-treatment control, the active control, the dose-response study, and the historical control.

Now, these are generic considerations of trial design, and I think it is critical to understand that they should not be applied willy-nilly to all drug classes. Some drug classes have one design that's appropriate, others another; and in particular, in the study of antidepressant drug products, the Division will not consider evidence, as you might expect, derived from studies that are controlled historically, that use no-treatment controls; and, most controversially, from studies that are active-only controls.

Now, I think you understand that the community accepts that no-treatment controls and historical controls are open studies, and can't be blinded, and therefore it is fairly obvious why the subjective reports of investigators and patients couldn't be relied upon, in some studies.

The arguments on active controls, I think, is worth a little discussion, because, if you look at the fluoxetine submission, a large number of active control studies were done, and it is not unique to Lilly's submission, but it is quite a common practice.

Why are these studies so popular? Well, one, it's alleged that they're easy to get to IRB's, and I think they are. They appear to pose no added risks to patients. The original standard drug is standard therapy, and the new drug is presumed, perhaps incorrectly, to be an effective and safe agent when the study is conducted.

Beyond that, they are easy to recruit patients to. There is a lot of resistance to going into studies, as people will tell you, if there is a good chance that you will be assigned to a no-treatment condition, basically the placebo condition, even though we all know that the effect of placebo, or what is subsumed under placebo, can be quite dramatic in the treatment of depression.

In any case, the problem is that active-control trials, when they are used, are often designed not to demonstrate a difference between a new drug and the standard reference agent, but are designed to show no difference. This is the "inability to show a difference" situation, and under that situation, the interpretation of that outcome is ambiguous.

There is simply no way to know what that means, even though one could sanguinely assume that it means the drug is effective.

But if you think for a moment, there are a variety of things, even in trials with adequate statistical power to detect a given size of a difference, it could account for a

failure to distinguish drug and a standard control -- being sloppy, having the wrong incentive, as Dr. Temple has pointed out many times -- simply having a treatment-resistant patient set, having an investigator who is careless; all these things may contribute to the failure of an active-control trial to discriminate, and consequently we can't tell for certain.

When you can't tell the difference between an active control and a new drug, what it means, it may just mean that the new drug is no different from placebo.

Well, why do I say that? Well, it is not just academic speculation. In two NDA's, one of which we have publicly already approved, for nomofensine (ph.), and another which has yet to be discussed publicly, we had studies which compared three-way designs -- involved three-way designs, that is, placebo, a standard reference agent, and a new drug.

And in both of these NDA's, the majority of the studies of that design failed to discriminate the standard drug and placebo. That means that the risk of falsely declaring an active drug is effective, is substantive -- it's big, and that is why we won't rely on the active design for the regulatory decision on efficacy.

I might add that that does not mean that the active-control design, if properly done, is not a useful tool for the assessment of antidepressant drug safety. If you are going to run a long-term safety study, it may be quite useful. We just

won't use it for efficacy.

Now, what will we use for determinations of efficacy of antidepressants? I am impressed, as I have been taught by prior committees, that designs that will detect or show a difference are critical. The theme is that a difference demonstrateddbetween a new drug and a control condition, in the right direction, is pretty persuasive evidence of efficacy if one can exclude the other explanations for the difference.

And what are those explanations? They are fraud, which we hope doesn't happen; bias; and chance.

As you know, we have a systematic way of approaching those other types of explanations for differences. I might add that, under current regulations, the three types of design which can demonstrate a difference, are, as you might suspect, placebo, the fixed dose-response study, involving the same drug as the -- that is, two or three levels of the new experimental drug, or an active controlled study, which I have just, in a way, maligned, but under conditions which are designed to show that the experimental drug is better than the standard.

Now, that is a severe test of the drug, and we have applied it or expect people to apply it only rarely. But it would work, if you could show that you were better than the standard agent, and presumably the standard agent did not make the patients or persons worse than they would have been at baseline.

Now, what are the kinds of things we worry about, after we have gotten studies that can show a difference? Well, obviously, we want to make certain that the studies were randomized, to insure that there is no bias at baseline. We want to make certain that there is no evidence of fraudulent practice, and, you know, we do have a Division of Scientific Investigations, which regularly inspects the major sources of evidence for clinical studies, to determine whether something is awry.

We also, I think, spend a lot of time looking at how the conduct of the study or analysis of the study may reintroduce what randomization sought to exclude, that is, bias. And this is one of the biggest jobs of the review teams.

We have the statisticians help us in deciding that the analytical models are the correct ones, so we don't stretch the laws of chance regarding whether or not the difference observed could be due to chance, but the real tricky part of the review is the introduction of bias.

And let me, again, stress what we do. One of the biggest problems we have is the so-called evaluable case analysis. That is, all of the patients randomized to treatment are not evaluated, but a subset is, and often the subset is determined, post hoc, on the basis of rules not described in the protocol, for reasons that are open to question.

Under such circumstances, one doesn't really know if

the outcome, that is, an observed difference, is due to a drug effect, or the fact that the patients selected for the analysis were in some way strange.

So, consequently, the Division always asks sponsors to provide us with what we call an "intent to treat" analysis, and this is an analysis which involves every patient, who was randomized to treatment, in our hands, our definition, and who received at least one dose of the treatment medication. Now, that is not as severe as some academicians demand, but it is, I think, a fairly good operant definition.

Now, if that study, that type of analysis, produces a different outcome than a so-called evaluable patients analysis, that doesn't mean the study is no good. It simply means that additional analysis of that study must be conducted to make certain what the cause for the difference is, and then we get into a case of looking at who left, why, how, what were the selection rules, do they seem to be self-serving, are they perfectly reasonable, and the like.

But I think it's an important analysis that firms must do, and if firms don't do it, the staff must do it.

Another thing that we can't control is the issue of patients who prematurely end or leave studies -- terminators, the dropout question.

As you will hear in the staff's discussion of fluoxetine, the differential rate of dropouts between assigned

treatments can introduce significant biases in the evaluation of outcome.

One of the things, therefore, that we try to do is look at studies in more than one way, once again with two analyses. One is the so-called -- I guess it isn't so-called so often, but I will call it the observed cases analysis.

This is an analysis that looks at the patients who are actually rated at the time points required. It doesn't carry forward any additional scores or information from the past. It is the actual cases observed analysis. It has its biases, and it is affected in different ways by dropouts.

Then we look at something we call the last observation carry-forward analysis, or the endpoint analysis, and we look at that, and see if that and the observed cases analysis differ. If they don't, no problem. If they do, again, we go into an analysis of why and how, and better, again, that the sponsors and firms should do this in the submission, rather than ourselves.

But those are some of the things that staffs spend a lot of time on, and you will see, in this particular discussion this morning by our staff, how the differential rate of dropouts from a study led us to conclude that we should do something about pooling, and a particular treatment by interaction in a pool.

Speaking of poolings, I ought to mention that we have

a fairly clear understanding internally of what we do. If you plan a study, multicenter study, of many sites, as a single study, it will be treated as a single study. You cannot, after the fact, go back and extract the winners from among many losers, and promote those as independent investigations.

On the other hand, if you have several studies that were not planned to be pooled, and you try to put them together to get a significant P-value, we won't accept that either. That, to us, is a picking through the crop to find the best items, and packing the top of the case with them. It is somewhat deceptive, and we don't really allow that either.

So I think the only pooling that we are talking about in antidepressant drugs, involves preplanned multicenter studies, and it would be useful if people would describe to us the extent of the pool. Very often, the pooling occurs, and it's ambiguous how many centers, how many patients, and I recommend -- and again, I'm not talking so much to the committee, but to the audience, that an effort be made to specify how many patients in how many centers would be involved in the ultimate pooling, in the protocol, because then there will be no dispute after the fact about how the pooling was generated.

Well, so far, I've just really gone into how we approach the efficacy question, and I think that is a generic instruction on antidepressants. It's not the final word, but

it is the strategy used by our staff.

The other big issue, of course, is safety. Safety, I'd like to say just a couple of words about. The law, as I mentioned, three out of six major requirements goes into the issue of being sure the drug is safe, being sure it's not unsafe, being sure it's safe as labeled for use, et cetera.

Obviously, when Congress passed the Act in '38, they had the sulfonamide tragedy in their minds, and probably were very concerned about issues of safety. We still are, very much so, and one of the things we all come to realize is that "safety" is just a relative term. There is no way to prove absolute safety. No drug is absolutely safe, in the absolute sense that might be understood by a layman.

So, consequently, all our judgments about safety are relevant ones, and again, our ability to detect risk in a drug is pretty much a function of the incidence of risk in the underlying treated population, in the number of patients we have treated. And the number of patients treated also must include the length of time such patients are treated.

Now, because of the way NDA's are done, our qualifications at the time of approval of a drug as safe, is that it is safe for the most common adverse risks that we can suspect. Remote or rare events, or events that are time-conditioned, that is, if something has to happen to a person, if they have to undergo some metabolic induction, or they have to have some

type of immunologic change -- if that event is time-dependent, it is very likely that we run a big chance of missing it.

Why? Because the number of patients at risk for being observed in an NDA for a great length of time, that is, for over three months, is vanishingly small, compared to the number that might be available in four weeks; and, again, the rate of risk, small risks in particular, depends on our ability to detect it on the number of patients observed.

I had a concrete example. If you had a drug, for example, that we knew caused seizures at the rate of one in 500 patients exposed for six months, you would literally have to study 1,500 patients for six months to be 95 percent certain of observing just one seizure.

So you can see, there is a substantive risk of missing not-that-uncommon events if you don't follow patients for a long time. I am emphasizing all of this because all judgments about safety are relative ones. They must be qualified in the context of how long, and how many patients have been observed.

On the other hand, as I have said, no drugs that are unsafe, and the policy of the agency at the present time, and I think it always has been, and was the Congressional intent -- that any drug can be approved if it's effective, provided -- even if it's dangerous, and I mean, there will be absolute exceptions to this -- provided that the labeling adequately

describes what those risks are, and what the relative risks and benefits probably are. "Probably" means you don't know that for certain.

The danger is, ADR would not keep an effective drug off the market with adequate labeling. Now, labeling might go into, is this the antidepressant of first or second choice; should this drug be used only in cases that fail in all other treatments; or, simply, a very prominent display in the labeling of that risk?

But, again, I want you to think carefully about risks and make sure that we have a good handle on them, and I think the safety review that Dr. Kapit will present, will illustrate some of the strategies that we have used to approach risk, in terms of when in the course of drug development we've looked, and how.

Now, that about concludes my introductory course in food and drug law, I guess, and how we try to apply it to the process of drug review.

Before I turn the discussion over to our staff, I would like to make a couple of observations, again. Remember, the subject for today of fluoxetine is not on the approval of fluoxetine, per se. We are asking the committee's advice on whether or not the evidence that bears on safety and efficacy is as we believe it is. There is still additional safety information that must come in, there are questions about the

metabolism of fluoxetine, its apparent nonlinear pharmacokinetics, the possibility that blood levels of fluoxetine and its long-acting metabolites may be accumulated. These have yet to be decided, but I believe they are labeling issues, and we will require further review.

There is additional information about the dose response of fluoxetine, that we will expect the firm to submit, and we will have additional discussions with them about how to predict this.

Also, there is a mandated safety update that has to be submitted, but again, we can move fairly far along in the process, if you will look at what we have in hand and offer good judgment on that.

Now, who is going to make the presentations? Well, Dr. Lee hesitated for a moment when she said that she was working for the FDA, today. Dr. Lee has worked until very recently for the FDA, and is now a special government employee. She was the primary clinical assessor of fluoxetine's evidence of efficacy. She now works for a -- can I give you a little applause -- Memory Associates, down in Bethesda, a totally independent assessment laboratory, and is going to present the evidence on fluoxetine's efficacy as an antidepressant today.

Supporting her will be Dr. Chi, the biometrician, in the Division of Biometrics, who has worked with Dr. Lee. He

will discuss some interesting aspects of the data analysis, pointing out what we did with -- I mean, primarily. He will discuss a lot of things, but I think an interesting part of his presentation will be what we did with pooling 27, which is a multi-site investigation.

And following Dr. Chi, we will have Dr. Kapit, who is the clinician on the team, physician, who was the safety reviewer on fluoxetine, and he will present the results of his review.

DR. DETRE: If I may interrupt for a second, Mr. Abramek wanted to make a quick statement.

MR. ABRAMEK: Are you done, Dr. Leber?

DR. LEBER: (Indicated yes.)

MR. ABRAMEK: Fine.

Dr. Detre, I would like to ask for a recess of two minutes.

(A short recess was taken.)

DR. DETRE: On the record.

Dr. Leber will make another brief statement.

DR. LEBER: Fortuitously, the Associate Commissioner for Management and Operations, Mr. Gerald Myer, was in the room, and heard Dr. Preskorn announce that he has been approached by Eli Lilly to consider doing a study on fluoxetine.

We have discussed the matter in a short committee

meeting, and have decided that the agency will grant a waiver.

We do not believe, in any sense of the word, that one could construe this to be a conflict of interest, and we are granting a waiver. I don't know -- I hope, if I'm saying anything wrong, Mr. Myer, in terms of the technical terminology, please -- because this will be in the record.

MR. MYER: That will be fine.

DR. LEBER: Fine.

Obviously, we will act as though what you have said has no meaning whatsoever in terms of your participation today. Sorry for that interruption, but we were lucky to have Mr. Myer here.

With no further ado, and if it's all right with the chairman, Dr. Lee.

DR. LEE: As we mentioned earlier, I am going to give an overview of the efficacy of the submission. Dr. Chi will go into more detail on some of the issues. Are these mikes okay?

This submission contains three placebo-controlled studies. One of these was with the standard drug -- that's cimetidine. There were also 12 active drug-controlled studies. These were studies without placebo.

The active comparisons in these 12 studies were imipramine in three, amitryptilene in three, doxophen in four, and two compared fluoxetine OD and twice daily.

I should say, as you probably all know, there were other studies in the submission as well, but they don't bear directly on efficacy, so they won't be discussed here.

Of the three types of designs used in the submission - that's the three-way, the investigational drug, standard drug and placebo, the investigational drug versus the standard drug, and the third type is investigational drug versus placebo as Dr. Leber mentioned, we consider the three-way design the most definitive.

Another way of saying our reasons -- the three-way design allows us to evaluate the discriminability of the design of that particular trial. Is the trial capable of discriminating between active and inactive treatments?

The use of placebo and the standard drug allows us to evaluate the appropriateness of the sample, and also how well the study was run.

Now, we can't say anything specific about those, but it gives us our sense about the study.

The three-way design allows one to make a judgment about the investigational treatment, in that, if patients respond to the standard treatment, and also the investigational treatment, but not to the placebo, one can conclude with some certainty that the sample was appropriate, and that the investigational drug is having a similar effect to the standard drug.

However, the finding of a similar response between the investigational and standard drugs, in a drug/drug study, does not allow the same conclusion, because other variables -- placebo response, a non-critical investigator -- could result in the same outcome.

Hence, a drug/drug design cannot be considered definitive in the testing of an antidepressant.

For these reasons, in the following, I will restrict my discussion to the placebo-controlled studies, and particularly to protocol 27, a three-way multicenter study, and protocol 19, a two-way investigational drug/placebo comparison.

Protocol 27 -- this was a six-week, double-blind comparison of fluoxetine, imipramine, and placebo, in approximately 700 outpatients with a diagnosis of major depressive disorder. That was based on DSM-III criteria.

On entry, the patients were also required to have a score of at least 20 in the 21-item AMD total, and a score of 8 on the Raskin depression scale, and this score had to exceed or equal the coded anxiety score. This was to insure the selection of at least moderately severely depressed patients.

The exclusions were pretty standard -- serious illness, pregnancy, serious suicidal risk.

Now, there is another division in the data, and that is between evaluable patients and non-evaluable patients. What I am going to be showing you is the group of evaluable

patients, and then total group of patients.

Now, the non-evaluable patients -- there were a number of definitions, a lot of definitions, but the main one that you need to remember is that it was less than two weeks of treatment. So if a person hadn't had two weeks of treatment before they were dropped from the study, they didn't go into evaluable analysis.

Now, the study began with a one-week -- that is, four to ten days' range -- single-blind placebo phase, and then, following that, the patients were reevaluated, and if they still met the entry criteria, that is, a Ham. D. of 20. Also, the Ham.D. couldn't decrease more than 20 percent during that one-week placebo baseline.

They were then entered into the six-week -- it's a six-week double-blind phase. Patients were seen twice during the baseline, the beginning of the baseline and the end, and weekly during the trial.

The efficacy ratings during the trial consisted of the Ham.D. -- that's the Hamilton rating scale for depression. We call it the Ham.D. -- the Raskin depression rating scale, the coded anxiety scale, the physician CGI -- that's the clinical global impression, provides a number of scores. The main ones we have looked at are the severity of depression and the change in condition. The CGI for the patient, there was certainly a changed score in that one; and they used the SCL-58,

a symptom checklist 58, for the patient. I am not going to include the safety evaluations here.

The dosage -- the drugs in this three-way study were administered t.i.d. For fluoxetine, the dosage ranged from 20 to 80 milligrams daily, through a rather interesting arrangement, actually. The fluoxetine was administered in an active form at a.m. and at noon, or early afternoon. The evening dose was placebo.

For the imipramine, there was -- it was probably a half of it, like a quarter of the dose in the morning, a quarter at lunch, and a half in the evening, so that they managed to -- in this way, they could approach the way we usually administer imipramine, because I think imipramine is given morning only and evening, and they could still blind, and give their drugs in the morning and at noon.

The dosage for imipramine was 75 to 300 milligrams daily. As I said, it was t.i.d., administered t.i.d.

Now, in the results, the sponsor did two complete sets of analyses. You have heard a little bit about this. One was on all subjects who at least had one on-drug rating, and the second analysis was of the evaluable patients.

Some of what Dr. Leber said, I have in mine as well, so I'm skipping it here.

The comparison of the total group analysis with the evaluable group analysis will give you some idea if there was

some kind of bias for rejection of patients, and also suggests to you, one of the big problems with dropouts is, when you end up with a small cadre at the end, you can't be sure who this is representative of, and how it differs from the actual patients who were entered in the study, where we do have some idea of their characteristics. So this comparison of these techniques, if it works out all right, these two analyses can be helpful there. Can we see the first slide?

This is to give you an overview, a summary, of the NDA studies we're looking at. This is the three studies that included placebo.

Now, as Dr. Leber said, protocol 27 was submitted as a pool. I would like to show you here what the scores of the individual investigators are, and then I'll show you another slide, what the pooling itself looked like.

Now, in protocol 27, there were six investigators. What I've shown here as well is the total group and the evaluable group. The total group is the clear section. The evaluable group gets a higher score. This is the change score, the mean change score, for each group, and what you can see here is that the total group -- that was including everybody, the distance was not quite as large between the two treatments, between baseline and completion, as they were in the evaluable group.

Now, each study, each investigator -- I've shown

fluoxetine, imipramine, and placebo, in that order, across for protocol 27.

For five of the six investigators, imipramine produced the most improvement, just on a rank-order basis, followed by fluoxetine, followed by placebo. The sixth investigator, who I moved right down to the end of protocol 27 there, the last of the protocols I'll discuss in a minute, is Dr. Cohen. His study found that fluoxetine was much more effective, and gave a much greater response than imipramine, and again, than placebo, in this study.

Now, Dr. Cohen's study had a large number of dropouts in the placebo and imipramine groups, which meant that the significant endpoint analysis was largely a reflection of the poor scores in the placebo group, which dropped at week two, and compared with patients who got six weeks of fluoxetine, so that, in effect, what was happening in Dr. Cohen's study in the endpoint analysis was, we were considering two weeks of treatment, with one group, versus six weeks of treatment with another.

And, as you all know, we can't be sure, after two weeks of treatment with depression, that you don't have an active treatment.

Now, it could be said that the fact that they had to drop all of the placebo patients so early, was a reflection of something going on with fluoxetine, but it is also possible

that this precipitous removal of patients could have eliminated the possibility of later responses.

Now, this combination of six investigators also produced a very large treatment by investigator interaction, and we asked the sponsor to analyze the pooling, excluding Cohen. Next slide?

What this is, is pooling for protocol 27, minus Cohen. It's the three key depression variables -- there are others, and I did it for the evaluable patients in the first set, and for all patients in the second set.

You can see that, with the pooling, even excluding Cohen, actually, they were highly significant, most of these, and again, it's the same rank order as most of the studies, with imipramine followed by fluoxetine, followed by placebo. This was true for the Ham.D., the Raskin depression, and the global improvement. It was also true in the all-patient analysis.

Over on the right side, you can see the two protocols that were submitted, that were fluoxetine versus placebo. The first one was by Fabre -- a marked difference between fluoxetine and placebo, very significant. The second study was Rickels, and there was no significant difference, so Rickels, we won't hear discussed for the rest of the day, probably.

I have also summarized these results in the third slide. It's saying much the same thing, again, just in a

slightly different way. The material in the body content of the table — if there were three pluses, that meant there was significant difference between the treatments on at least -- on all three key variables.

Now, the key variables were the Ham.D. retardation and total score, the Raskin total score, the CGI severity and change, and the Hopkins depression factor. So the three pluses, positive on all; two pluses, significant on at least three key variables, one plus is significant in scattered variables, zero is not significant in any variable, and of course, it wasn't applicable to the comparison with imipramine.

So here we can see that in the protocol 27, if you look down the first six studies, five of the six, we could approve for use today with no trouble at all. With fluoxetine, if we skip the individual studies, which we have to do, if you come down to the final line under protocol 27, this is the new pooling. This is the one I just said, where we asked them to exclude Cohen.

It does support both fluoxetine and imipramine. Dr. Fabre's study is highly positive for fluoxetine, and Dr. Rickels' wasn't.

Comparisons between imipramine and fluoxetine are shown in the third column. Dr. Cohen's study, as I mentioned already -- this was the only one where fluoxetine was significantly better or produced more improvement than imipramine.

There were two other studies, Dunner and the pooling, where imipramine was significantly better than fluoxetine.

So I guess that's my talk for now. (Pause.) Should I take questions now, or --

DR. LEBER: Yes, I would like to mention that, because of the -- there was some confusion about our need for that meeting, in between the short agenda break, but in general you can ask questions when a speaker is completed, or we can wait until both FDA and the sponsor have presented, and then have it during committee discussion, or if you feel there is a matter you would like clarified, you can ask and interrupt them. Nobody would really object.

I would hope we wouldn't start substantive discussion, though, until everything has been on the table and presented.

Any clarifying questions?

(No response.)

The next presenter is Dr. George Chi, from the Division of Biometrics, who has looked at the methods of analysis, the models used, and will now present what we did and why we did it with protocol 27.

DR. CHI: What I'm going to say is going to complement what I have written in the review, so if you have already read the review, please bear with us for a few minutes.

I think Dr. Lee did a very good summary, and I think

she has said everything I wanted to say. So the only way I can do is to overload you with a lot of figures.

The volumes of the fluoxetine application submitted to the Division of Biometrics contain three randomized double-blind parallel placebo-controlled studies, and twelve active studies. Can I have the first slide, please?

And I shall focus here on the efficacy results of the three placebo-controlled studies, namely, protocol 19 by Fabre, protocol 25 by Rickels, and protocol 27, which is a multicenter study. And as Dr. Lee mentioned, the Rickels study did not differentiate between fluoxetine and placebo, and hence will not be discussed further. May I have the next slide, please -- well, not quite yet.

Throughout these studies, standard non-parametric methods have been used, and weekly analysis, which is just observed-cases analyses each week, and endpoint analysis, which is the last observable carry-forward analysis, were performed on all patients' data, as well as observable patients only data.

In endpoint analysis, a patient's last available visit was used. I shall focus mainly on the sponsor's results based on available patients, and endpoint analysis of the available patients, because generally the results based on all patients' data are similar, as you will see in a couple of the slides later.

The results of the weekly analysis will be used for illustrating some of my arguments, and other details will be found in my review.

Dr. Lee suggested to me that I should only look at the following five efficacy measures. Can I have the next slide? And these five efficacy measures are Ham.D total, Ham.D retardation, Raskin depression, severity of depression, and global improvement. Next slide, please.

Protocol 19 involved only investigator Fabre, so just one investigator study. The endpoint analysis, based on the available patients from this study, showed that fluoxetine -- oh, let me backtrack a little bit. This is a summary table for all of the placebo-controlled studies. The top half of the panel is for available patients only. And we have the five efficacy measures in the first column, and you see that the Fabre study was very significantly in favor of fluoxetine for Ham.D total, Raskin depression -- I mean, for Ham.D total, severity of depression, and global improvement, and marginally so for Ham.D retardation.

The result is significantly more so for all patients' data, which is at the bottom half of the panel.

In the Rickels study, you see there is not much difference between fluoxetine and placebo.

Now, on the right side of the table is the multi-center study, protocol 27, and the first column corresponds to

the results for Dr. Cohen, and you see the results are very significant, in fact, too significant to believe.

And for the other five investigators, there are scattered significant among the various efficacy variables, but if you look at the last row, you see that, numerically, the predominant direction of comparison is in favor of fluoxetine. Except for a few cases that are marked with asterisks, those are the comparisons where fluoxetine is -- didn't do as well as placebo, but then the P-values are not significant at all.

Okay, next I will go into the details in the study by Fabre and the multicenter study, next. Protocol 19 involves only investigator Fabre, as I've mentioned already. May I have the next slide, please?

The endpoint analysis, based on the available patients from this study, show that fluoxetine is significantly better than placebo in Ham.D total, severity of depression, and global improvement, and marginally so in Ham.D retardation.

And this table gives you the results of the summary for the five efficacy measures. The next table, please.

Similar results, as I mentioned before, were observed with respect to all patients' data.

This table gives you the distribution of the last available rates for available patients, and there is no

significant difference between the two treatment groups. Next table, please.

This is the weekly comparison between fluoxetine and placebo, based on available patients only. And you see that, starting with week 1 through week 4, and in some cases in week 5, fluoxetine beat placebo, significantly in many cases, and marginally so in most others. Next slide, please?

And this is the table which is based on all patients' data for Fabre's study, and it indicates that fluoxetine is much better than placebo in all five efficacy measures.

No major statistical issue arose with regard to the design, conduct, and analysis of this study. The results of the study appear to demonstrate the superiority of fluoxetine to placebo.

Protocol 27 is a multicenter study. It contains also imipramine, as you know. However, for the purpose of efficacy, I shall only focus on the fluoxetine-placebo comparison.

The results for each investigator are listed in table 1, which you have already seen. One observes that Cohen's study provided an unusually strong positive indication for fluoxetine across all five efficacy measures. For the remaining five investigators, even though fluoxetine was generally numerically superior to placebo for most measures, as I have already mentioned, only some marginally positive results were observed in (inaudible). Could I have slide 7, please?

This table shows the results for Ham.D total, based on protocol 27, which is the endpoint analysis of available patients only. You see, by looking at individual investigator results, imipramine appeared to be better than fluoxetine, which in turn is better than placebo, but not statistically -- there is no statistical significance between fluoxetine and placebo comparison, if you look at the last column, whereas, in Dr. Cohen's results, the significance reaches the level of .0001. May I have the next slide, please?

The significantly positive results of Cohen contribute to the highly significant treatment by investigator interaction detected, at P=.0008. This may have prompted the sponsors to present a separate analysis for each of the investigators. However, in view of the fact that the study was designed as a multicenter study, it would have been more appropriate to pool the data from the five investigators and analyze it separately from Cohen's.

This idea was conveyed to the sponsor, and I have discussed the results of Cohen and the results of pooled data in more detail.

So, the study for Cohen -- the endpoint analysis performed in the study gives the impression that fluoxetine is significantly superior to placebo, with a two-sided P-value of .0002. May I have the next slide, please?

Is that table 4? Yes, I need table 4. Thank you.

The first table on the right, the P versus P comparison -- the P-value, you see, is all less than .0002, as far as all five efficacy measures. However, the weekly comparison, which is the next table 5, reveals only scattered significance. For F versus P, fluoxetine versus placebo, comparison at two weeks is .01, and at four weeks, .06, and at six weeks, .1. And for this comparison, it is .05 and .13, and there is no significance in the other week, and some of these are quite dose-marginal.

So, how does one account for such a discrepancy? You find a very significant result in endpoint analysis, but you don't find much significance when you look at a weekly analysis.

I guess you know the answer by now, and it lies in the differential early termination rate observed among the available patients, between fluoxetine and placebo, as well as the imipramine group. Let's show the next slide, please, table 6.

From this table, you can see that, if you look at the number that's in the rectangle box, the total number of available patients terminated before six weeks. There were only 24 percent of the fluoxetine group, but there were 52 percent, and 69 percent, in the imipramine and placebo groups, and the P-value is less than .005 for the fluoxetine group and placebo comparison, and P=.01 for the fluoxetine and imipramine.

So the differences came mainly into the -- well, may I have the next slide, please? This slide compares the distribution of available patients by last week of available visits between the three treatments, and you see that, in the second week, 40 percent of placebo patients had their last available visit, and only 9 percent of the fluoxetine group, and 29 percent in the imipramine group. May I have the next slide, please?

So we see that the differences mainly came from the second week. Since about 40 percent of the evaluable placebo patients were terminated after the second week, any comparison of placebo at five and six weeks will be biased in favor of fluoxetine, because it doesn't account for spontaneous improvements in the placebo group.

On the other hand, an analysis based on just the first two weeks of the trial is also of questionable validity, because the patients have not received the full benefit of the treatment.

So, the preceding discussion is also applicable to all patients' data. And my conclusion for Cohen's study is that it is difficult to draw any valid statistical inference, based on the results of his study.

Next are the pooled data, pooling the five investigators by excluding Cohen. For the pooled data, there appear to be no significant differences in patient characteristics

between this patient population, and the pooled data in the original total population. There is also no significant difference between treatment groups with respect to the baseline characteristics that I could observe, and there is also no significant treatment by investigator interaction. That is a calculated P=.08, so that is very insignificant.

The endpoint analysis, based on the evaluable patients -- may I have the next slide, please, table 7-A? Right, thank you. The endpoint analysis, based on the pooled data on the available patients, tells that fluoxetine is significantly better than placebo, relative to all five efficacy measures that are listed down this column, and in fact quite significantly so.

May I also have the next slide, please? There was also no apparent difference in time and frequency of early termination. "Non-significant" refers to a P greater than .25.

There is a slightly larger percent here for placebo, but there were no significant differences in a comparative distribution. May I have the next slide, please?

In the weekly comparison, I asked the sponsor to provide analysis only of weeks 3, 4 and 6. I think the result of week 5 is probably similar.

So from the weekly analysis, you can observe that fluoxetine also is significantly better than placebo at -- not at week 3, but at week 4, possibly at week 5, and very

significantly so at week 6. It is true across all five efficacy measures. May I have the next table, please?

And similar results can also be observed, based on all patients' data, and based on the intent to treat analysis. You see that the significance is similar to what we observed earlier across all five efficacy measures.

May I have slide 15, table 10? Okay, this analysis was done by the sponsor in the original submission. They did a pooled analysis by pooling the five investigators, excluding Cohen, and also excluding all patients with concomitant psychotropic medication, and the results were also similar, but not as strong as before.

So the results of the various analyses, based on the pooled data, were significant, and were supportive of the efficacy of fluoxetine.

In conclusion, then, based on the results of these two placebo-controlled studies, and appropriate attention paid to the differential dropout rate associated with Cohen's study, there appears to be sufficient evidence to indicate the effectiveness of fluoxetine in treating unipolar depression in outpatients diagnosed as having primary major depressive disorders, in either single or recurrent episodes, and that concludes my presentation.

There is just one last thing I want to mention. I think there were some tables to be passed out on the table

earlier, and I take it you have all picked them up. I think those were tables submitted by the sponsor in the original NDA, and I believe that format is very good, and I requested permission from the sponsor to distribute it to the other manufacturers. And if you haven't picked them up, you can ask Eli Lilly for a copy.

Thank you.

DR. DETRE: Thank you very much.

Ladies and gentlemen, how about a five-minute break?

(A short recess was taken.)

DR. LEBER: Are we on? Okay, we're back on the record, I guess.

We would now like to continue the FDA's presentation of its review of the fluoxetine NDA. The next section deals with our assessment of its safety. Dr. Richard Kapit, psychiatrist from our staff.

Dr. Kapit?

DR. KAPIT: Fluoxetine is a straight-chain phenylpropylamine, which selectivaly inhibits the uptake of serotonin into neurons. It has little effect on noradrenergic or dopaminergic neurons.

Fluoxetine appears to be a relatively safe drug. In the course of reviewing the fluoxetine NDA, we evaluated the safety data of 1,427 individuals who were exposed to fluoxetine in 46 studies.

The results of this analysis revealed no indication of any clinically significant adverse effect which would preclude the approval of fluoxetine for marketing.

It is necessary, however, to qualify this statement. Since the submission of the fluoxetine NDA, additional data have continued to accumulate as a result of ongoing studies of fluoxetine, both in the U.S. and abroad. In consequence, the NDA presently includes perhaps one-half to two-thirds of the data currently available on fluoxetine.

It will be necessary to obtain and analyze an update of the safety information on fluoxetine before it is possible to make a final decision regarding approval.

Based on the subset of the total fluoxetine data which has been reviewed by the FDA up to the present time, none of the adverse effects identified were of sufficient magnitude or severity to preclude marketing. However, it should be understood that the size of the data base did not allow us to include events that occur at incidences of less than about one in 200 exposures.

Furthermore, although 1,500 patients were exposed to fluoxetine -- nearly 1,500 patients were exposed to fluoxetine, as reported in this NDA, only 218 received the drug for more than six months, while less than 100 continued to take it for more than a year.

Clearly, the long-term experience with fluoxetine is

limited.

Turning now to the particulars of the data reported, 1,427 patients were exposed to fluoxetine. Of these, 92.4 percent received 40 to 80 milligrams per day, and about one half of them received the drug for more than two weeks, but less than three months. One-third of the patients took the drug for longer than three months, and one-sixth for less than two weeks.

The most significant of the adverse effects observed were the induction of clinically serious dermatologic hypersensitivity reactions, and the precipitation of psychotic episodes.

Though less immediately serious, fluoxetine does appear also to cause significant weight loss in some patients.

Certain laboratory parameters may be affected by fluoxetine. There were three cases of leukopenia below 3,000 reported in the NDA. In addition, there was a slight decline in mean serum calcium level among patients exposed to fluoxetine, but this did not appear to be clinically significant.

Each of these adverse clinical effects, as well as some other findings, will now be discussed separately.

Twelve patients had dermatologic sensitivity reactions. Two of these required hospitalization. These were the case of an elderly woman with rash and fever, and the case of a young woman with erythema multiforming. Both recovered.

Six of the 12 cases were probably caused by fluoxetine,

while the other six cases -- while, in the other six cases, other drugs had concomitantly been prescribed. In one case, a sequence of events in the challenge-dechallenge-rechallenge pattern confirmed the etiologic role of fluoxetine.

Ten cases of psychotic episode occurred during fluoxetine treatment. Most of these appeared to be the result from the precipitation or the uncovering of manic affective illness. This rate of recurrence of psychosis, in a sample of over 1,000 depressed psychiatric patients, that is, a rate of about 1 percent, appears to be in line with that seen in other NDA's, and it is possible that a number of these cases may result from misdiagnosis, or spontaneously occurring new psychotic illnesses, rather than from the effect of fluoxetine.

Among the patients reported in this NDA, this reviewer found three cases of white count below 3,000. Of these three, only one patient experienced a persistent decline of white count that was probably attributable to the drug. Thus, fluoxetine does not appear to cause a large number of cases of significant leukopenia. However, the time-adjusted risk of leukopenia may be higher than these data suggest, and calculation of this risk will require further analysis as more data becomes available.

Also, it should be noted that recent information from the company indicates that other cases of leukopenia may have occurred since the submission of the NDA.

Fluoxetine did not appear to have significant effects upon cardiograms or chest X-rays among the patients reported in the NDA. However, 30 patients developed ophthalmologic abnormalities while being exposed to fluoxetine. Three of these cases were described in the company's submission, and did not appear to be drug-related abnormalities. Clearly, a full report of the ophthalmologic findings of patients exposed to fluoxetine is necessary, and the company has been asked to provide this information.

This new drug did show statistically significant effects upon certain vital sign parameters, namely, body weight, pulse, and blood pressure. Fluoxetine caused a reduction of weight not seen on other treatments. All other active drugs used as controls -- imipramine, amytryptilene, and doxipen, caused weight gain.

Patients on fluoxetine lost an average of 2-1/2 to 3 pounds during treatment. This effect may possibly be related to the more prominent side effects produced by fluoxetine, nausea and anorexia. In addition, fluoxetine simultaneously caused small but significant lowering of both pulse rate and blood pressure.

Mean pulse rate decreased a few, less than five, beats per minute, while mean blood pressure levels declined a few, less than five, millimeters of mercury.

The side-effect profile of fluoxetine differs

considerably from that of standard tricyclic drugs. Tricyclic drugs are usually sedative and anticholinergic in their effects. With fluoxetine, however, the only putative anticholinergic effect experienced frequently was dry mouth, which occurred in 15 percent of patients. In contrast, nausea was experienced by 25 percent, but nausea was rarely accompanied by vomiting.

Although constipation did occur in 8 percent of fluoxetine patients, diarrhea occurred in 11 percent. Drowsiness was experienced by 15 percent of patients, but nervousness was experienced by 21 percent, and insomnia was a problem for 17 percent.

The side effect profile of fluoxetine appears to be more that of a stimulant drug than do the profiles of the tricyclic agents. The five most frequent adverse effects caused by fluoxetine were nausea, 25 percent, nervousness, 21 percent, headache, 18 percent, insomnia, 17 percent, and anxiety, 15 percent.

As noted previously, fluoxetine caused more diarrhea than constipation, and in one controlled study of obese patients, the drug demonstrated some efficacy as an appetite-suppressing agent.

Statistical analysis of the safety data performed by Dr. Chi revealed a statistically significant serum calcium level among patients exposed to fluoxetine. Data from the NDA indicate that mean serum calcium declined 0.09 milligrams per

deciliter, while the largest decline seen in any patient was 1.7 milligrams per deciliter. Thus, although the calcium decrement was statistically significant, it does not appear to have been clinically significant, nor is it clear what significance to attach to this finding.

Possibly, fluoxetine's tendency to produce nausea, anorexia, and weight loss leads in some patients to diminished intake of calcium and/or Vitamin D, and that this is reflected in a small decline in mean serum calcium levels.

It may be of interest briefly to describe the methods of analysis used to evaluate the safety data submitted in this NDA. Each individual safety summary was reviewed for each study separately. Following this, early termination summaries were inspected for each patient in a controlled study, who began but did not complete treatment. Frequencies of adverse clinical events among early terminators were calculated.

All individual laboratory test results were examined for each patient who participated in a double-blind study. On the basis of early termination summaries and lab test results, a sample of about 50 cases were selected, and individual case reports were reviewed for those 50 cases.

Cross-tabulation matrices were constructed for certain selected laboratory parameters which are often affected by drug toxicity. Length of exposure to fluoxetine was computed whenever possible for each patient exposed to fluoxetine.

Special summaries prepared by the company were reviewed, which included reports of cardiovascular, chest X-ray, ophthalmologic, vital sign, and adverse effect data, and clinical events requiring further comment.

I would like now to display a few tables, which will highlight a few of the results of the safety review.

As indicated, these are the rates of early termination in 16 controlled studies. We have the number of patients for each drug group at the top of the column, and then we have the total early terminations, the terminations due to adverse effects, terminations due to lack of efficacy, and the terminations due to other causes.

Looking first at the total early termination rate, we can see that the highest rates were highest for placebo, and next for imipramine, and that the -- that fluoxetine was comparable to amitryptilene, and somewhat greater than doxiphen.

The rate of terminations due to adverse effect -- imipramine has the highest rate here, fluoxetine is comparable to amitryptilene, and doxiphen, and the placebo group would understandably have the fewest rate of terminations due to adverse effects.

Terminations due to lack of efficacy -- no particular difference between the active drugs, but the placebo group obviously has the highest rate due to termination for lack of efficacy. Okay, the next transparency, please?

These are the adverse effects rates among the early terminators. We looked at early terminators in detail, because we felt that safety problems with the drug would most likely show up in this group. And in this particular group, the N's for each group, number of early terminators, were at the bottom, and the numbers in parentheses refer to the percent of the N.

Now, I did my own grouping of adverse effects, in which I grouped together similar terms, and some of that is reflected in the labels of the categories at the left, and one can see that the fluoxetine group had most frequent termination for anxiety, nervousness, for insomnia, dizziness, and nausea.

Imipramine had the most frequent terminations for dry mouth, 43 percent, sedation, dizziness, and other anticholinergic effects. The placebo group, quite simply, had few terminations for adverse effects. Next?

These are the ten most common adverse effects among fluoxetine patients -- nausea, nervousness, headache, anxiety, insomnia. The company separated nervousness and anxiety. I believe this reflects the characterization that fluoxetine is more of a stimulant.

It can be seen that certain adverse effects of fluoxetine may create liabilities. In particular, fluoxetine causes nervousness, insomnia, and diminished appetite and weight loss. These are symptoms from which depressed patients frequently

suffer as a result of their primary illness, and it may be that fluoxetine treatment may, at least temporarily, aggravate some of these problems.

On the whole, however, fluoxetine appears to be a relatively safe drug, and there is no problem that I cited just a moment ago which could not be handled by lowering the dose, perhaps, or changing the treatment.

Since it has been demonstrated that fluoxetine treatment may be of significant benefit to patients suffering from depression, it would appear that the benefits of fluoxetine treatment substantially outweigh the risks associated with taking the drug.

On the basis of the data submitted in the NDA, it may be asserted that there was no indication that fluoxetine causes any adverse effect of such severity or frequency as to preclude the marketing of this agent.

DR. LEBER: Anyway, that concludes the formal presentations from our staff, and I think it's up to the chair to decide whether they want to query us, or go on to the company.

DR. DETRE: Any questions from the committee? Yes?

DR. STANLEY: Dr. Stanley. I'd like to ask Dr. Kapit just a few questions on that cluster of symptoms that he had mentioned, the anxiety, the nervousness, the weight loss and the insomnia, and I guess I would agree that that would be kind of consistent with a stimulant -- a more stimulant-like

profile, and I was wondering if there were sufficient data at this point to determine whether the differential effect occurring within the more acute use, say, the patients within the six-week trial, compared with -- I believe you said something like a third of the patients have received fluoxetine for longer than three months. Do you have a sustained weight loss during this period of time, or sustained nervousness, or is there any tolerance to these?

DR. KAPIT: Weight loss did not turn out to be a long-term problem with the patients who were treated with major depression. It was most significant in the study of obese patients that was run by the company.

In particular, among geriatric patients, no geriatric patient was terminated for weight loss. One thing that did emerge that was of interest in the long-term studies is that the pool of long-term patients -- the most frequent reason for termination was anxiety and nervousness, whereas in the short-term studies, the most frequent reason was the nausea.

So it does seem that the anxiety -- the nervousness is a problem that may not go away with time, and possibly might get worse.

Was there some other point that you wanted to address?

DR. STANLEY: Yes, the related -- I guess the insomnia, whether there was a tolerance.

DR. KAPIT: I don't have any indication as to whether insomnia -- it didn't seem to change, long-term versus short-term.

DR. STANLEY: Okay, and do you have any information on the relative proportion of individuals receiving either fluoxetine or a reference compound, that were receiving additional psychotropic medication, maybe to control nervousness. I mean, is it more than it appears already?

DR. KAPIT: I don't have that information at hand.

DR. LEBER: Dr. Lee may have it.

DR. LEE: I think that's something you should ask the sponsor to display. There was one point in the pooling that I showed you, the first pooling, where Cohen was still in the study, and someone pointed out to me that we had it only as a slightly positive trial, and when we took Cohen out, it became highly positive, and I was asked, why did this happen?

One thing that the sponsor did, and perhaps should explain to us, but it might be related to your question. They took out everybody from the pooling, when they analyzed it, who received concomitant medications, even if these were concomitant medications that were allowed by the protocol.

So I don't know if I want to speculate on it, but there might have been some sense that the concomitant medications were helping patients deal with the side effects, and to get a truer picture of the drug effect when you take them off.

DR. LEBER: One clarification, Hillary. We did have an all-patients analysis, so that they may have done a pooling without Cohen that was also an all-patients pooling, and it would have included those, as well --

DR. LEE: Yes, we --

DR. LEBER: -- because those results weren't changed.

DR. LEE: We've brought all that, yes.

DR. LEBER: So I don't think it affected the efficacy, but it may be that you're looking at an adjunctive effect of the --

DR. LEE: Yes.

DR. LEBER: -- some other concomitant med. that makes it easier to use this drug, and this isn't the first time we may have seen that.

One other comment I would like to make, because I think Rich sort of answered the question, but perhaps didn't lay out what the ground rules would be.

It is rare that we have anything in NDA analyses that tells us what the time distribution of risks are. I think it is something we would like to get, and certainly, as I mentioned earlier, it is nice to adjust risks for their time of occurrence and the number of patients at risk at that time.

Issues of tolerance, number of patients at risk, and when they have not been formally looked at, and I think the answer is, we don't really know. It appears that, as Rich

Kapit said, to be a clinically important problem.

On the other hand, whether tolerance develops to the anxio-induction or anxiogenic effects, I think that might be easily assessible by looking at what the reports are on a weekly basis, over the number of patients who are still in the study, unless investigator behavior changed, and we don't know whether they continue to report as they reported the first time. But we might try to look at that, and also ask them to discuss that. We don't really have hard data on that.

DR. DETRE: But I understand we have some data on what percentage of patients in the various trials received concomitant medications, right?

DR. LEBER: Yes, we do.

DR. DETRE: Anybody, any other questions?

(No response.)

Dr. Leber, who comes next?

DR. LEBER: I believe the floor is turned to Eli Lilly.

DR. DETRE: Okay.

Just for the record, would you kindly state your name?

DR. THOMPSON: Leigh Thompson. Perhaps we can sum up by saying we agree with the very comprehensive analysis of Dr. Leber and his staff, Dr. Lee, Dr. Chi, and Dr. Kapit. It would be inappropriate, however, not to have at least a brief summary

of some of the science of this drug. It has been a long time since July of 1972, when Dr. David Wong discovered the specificity of the action of fluoxetine, and we would like some of the scientists who participated in the development of the fabric of the role of serotonin neurobiology to have an opportunity to describe some of their science.

Beginning that will be Dr. Ray Fuller, who has been the needle weaving through the fabric of neurobiology, the thread of serotonin in discovering the role of fluoxetine, and Dr. Fuller will describe some of the basic studies.

DR. FULLER: Well, I am going to talk about the animal pharmacology of fluoxetine, that led us to be interested in it as an antidepressant drug.

The structure of fluoxetine is shown here, and as you have heard, it differs from most of the earlier antidepressant drugs that contained a few three-ring systems, hence their name, tricyclic drugs, and some of the differences between fluoxetine and those drugs may relate to their structural dissimilarity.

The preclinical pharmacology of fluoxetine showed that it is a highly selective inhibitor of serotonin uptake, without other detectable pharmacological effects. For example, it does not inhibit norepinephrine uptake in vitro, except at higher concentrations, and in vivo it blocks serotonin uptake without any effect on catecholamine uptake.

Secondly, it blocks uptake without affecting any meurotransmitter receptors directly, and I will describe the kinds of evidence from animal studies that support these statements.

Fluoxetine inhibits the uptake of serotonin in vitro by right-brain synaptosomes, producing 50 percent inhibition at a concentration of 70 nanomolar. In contrast, concentrations about 100 times higher are required for inhibiting the uptake of norepinephrine or dopamine, and at the doses that are used in vivo, fluoxetine only inhibits the uptake of serotonin without inhibiting the uptake of catecholamines.

Evidence for that comes from several kinds of animal studies. From the most direct experiments, that we refer to as ex vivo experiments, synaptosome is prepared from the brains of animals treated with fluoxetine in vivo, picked up less serotonin in vitro, whereas there is no inhibition of norepinephrine or dopamine uptake.

Evidence that is entirely in vivo comes from experiments with depleting drugs like parachloroamphetamine, H-7512, and fluoramine, which deplete serotonin by a mechanism that requires the function of the uptake carrier. So their depletion of serotonin is blocked by fluoxetine, as well as by other serotonin uptake inhibitors.

Now, in contrast, fluoxetine does not block catecholamine depletion by drugs like 6-hydroxydopamine, H-7777, or

alphamethyl pyrixine, which deplete catecholamines via an action that requires the uptake carrier on catecholamine neurons. Again, fluoxetine does not block their effect, but it does block the depletion of serotonin.

So, fluoxetine doses of 10 milligram per kilogram or less, in laboratory animals, block the uptake carrier on serotonin neurons, not the uptake carrier on norepinephrine, dopamine, or epinephrine neurons in the brain.

This is a representation, a diagram, of what goes on in a serotonergic synapse. The serotonin neuron, at left, synthesizes serotonin within the nerve terminal. Serotonin is abbreviated here, 5HT, for 5-hydroxytryptamine.

That serotonin is stored in granules or vesicles from which it is released, at nerve impulse, into the synaptic cleft, where it acts on receptors, like the post-synaptic receptor, to completeethe process of neurotransmission across this synapse.

Serotonin is then inactivated by being taken back up out of the synaptic cleft, into the serotonin neuron that released it, through the action of specific membrane carriers.

Fluoxetine inhibits this uptake process, resulting in a prolongation of the serotonin action in the synaptic cleft on the synaptic receptors.

Now, I have described the evidence that fluoxetine does inhibit this uptake carrier in vivo. How do we know that

the concentration of serotonin in the synaptic cleft is actually increased, and that inactivation of synaptic receptors is increased after fluoxetine treatment?

There are no methods for measuring directly the concentrations of serotonin within a finished synaptic cleft, but cytofluorometric analyses, and also in vivo voltimetric analyses, have indicated that extraneuronal concentrations of serotonin in brain are increased after fluoxetine, and there are extensive animal data indicating that the activation of synaptic receptors is increased by fluoxetine, due to the increased action of serotonin on those receptors.

For example, fluoxetine decreases serotonin turnover, as measured neurochemically by several different methods, and as an electrophysiological correlate to that, the firing of single neural units in the serotonin-rich midbrain, region of the brain, is decreased by fluoxetine.

This decreased firing of serotonin neurons and decreased serotonin turnover presumably results from increased serotonin stimulation of synaptic receptors, possibly, in that case, pre-synaptic autoreceptors.

Now, there is no gross disruption of behavior that is seen with fluoxetine. For example, there is no change in locomotor activity, but certain serotonin-related behaviors are affected.

For example, fluoxetine suppresses neurocidal

activity in rats. It propitiates the 5-hydroxy-tryptophane induced head twitch in mice. It reduces limb sleep, and potentiates the 5-HTP reduction of limb sleep in rats and in cats. It reduces food intake -- that's basically carbohydrate intake, and also reduces ethanol intake, or acts synergistically with 5-hydroxy-tryptophane.

Fluoxetine also produces certain neuroendocrine effects that are characteristic of serotonergic drugs, such as an increase in serum corticosterone concentration through increasing CRF and ACTH release, and potentiation of the 5-hydroxy-tryptophane in elevation of serum prolactin concentration.

Other indications of enhanced serotonergic function after fluoxetine treatment of animals, includes potentiation of the analgesic effect of morphine, and potentiation of the antihypertensive effect of 5-hydroxy-tryptophane.

Fluoxetine has found widespread use in animal experimentation, as a drug for selectively enhancing serotonin function.

Now, in all of the animal studies, the duration of uptake inhibition and the functional changes that result from that, was very long. In rats, for example, a single 10 mg/kg dose of fluoxetine inhibits serotonin uptake, and produces effects like (inaudible) for more than 24 hours.

This long duration is due to the persistence of the

demethylated metabolite, norfluoxetine, which is as potent and selective an inhibitor of serotonin uptake as fluoxetine itself.

And I want to emphasize that particular point. This slide compares fluoxetine to two other serotonin uptake-inhibiting drugs, torimipramine and zimelidine. All three of these drugs inhibit serotonin uptake in vitro, and all three are metabolized by indemethylation in vivo.

The influence of that metabolism on their pharmacologic activity is very different, however. Norfluoxetine, like fluoxetine, is a potent and selective inhibitor of serotonin uptake, so metabolism does not influence the selectivity of uptake inhibition.

The activity of the metabolite accounts for the long duration of uptake inhibition after a single dose of fluoxetine.

Fluordisipramine (ph.), in contrast to its parent drug, preferentially inhibits norepinephrine uptake, so the selectivity of fluorimipramine as a serotonin inhibitor is lost by metabolism.

Norzimelidine is a more potent serotonin uptake inhibitor than zimelidine, and norzimelidine brain levels are much higher than those of the parent drug, even at early times, in rats.

If this metabolism is blocked, efficacy is decreased. So metabolism is necessary for maximum efficacy of zimelidine.

Metabolism destroys the selectivity of fluorimipramine, whereas metabolism does not influence the pharmacologic specificity of fluoxetine, but only ensures a long duration of action.

Now, an important thing that fluoxetine does not do is to have affinity for receptors, like cholinergic, histaminergic, and adrenergic receptors. Many antidepressant drugs, basically the tricyclics, block these receptors. Amitryptilene, as shown by these radiologic binding data, has high affinity for the muscarinic-cholinergic receptor, or the histaminergic H-1 receptor, and for the alpha-1 receptor.

Blocking these receptors is believed to be associated with side effects, clinically.

Other receptors, like the serotonin 5-HT2 receptor, are also blocked by amitryptilene and several other antidepressant drugs.

Fluoxetine, in contrast, has little affinity for any of these receptors, or others that have been tested. As a rule of thumb, I would consider that IC-50 values of greater than 1,000 nanomolar, probably means that there is no significant effect on these receptors in vivo.

Fluoxetine certainly does not have these effects of anticholinergic drugs or alpha-blocking drugs in vivo, in animals.

Another effect of tricyclic antidepressant drugs is their effect on the heart, to produce an increase in the heart

rate and changes in the ECG.

Fluoxetine was compared to amitryptilene in anesthetized dogs by infusing the drugs intravenously, over time, to take blood levels up to higher than are found at therapeutic doses clinically. Amitryptilene increased heart rate, and decreased both volume, mean arterial pressure, and cardiac contractility.

Amitryptilene also slowed both intramyocardial and infranodal induction, as indicated by increases in the QRS duration, the PK interval, and the HV interval, as other tricyclic drugs were well-known to do.

Neither fluoxetine nor norfluoxetine had any major effect on heart rate, blood pressure, or other cardiovascular parameters, including the ECG.

Again, these cardiovascular effects of tricyclic drugs are well-known, and are attributed to anticholinergic and anti-alpha-1 effects, as well as to direct quinidine-like effects on the heart, and fluoxetine did not have these effects.

So, in summary, the animal data have shown that fluoxetine selectively inhibits serotonin uptake, and lacks direct actions on neurotransmitter receptors, as well as direct cardiac effect.

Those characteristics of the drug are what led us to be interested in it as an antidepressant drug and to test it clinically.

DR. THOMPSON: Dr. Lou Lemberger was recently president of the American Society for Clinical Pharmacology and Therapeutics. Dr. Lemberger has guided the research, both in clinical pharmacology and other clinical therapeutics, since the beginning of the story of fluoxetine.

DR. LEMBERGER: Thank you.

As Dr. Fuller has just discussed the preclinical pharmacology of fluoxetine, which was of interest to us, and so we tried to confirm and further demonstrate the activity of this compound in clinical pharmacology.

Fluoxetine inhibits the uptake of tritiated serotonin into human platelets, in vitro and in vivo. It has no effect on catecholamine uptake in man at clinically effective doses, which I will show in a few slides, and it maintains its specificity for inhibition of serotonin uptake after chronic administration.

Its normetabolite is also a specific inhibitor of serotonin uptake.

In this slide, fluoxetine was given at 30 milligrams a day for seven days, and then at 20 milligrams a day for the remaining 23 days. You can see that the fluoxetine levels increased, and norfluoxetine levels increase. When the drug is discontinued, the blood levels disappear.

If one looks at the uptake of tritiated serotonin into platelets which have been harvested from these patients ac

various times, you can see that, early on, there is an inhibition of uptake which is maintained throughout the period of drug administration. When the drug is discontinued, the ability of the platelets to take up serotonin returns towards normal.

This should read, "endogenous levels of serotonin in platelets." And when fluoxetine is administered, endogenous levels of serotonin in platelets decrease, because the platelet has no biosynthetic mechanism, and accumulates the serotonin from the circulation, but as the drug is discontinued, this again returns towards normal.

To demonstrate the specificity of fluoxetine as a serotonergic uptake inhibitor, and the lack of effect on noradrenergic systems, we compared that generated with fluoxetine with earlier studies with nisoxetine, a clinical investigational new drug. We looked at changes in blood pressure on the drug, at the rate of change in blood pressure on placebo, and by definition, the placebo value is 1.

And if one infuses norepinephrine into patients, one would expect, with a specific norepinephrine uptake inhibitor, to get an increased sensitivity, as was demonstrated on this slide.

One requires much less norepinephrine to get the same blood pressure effect, whereas with fluoxetine, you see, there is basically no change in response to norepinephrine.

Similarly, if one gives tyramine, which must be taken up by the nerve ending, the noradrenergic nerve ending, to release norepinephrine, using the same ratio -- placebo here would be 1, one sees a decrease in the responsiveness of tyramine, and one needs a larger dose of tyramine to get the same blood pressure effect in the presence of a specific norepinephrine inhibitor. But in the presence of fluoxetine, there is basically no effect of this compound on the noradrenergic system.

We did a study where we looked at fluoxetine administration chronically, given fluoxetine at a dose of 60 milligrams daily for 45 days. We measured both the amount of norepinephrine to raise levels of blood pressure, and also the amount of tyramine to raise blood pressure.

You can see, the open bars are the norepinephrine data. This is the placebo period, this is the fluoxetine period, and when the drug is discontinued, there is no change in the sensitivity of the noradrenergic system.

Likewise, similar data is seen with the tyramine administration, indicating that there is no effect of both fluoxetine or its normetabolite, which builds up at that time, or any other metabolites, as a matter of fact, on the catecholamine system, again indicating specificity.

Now, if one looks at the physiologic disposition of fluoxetine, and predominantly its absorption, the drug is well

absorbed after oral administration. Its relative bioavailability approaches 100 percent, and peak plasma levels occur at about six to eight hours.

There is no effect of food upon the overall absorption, that is the area under the curve, of fluoxetine, although the rate of absorption and the time to reach the peak plasma concentration are somewhat delayed. Plasma concentrations demonstrated dose proportionality.

We administered C-14-labeled fluoxetine, and demonstrated that one could collect approximately 80 percent excreted in the urine, approximately 14 percent in the feces, over a specific time period.

If one looks at the metabolites, fluoxetine and its glucuronide are excreted unchanged in the urine to about 18, 19 percent. Predominantly, the majority of the material goes on to norfluoxetine, which, again, norfluoxetine and its glucuronide are excreted in the urine, and a large portion of it is present as puric acid. The label is in this position of the molecule, and one isolates a label on the puric acid. We have isolated about 55 percent of the metabolite. We are in the process of working on these intermediates, to isolate them in large enough quantities to do a final determination.

If one looks at the distribution and size of pharmacokinetics, fluoxetine possesses a long terminal half-life. As Dr. Leber mentioned before, the half-life is one to four

days, with a mean of about two days after single oral doses, and approximately four days after chronic administration.

Norfluoxetine is an active metabolite. It also has a long terminal half-life of about four to fifteen days, with a mean of about seven days.

Two to four weeks are required to achieve steady-state. Patients receiving the drug for greater than one year display similar kinetics to normal volunteers, who have achieved steady-state within five weeks.

Fluoxetine is highly bound to the lipoproteins, greater than 90 percent, and it is not displaced, nor does it displace, a variety of other drugs which we have looked at.

If we look at the pharmacokinetics in special populations, the kinetics are similar in normal volunteers. In healthy elderly volunteers receiving single doses of fluoxetine, the kinetics are similar, in elderly depressed patients receiving the drug chronically, and in normal volunteers receiving multiple doses of fluoxetine in order to achieve steady-state.

After single doses, the kinetics of fluoxetine are similar in normal volunteers, and in patients with varying degrees of renal impairment and hepatic cirrhotic patients. Studies among these are currently in progress.

We looked at a variety of drug interactions, and this is a basic outline, where we had a control baseline period.

They received a test drug and the drug in question, whether it was warfarin, butamide and so on. They had a washout period. The kinetics of the test drug were measured here. Fluoxetine at either 30 or 60 milligrams was given, and then the test drug was administered. This was single-dose, and then fluoxetine was given at eight doses, and the test drug again given.

This was done not only to study the kinetics of the effect of fluoxetine on drug interactions, but also the metabolites that may build up during that time frame.

This slide just summarizes the various drugs that we looked at in detail. We chose drugs that would be a prototype of different metabolic reactions -- aromatic hydroxylation, oxidation, endeoxidation, side chain oxidation, glucuronidation and so on, and also we looked at two drugs that affect protein binding.

The effect of fluoxetine on the test drugs showed no difference in the blood levels, either after single-dose or after eight days' administration of fluoxetine, on the test drug, and the test drugs had no effect on fluoxetine blood levels.

We also, in all of these cases where applicable, looked at the pharmacologic parameters. For example, in the case of warfarin, we saw no change in the total time. In the case of parabutamide, we saw decreases in glucose and increases in insulin with the parabutamide, and there was no change with

fluoxetine.

We looked at psychomotor studies in diazepam and ephrinol, and again, fluoxetine, either in single doses or multiple doses, did not affect the psychomotor performance with either ephrinol or diazepam.

So, in summary, clinically, fluoxetine is a selective inhibitor of serotonin uptake. It is well absorbed, and its overall absorption is not affected by food, and it demonstrates dose proportionality. It is excreted primarily in the urine, about 80 to 85 percent, and it is excreted as the parent drug and polar metabolites.

Fluoxetine and its normetabolite, norfluoxetine, have long half-lives, approximately two days and seven days respectively, and are highly bound to plasma protein.

After single oral doses, fluoxetine displays similar kinetics in the elderly, renally impaired, when compared to normal volunteers.

Fluoxetine does not appear to give any clinically significant interactions with a variety of test drugs.

Thank you.

DR. LEBER: Lou, I'd like to make a point, though.

DR. LEMBERGER: Yes?

DR. LEBER: I think that we had not intended to discuss in any detail several of the points that you're raising about the metabolism of fluoxetine. It's not that they may not

be so, but some of the points raised, for example, about dose proportionality, may be questioned, and although we have not yet finished our formal review -- and so I'm really just saying to the committee, we had not intended to discuss this. What you hear presented by Dr. Lemberger, comprehensively and clearly, is the firm's interpretation of data they have seen, and we have yet to critically analyze or have pass a supervisory review.

There may, in fact, be disagreements on issues that I am not even aware of yet. For example, the influence of food on the availability of the drug -- I think in particular the dose proportionality claim, I already know, we believe is not so. And there is some evidence to show non-linearity, and that is, as the dose increases, the dose-corrected AUC goes up in disproportion for the parent drug.

And so I think those are issues that we don't want to discuss in front of this committee, but we will probably do it afterwards, in terms of working with our pharmacokinetic expert.

DR. LEMBERGER: Okay. When we were asked to present, we were not sure that this was the case. One of the issues that you did bring up was the norfluoxetine, and therefore we felt somewhat obligated to try and address this.

DR. LEBER: Well, I think you have a right to present the data. I was simply providing that little boxed

warning to suggest to everybody that this is your view, and there is nothing wrong with saying that your view is correct. In fact, it may be precise, accurate and to the point.

But I want everyone to understand that our group has not candled the egg with the same degree of intensity that we looked at the efficacy data, and I think that is just important for -- I can't make an informed criticism, or even critique, and I don't think we want to do it at this point. So, just as long as the record --

DR. LEMBERGER: Okay. Thank you.

DR. THOMPSON: Dr. Robert Zerbe is director of neuroendocrine research at Lilly, and has guided many of the clinical studies, including some of the more recent ones that Dr. Leber referred to.

His presentation, however, will be restricted to studies that you have seen, that were presented in the NDA, and will be very similar to the analysis of Dr. Lee and Dr. Chi, with one exception, and that is that, although we have excluded in the NDA the pooling of the investigator that was mentioned, it is our belief that that study was done appropriately, under double-blind conditions, and we excluded it because, statistically, it showed a treatment by investigator interaction.

DR. LEBER: By the way, that is a good point, and I think I ought to clarify something for the record, too.

Dr. Chi said, I believe, if I'm not misquoting him,

that it was difficult to believe data, and maybe that's what everyone is picking up on, in that particular subset.

I think what he meant was that a clue to the fact that it didn't fit with the rest of the pooling was the fact that the P-values for the Cohen study, and the direction of the differences between treatments, were markedly different, and this was a signal to look further into the data, not -- and I emphasize, not to question the integrity of the investigator or anybody else.

It was simply an analytical clue, and if you're speaking to that, I felt we ought to correct it before you do.

DR. ZERBE: Thank you.

This presentation deals with the efficacy of fluoxetine, and the efficacy analysis that will be presented today is based on eight placebo-controlled studies, and we feel demonstrates exactly the conclusions that have already been reached by the FDA, that is, that fluoxetine is significantly better than placebo in the treatment of patients with major depressive disorder.

The study design used in these investigations is shown here. All of the studies to be described today were started with a one-week, single-blind, placebo treatment period, to identify transient placebo-responsive depressive problems.

If, during this period, the Hamilton depression scale

rating fell by more than 20 percent, the patients were excluded from participation in the trial.

Patients who failed to respond to one week of placebo therapy were randomized to treatment groups for double-blind evaluation of efficacy.

In six of the eight studies, three treatment groups were used. These included fluoxetine, in doses of 20 to 80 milligrams per day, placebo, and imipramine, in doses of 75 to 300 milligrams per day.

In two of the eight studies, only fluoxetine and placebo were compared. The study treatment period was six weeks in the three-celled studies, and five weeks in the two-celled studies.

Patients selected for participation in this protocol were limited to adult outpatients with major depressive disorder, as determined by the DSM-III criteria. Only patients with unipolar depression were included in the studies. A score of at least 20 on the 21-item Hamilton psychiatric rating scale for depression was required, as was a score of 8 on the Raskin depression scale.

To eliminate patients who had primarily anxiety, the Raskin score was required to equal or exceed the Cobe anxiety scale.

The dose of active medication was rapidly escalated to daily levels which were felt to be therapeutic. The

escalation could be halted by the physician if efficacy was demonstrated at lower doses, or adverse events limited further increases in dose.

Thus, with fluoxetine, the starting dose of 20 milligrams was increased over one week to maintenance doses of 40 to 80 milligrams.

In the six three-celled studies, including imipramine, imipramine was started at doses of 75 milligrams, and was increased to 100 to 150 milligrams after one week. Further increases were allowed each week to a maximum of 300 milligrams per day.

The number of patients entering the various treatment groups of each study were essentially equivalent, except the study of investigator 3, which by design had a smaller placebo treatment group. Two of the six three-celled studies had over 50 patients in each of the treatment arms.

A total of 279 patients received fluoxetine, and 276 received placebo.

The demographic characteristics of the patients participating in the studies were not different between groups. Shown in the top two rows are the characteristics of the patients who participated in the eight studies which compared fluoxetine and placebo. In the bottom row are the characteristics of the imipramine-treated group, from the six studies which included an imipramine treatment arm.

One can see that the groups are quite similar in mean age, as well as age range, the percent of female participants, and the mean Hamilton depression score at baseline.

Only evaluable patients were used in the efficacy assessments to be presented today. Patients were not considered evaluable for the following reasons: first of all, a break in therapy, defined as more than two days, or three doses of missed medication in the first two weeks, two or more missed office visits, protocol exclusion, or insufficient duration of therapy, defined as less than two weeks of study drug.

These criteria were defined by the protocol prior to initiation into the study.

Shown here are the changes in Hamilton depression scores for the three treatments. For fluoxetine and placebo, numerical results are pooled from all eight studies. The imipramine data include results from only the six three-celled studies.

In the fluoxetine group, 195 patients were considered evaluable. These patients had a mean decrease in their Hamilton depression score of 12.55. This compared favorably to the placebo group, which had a decrease of only 7.52.

In the smaller group, treated with imipramine, the decrease in Hamilton depression score was also much greater than with placebo. Thus, the change in Hamilton depression scores observed in these studies indicates that fluoxetine is

superior to placebo, and comparable to imipramine, in the treatment of depression.

A statistical analysis is provided in the next slide. Shown here are the results of the eight individual studies. At the top, the results of the individual three-celled studies, and at the bottom, the results of the two two-celled studies.

Mean improvement is shown on the left, and comparative probabilities on the right. Note that two studies stand alone in demonstrating the efficacy of fluoxetine over placebo, investigator 2, which incidentally is Dr. Cohen, as previously mentioned, in the three-celled group, and investigator 7 in the two-celled group.

The data from the six three-celled studies, having been generated from the same protocol, could have been pooled. Investigator 2, however -- that's Dr. Cohen, appeared to be different, in that the placebo group was less responsive, and the fluoxetine group more responsive, than respective groups in the other five studies.

Therefore, to ensure against possible bias introduced by an unusually favorable result, we will confine our discussion of pooled data to those including only the five of the six three-celled studies, that is, excluding investigator 2. Analysis of such a five-celled pool on the Cobe-Hamilton depression score indicates, as you have already seen, that

fluoxetine is superior to placebo, the probability of alpha error being 0.014.

Similar results are obtained from the clinical global impressions, in which the investigators were asked to rank the severity of the depression at each visit, on a scale of 1, which indicated no depression, to a scale of 7, which indicated maximum depression.

Again, in the overall pool, both fluoxetine and imipramine are numerically more efficacious than placebo, and comparable to each other.

Individual study results for improvement in the rating of depression severity are shown here. In three studies, 2, 5 and 7, the results demonstrate significantly more improvement with fluoxetine than placebo. In two other studies, 3 and 6, there was a borderline significant difference.

The pooling of five three-celled studies, excluding investigator 2, showed superiority of fluoxetine over placebo with a probability of alpha error equal to 0.002.

The clinical global impressions of improvement over the pre-treatment period were also assessed. Investigators ranked improvement on a 1 to 7 scale, and the changes from baseline to endpoint are shown here. Again, a similar impression of efficacy was obtained. That is, both fluoxetine and imipramine are superior to placebo and comparable to each other.

Individual study analysis shows that in three of eight studies, 1, 2 and 7, fluoxetine is shown to be superior to placebo, and in three others, 3, 5 and 6, this difference is of borderline significance. Pooled analysis, excluding investigator 2, showed a significant superiority of fluoxetine over placebo, with a probability of alpha error of less than 0.001.

The reasons for discontinuation from the three-celled study are shown here. This pool excludes investigator 2. In the fluoxetine group, 98 patients, representing over 50 percent of those enrolled, completed the study. Roughly equal percentages of the fluoxetine-treated group dropped out for adverse events or lack of efficacy, in the fluoxetine group.

The dropouts because of lack of efficacy were significantly lower with fluoxetine than placebo, another indication that fluoxetine is an effective antidepressant.

In summary, out of eight studies, the following indicated statistically significant or nearly significant differences between fluoxetine and placebo, all in favor of fluoxetine. In the Hamilton depression total, two studies were significant. For the CGI severity of depression, three studies were significant, and two studies were nearly significant, and for the CGI global improvement, three studies were significant and three studies were nearly significant.

Thus, for each indicant presented today, at least

two individual studies in the pool of five three-celled studies demonstrated superiority of fluoxetine over placebo.

It is important to note three points about the data which I have presented today. First, only three efficacy indicants, the total Hamilton depression score, clinical global impression of severity, and clinical global impression of improvement, were presented today.

In the study, 13 different indicants, some clinical, some patient, were assessed. Statistical tests of the indicants not shown today yields results similar to those which were presented. Second, as noted previously, only evaluable patients were presented today.

If all patients, regardless of evaluability, were analyzed, the same efficacy conclusions would be reached. And, third, the statistical assessment presented is based on endpoint analysis. An endpoint is defined as the last patient visit. Thus, patients who dropped out early are included in the analysis, provided they meet the previously mentioned evaluability criteria.

A statistical evaluation of only those patients who completed the full six weeks of treatment yields results which were at least as favorable as the endpoint analysis.

This then leads us to conclude that fluoxetine is an effective antidepressant which is significantly better than placebo in the treatment of major depressive disorder.

Thank you.

DR. DETRE: Thank you. Could I just ask one question, if I may? The statement was made that only patients with unipolar depression were selected for these trials. How were the bipolar ones excluded?

DR. ZERBE: The --

DR. DETRE: I wanted to know, by what criteria was it determined that patients are unipolar?

DR. ZERBE: The diagnosis of unipolar depression was based primarily on the clinical history of the patient, not having previously demonstrated evidence of bipolar illness.

DR. DETRE: Thank you very much.

DR. LEBER: Can I ask you another question? This is an example of the double-entry ledgers that we run into -- how many studies are you reporting on? Eight, two, or three?

DR. ZERBE: We're reporting on eight studies.

DR. LEBER: How do you describe them as eight studies? I thought the six three-way pool was one study. You can't have it both ways.

My point is very clear. If you want to rely on the pooling, then it's a pooled study, and I believe that your protocol called for a multicenter trial. If you want to say that you have six independent studies, then you don't have quite the overwhelming majority of studies all going the same way. You basically are trying to take advantage of presenting the

data in more than one way, and doubly counting studies. For example, you then go back and do a pooling of eight studies, to do a comparative overall analysis.

And one of the things I find most distressing, for a disinterested and dispassionate assessment of data, is the throwing together and the obfuscation of what is, in fact, the data bases we're looking at? Anybody who chooses, after the fact, can look through yesterday's headlines and prove that, in fact, nothing happened that did, and everything happened that didn't.

And I think that our major problem right now is trying to look at the evidence, and frankly, I think we did spell it out. And I think that your presentation -- my concern is that I don't even know what the company's stand is. Did you plan this as a six-way study, an eight-way study, or were they planned as individual studies?

DR. ZERBE: It was by an identical protocol, with the intention of pooling the data, and I think the only reason -- I'm sorry if we misled you, to suggest that we were double-counting them, I think we just tried to demonstrate different approaches to looking at it. I don't think the bottom line --

DR. LEBER: In this case, the bottom line doesn't change, you're absolutely right. But the point that I'm trying to make is that it is very hard, looking at a mass of data, to

know what anyone is talking about.

One of the critical things for us to do, if we're going to discuss anything, is for us to have a common data set. And my experience over the years has been that the times when we get into disputes that are meaningless is when everyone is talking about a different group of studies, and I think it may be important.

You may want to use numbers, for various reasons, to describe individual studies, but I think that if there is a point of contention right now between the agency and yourselves about the nature of the data base, we ought to get it on the table.

I am impressed that you have, at the most, three placebo-controlled studies -- one that was conducted at six different sites, and two independent placebo-controlled studies, and they should be counted as they are.

To redisplay them in different ways, I think, makes it difficult to follow the argument. I didn't say you couldn't do it. I just think, for purposes of the discussion in a common meeting, it's difficult.

DR. ZERBE: I don't think there's any disagreement with our approach. It's just an alternative way of looking at it, not trying to change any of the conclusions based on that.

DR. THOMPSON: Dr. Joe Wernicke joined Lilly about a year ago, and has been the clinical scientist primarily

responsible for our studies with fluoxetine since that time. He will discuss the safety profile, and although most of his presentation will be restricted to the data in the NDA, on a little over 1,400 patients, several of the key slides, addressing serious side effects, such as death and suicide attempts and overdoses, will be in fact up to date, including data on more than 3,100 patients given fluoxetine worldwide.

DR. LEBER: Again, the same caveat applies. The staff has not looked at this data. This data will be looked at in its submission that will eventually be made. But once again, you must look at this -- and I feel like a judge telling the jury a set of instructions -- as recognizing that this is the firm's only interpretation of the data. Only they have looked at it; we haven't.

DR. WERNICKE: I would like to review the side effect and safety profile of fluoxetine briefly, and what I would like to cover are the adverse events we have seen in the NDA, and in individual groups, and also talk a little bit about some other safety issues that pertain to fluoxetine.

And as Dr. Thompson has said, some of these will be more comprehensive than the NDA, and I will point that out at the time.

This slide shows the adverse event profile that Dr. Kapit already showed. At the bottom are the percentage of patients who reported that adverse event at any time during

treatment, without any preconceived notion or idea as to causality. The open box reports the percentage of patients who reported that adverse event, and the closed box, the percentage of patients who discontinued treatment at the time that adverse event was reported.

The most frequently reported are nausea, nervousness, headache, insomnia, anxiety, and so forth.

Now, let me talk specifically about the placebo-controlled studies, about which -- from which you have already seen the efficacy data. Here are the reports on discontinuations because of adverse events for fluoxetine and placebo. In order, they are nausea, dry mouth, headache, nervousness, insomnia, and so forth. The stars indicate significant difference against placebo. The only significant difference is of course with fluoxetine, with discontinuation. There are a few that are significantly different.

The patients who reported any adverse event during the trials are 79 percent with fluoxetine treatment, and 60 percent with placebo treatment. Discontinuations because of adverse events were 16 percent with fluoxetine and 3 percent with placebo.

This slide only shows the most frequently reported, so here I would like to show others where there were significant differences between fluoxetine and placebo treatment.

To put this into a more clinical perspective, on this

slide, I would like to show the fluoxetine versus pooled comparator adverse event reports, and these include imipramine, amitryptilene, and doxipen, from those studies.

We see again that nausea is the most frequently reported with fluoxetine; dry mouth, nervousness, drowsiness, headache, and so forth. The ones that are significantly different are nausea, nervousness, anxiety, and insomnia, and Dr. Kapit already alluded to those being perhaps related to fluoxetine.

They are tricyclic antidepressants, as we know from the literature, and clinical experience, are associated with anticholinergic adverse events -- dry mouth, drowsiness, dizziness, constipation, and vision disturbance.

Discontinuations were fairly infrequent with fluoxetine, insomnia being the only one in this group that was reported, that was associated with significantly more discontinuations, as opposed to dry mouth and some of the anticholinergic effects being related to the tricyclics.

Other adverse events which were significantly more frequently reported, and led to discontinuation, are listed in this slide.

Rash, as Dr. Kapit has already told you, is probably our most significant adverse event in terms of potential seriousness. It occurs in about 3 percent of patients treated with fluoxetine. Two-thirds of those continue treatment

without difficulty, although 1 percent discontinue. The frequency of rash was the same as with imipramine in the controlled study. The rash description varies quite a bit. Most of them are mild. However, we have, out of 3,000 patients, approximately, treated with fluoxetine, five have had a rash that has been associated with, occasionally, hives.

Some of these rashes may require treatment. However, all patients recover; and that is from our entire data base.

These are the deaths that have occurred during all fluoxetine clinical trials, which included about 3,000 patients, U.S. and Europe, and about 1,000 comparator placebo-treated patients.

Cardiac deaths -- there have been five. One of them was on doxipen. The others were primarily myocardial infarctions. We don't believe that any of these are related to treatment with fluoxetine.

There have been a number of suicides, eight in all -- four by hanging. One of these was in a placebo-treated patient. There have been a number of other suicides. Two of them were during the placebo period.

There is only one potential fluoxetine involvement in any of these, and this is in a 38-year-old male who took an overdose of clomazine, amitryptilene, and pentazocine. Fluoxetine is with a question mark, because it is not clear that

that patient took any fluoxetine. The bottle of pills was found, and the count wasn't clear, but certainly he did not take a lot. That patient was found dead. Notice that these are all males, a group that is at high risk for suicide.

Other deaths were a lung carcinoma and an infection.

I would like to go back to the suicides, and point out, again, that nobody apparently -- we feel certain, I'm sure, that nobody has killed themselves with fluoxetine, and in that regard, I would like to talk about some of the overdoses.

These are four that were reported in the NDA. Since then, we have had a number of others. In the NDA, we have one patient that took about a gram of fluoxetine, had some mild transient EKG changes. Since that time, we have had one patient that took, apparently, 3,000 milligrams of fluoxetine, had some transient EKG changes and two very brief seizures, but recovered uneventfully. All other patients recovered, also.

In that regard, I would like to go to the effects on the cardiac conduction. This is the heart rate as determined by the EKG's on double-blind studies.

As we expected from the literature, imipramine and amitryptilene were associated with a significant increase in the heart rate, whereas fluoxetine was associated with a smaller but statistically insignificant decrease in the heart rate.

The QRS complex, again from the ECG data of all the double-blind studies, is shown here. Imipramine and

amitryptilene are associated with the prolongation of the QRS complex, and fluoxetine really has no effect. We feel that that is the basis for its probable relative safety in overdose, and why the people that took the overdoses fared so well.

Laboratory studies were done during the treatment with fluoxetine, and we detected no trend toward abnormal. The percentage of patients with abnormalities was similar to the control groups, and the laboratories' abnormalities that were detected were not related to clinically significant observations.

This slide shows the total number of patients and the duration, as in the NDA. At that time, there were 74 that had been treated for over a year. The number over a year now is 179, with two patients having been treated for more than five years.

In summary, then, I would like to say that we feel quite comfortable in saying that the side-effect profile of fluoxetine is well-tolerated. The most commonly observed effects are nausea and insomnia and nervousness. Rash with occasional arthralgia or hives is seen infrequently.

Fluoxetine is relatively safe in overdose, with minimal effects on cardiac function, and fluoxetine is safe in long-term use.

That is the end of my presentation. I do have a slide here to address the question of insomnia.

DR. LEBER: May I ask you a couple of questions?

DR. WERNICKE: Certainly.

DR. LEBER: The second most common thing we saw in the data base, especially now that you've told me you successfully excluded all the unipolars, was psychosis. It happened in about, originally, 9 out of about 1,100 patients, or 10. Now it's up to 14, I understand? You didn't mention that. What do you think the psychosis is due to?

DR. WERNICKE: Well, as Dr. Kapit already alluded to, we feel that some of them may have been precipitated by treatment. Some may be unrecognized bipolar illness. It's not always clear.

There have been a number of patients that have reported that, but their frequency doesn't seem to be any higher than in comparators.

DR. LEBER: How does your incidence compare to that of the comparative drugs, that you have discussed everything else in comparison to?

DR. WERNICKE: Well, that's a little bit difficult to say. In the bipolar study --

DR. LEBER: No, no. Let's talk about the entire data base.

DR. WERNICKE: Okay.

DR. LEBER: That's what you have been talking about up to now, and I'm sort of curious, since it was the second

most common serious events, and I want to go through the three serious, life-threatening events, because you didn't mention them.

Oh, you did mention the rash, which could have -- if it were Stevens-Johnsons, or exfoliated, it would be very bad. Psychosis; and the last, of course, is leukopenia, that may border on agranulocytosis.

DR. WERNICKE: Right. Psychosis, we didn't -- I don't remember any cases that we observed with comparator drugs. Now, some of these episodes occurred late -- very late in treatment, and there were much fewer patients in prolonged treatment with the comparators. I have the breakdown of the --

DR. LEBER: If that's the case, that means the estimated risk of 1 percent is a massive underestimation of risk. You're telling -- and again, the timing of these cases becomes critical, because if this is something that occurs late, and the number of patients at risk late is much smaller, the actual case exposure estimate goes way up.

Now, we might be talking about a significant concern in the use of the drug. So, I mean, this is why we have to talk seriously about safety in the safety update. It is not something we can completely establish.

But one of the conclusions I was concerned about is the one that you say, safe in long-term use. That is difficult to say, because of the size of the data base, but we are

willing to say that that's the case.

[redacted] another serious thing Dr. Kapit found that you didn't talk about, probably because of numbers. It was leukopenia. Three cases were leukopenic. One apparently -- and I don't know what happened to that individual, probably reached levels that were -- was it agranulocytotic? Mainly -- so this is one of the things that we worry about. Not that it doesn't occur with other psychotropic drugs, but we just were interested in what was the follow-up.

DR. WERNICKE: Well, we have looked at all the patients with white count below 6,000, and there was no person that had a count below 1,000, total, at any time. We had some follow-up information on those patients.

DR. LEBER: What happened to the patients that had, say, neutrophil counts between, say, 2,000 and --

DR. WERNICKE: Most of them continued to go up. Where we had follow-up, they continued to -- they went up again.

DR. LEBER: Again, this is the kind of thing we'll look at in the safety update.

DR. WERNICKE: Right.

DR. LEBER: I just wanted it clear that we are not reaching any final conclusions about this kind of a thing. This is an interim assessment, awaiting a safety update and the

meeting of the minds.

DR. WERNICKE: Right, and we didn't exclude psychosis and leukopenia, because we wanted not to talk about it --

DR. LEBER: No, no.

DR. WERNICKE: We only had a little bit of time in here, and --

DR. LEBER: I understand.

DR. WERNICKE: -- and we wanted to give an overview of what went on.

DR. LEBER: Right. Are there any other questions?

Yes, sir?

DR. PRESKORN: I have one question. With the long half-life of this compound, how long does the rash last?

DR. WERNICKE: Well, that's an interesting question, because a lot of people weren't left to their own devices. The ones that weren't treated, it tends to last a few days to a week, maybe two weeks at the most. A lot of them, the severest ones, were treated with denephril or sometimes steroids. It varies, everything from gone the next day to, two weeks later it was still subsiding.

It was -- it's very difficult to get a firm grasp on that. The description varies. So basically, I would say a day to two weeks is the best guess we can make.

DR. LEBER: I have another question. What was the timing of the deaths? At the time we got the NDA, I think we

had one death, or was it two? None? It might have been a case in -- what I'm interested in finding out, of course, again, is that there is a possibility that this is a time-adjusted thing.

Did the deaths occur late? And, if so, that again would be an issue that we ought to discuss, because, again, the issue of the accumulation of a long-acting metabolite, whether or not it has linear pharmacokinetics, and then, of course, the issue of non-linearity of the parent drug, both of which may accumulate.

And that is something that we need to be concerned about, and we have unresolved. What is the distribution of deaths and time of treatment on fluoxetine?

DR. WERNICKE: Well, the one patient had the MI after three years of treatment. One was, I believe, after about six weeks. One lady had an MI, and died, actually, two months after the drug was stopped.

So, again, it is hard to make any firm conclusions about it, but it seems to be pretty scattered. The same is true for the suicides. Some were early, some were late -- no pattern that we could discern.

DR. DETRE: Is there any information on the effects of abrupt withdrawal?

DR. WERNICKE: Well, not systematically. We haven't followed patients. However, we do have a lot of investigators that have a patient population that they have followed, that

are truly private patients, and we have not had any reports of any problems in that regard. Remember, the drug does have a long half-life, so people essentially withdraw themselves from its use.

DR. LEBER: Do you have any blood level data on the patients who overdosed, because one of the problems in overdose estimation and safe passage is whether they really got the drug on board after they overdosed, or whether it all came out in the EW.

DR. WERNICKE: Right. That patient that took, apparently, 3,000 milligrams, their blood level data, the peak was about nine hours after the dose, and was about 1,700 nanograms per ml, which was a -- normal being about 300 to 400, so that is the only level we have. And, unfortunately, that wasn't the one with the highest dose, but at least we have that, and that is also when those two brief convulsions occurred. But that patient had had a history of seizures, I know, and then she recovered uneventfully.

DR. LEBER: There was, I know, a question about pseudo-seizures versus true seizures. Has any new seizure information come later in the data?

DR. WERNICKE: We haven't had anything else -- well, actually, that is not quite true. Dr. Chouinard has done a lot of EEG's on his patients, which he routinely does, and I -- if you would like, I could ask Dr. Chouinard to discuss those.

That is not part of our submitted data package.

DR. LEBER: Activity on an EEG that would be different from the ordinary seizures. I was really asking about something like a tonic-clonic seizure, or something that was recognizable as an absent state, or --

DR. WERNICKE: That one patient with the three-gram overdose had two definite generalized seizures. Now, there was one normal volunteer that may have had a brief seizure on awakening, and after, I believe, one dose of fluoxetine, this sort of awakening seizure.

That's very ill-defined, but that could be another one. There was one patient that fit the description, and the investigator's impression was probably pseudo-seizure. One patient may have had a transient ischemic attack, perhaps a focal seizure -- we can't be sure. She hasn't had any more, to our knowledge.

DR. LEBER: Any delirium?

DR. WERNICKE: Well --

DR. LEBER: Or are your psychoses deliria?

DR. WERNICKE: Well, some of them probably were. There was one mention of hallucinations, not delirium as such. I would say no, not that we have been able to detect.

DR. DETRE: Dr. Steinbach, do you have a question?

DR. STEINBACH: I have a question, can my patient drink while taking this medication?

DR. WERNICKE: Dr. Lemberger?

DR. LEMBERGER: We have done an interaction study, where we gave the subjects, in the paradigm that I discussed before, either 40 milligrams of fluoxetine or 60 milligrams of fluoxetine, as a single dose a week before they received alcohol. Blood levels of alcohol were measured both by a standard breathalyzer test, as well as by headspace analysis. So we measured it by both methods.

Then they received fluoxetine, and then the alcohol again, three hours after, and then they received eight days of fluoxetine, then another dose of alcohol, which was designed to give threshold levels that was comparable to drinking four shots. It gave a level of close to 60 milligrams percent over the time period.

And we did psychomotor performance studies throughout each of these things. There was no difference between the blood levels of alcohol whether given alone, or with the fluoxetine, either single doses or multiple doses, and again, there was no effect of fluoxetine on the psychomotor impairment that alcohol itself produces. It wasn't any exaggeration, so -- and this included stability of stance, tracking behavior, and some other things.

DR. THOMPSON: Those data on alcohol were confirmed by another study done in Germany, and have not been submitted in detail to the agency, but compared fluoxetine with

merprodiline (ph.). Merprodiline clearly impaired psychomotor performance, both alone and in combination with alcohol, in contrast to fluoxetine.

You asked two questions that I think Dr. Wernicke can address for you. One was the time course for insomnia, and we have data on the frequency with which that was reported by the patient, visit by visit. Want to show that one?

DR. WERNICKE: There was one other question, if we may, for a moment. Yes?

DR. THOMPSON: The -- we have data on that as well.

DR. DETRE: Dr. Chien, you had a question?

DR. CHIEN: No.

DR. DETRE: Okay, fine.

DR. ZERBE: On this slide, we have the reporting of insomnia over time. The red bars are up to a year of treatment, these are weeks down here, and this is just percent reporting, and it appears that some patients who have insomnia continue to report it. It just doesn't -- it seems to be fairly steady, about 9 percent.

The blue bars indicate first reports of insomnia, and I included that because it is difficult to tell from this, from just all reports, whether the same people have it, whether new people get it, and if you look at the first report, it looks like, if people have it in the beginning, those are the ones that are likely to continue to have it.

It doesn't seem to be something that pops up later, and that is true for all the adverse events with the -- all that we have looked at.

DR. DETRE: Dr. Chien and Dr. Preskorn still have questions.

DR. CHIEN: Among those who overdose with fluoxetine, or even become psychotic, do they show side effects, such as nervousness, insomnia, nausea, more than anybody who did not overdose, in side effects?

DR. ZERBE: Not nausea. Several of the -- one of the patients had spontaneous emesis. There was one patient that -- well, one who didn't really take an overdose, was mistakenly given double their dose, and became manic during that episode.

DR. CHIEN: The ones with the high overdoses, that wasn't really reported as part of their picture. That's not --

DR. ZERBE: It appears that, at very high doses, that doesn't become that prominent. However, we do have that one case where that recently occurred.

In terms of nausea, that was reported by one other patient, I believe, and then the one patient had spontaneous emesis. Some of them have reported no ill effects at all.

DR. PRESKORN: Was there a clustering of side effects, so that they weren't random, but rather were triad, or some sort of a cluster of side effects that patients were likely to get, is question number one, and question number two,

was there a difference between groups in terms of the use of the sedative-hynotic that was improved by the three different conditions?

DR. ZERBE: Well, sedative-hypnotics, I'll get to in a second. The clustering -- some people report more adverse events, and often, anxiety and nervousness were reported together. The reason they're listed separately is because of the way the data was collected.

Often, what investigators put as a symptom was nervousness, and then as a cause, was anxiety, so those tended to cluster somewhat, but not always. Some people just reported some, and some, others.

We looked for clustering like that, and it was just so diffuse, you could say, well, maybe there was an association, but then there were a lot of exceptions to that. So I would say probably no, but nothing certain that we could identify.

Now, in regard to the question on the use of the sedative drugs, what we did, in the three-celled study that you've heard about the efficacy on, the imipramine, fluoxetine and placebo study, we divided patients by educated, retarded, neither, or both, and looked at all patients, and looked at the use of benzodiazepine.

And as one might expect, patients that were educated tended to use more benzodiazepine than patients that were

retarded, who used less.

However, there was no difference, depending on what drug they took, whether they took fluoxetine, imipramine, or placebo. Therefore, although fluoxetine appears to be associated with some anxiety and insomnia, it certainly, in this study, doesn't appear to be associated with any more sedative use.

DR. PRESKORN: That is a single percentage of patients who have taken at least one dose of benzodiazepine. What happens if you look at that in terms of continuous dosing, total dose, cumulative dose? That might display something quite different.

DR. ZERBE: That, we haven't done. That's a more refined --

DR. PRESKORN: Also, that is a very small sample.

DR. ZERBE: Yes.

DR. PRESKORN: If you would tell us the retarded patients, that's interesting, because that's the group, if anything, who wouldn't need it.

The retarded group, I find a little interesting. Both active drugs show an increase. Both imipramine and fluoxetine may be excitatory, in that sense, in that group, but who knows?

DR. ZERBE: The N is so small.

DR. PRESKORN: Placebo has the least -- oh, I'm sorry.

Other way around.

DR. ZERBE: Fluoxetine has the least.

DR. LEBER: Good observation -- wrong data.

DR. PRESKORN: Thank you.

DR. ZERBE: But I don't think we can -- you know, the numbers are so small, I don't know that we can say much about that. We tried to answer that question post-hoc as best as we could from the data, but that was not designed to be part of the study. This was just use of benzodiazepine, if the investigator thought it was necessary.

Yes, sir?

DR. STANLEY: Is the side effect profile different for the patients requiring the benzodiazepines, say, in the fluoxetine-treated group? In other words, those requiring benzodiazepine -- do they show more of the anxiety and the nervousness, as it would seem, compared to those on fluoxetine who did not require benzodiazepine?

DR. ZERBE: We haven't looked at it in quite that way, but this would imply that they probably wouldn't, because the use wasn't related to what drug they were getting.

DR. THOMPSON: Remember that the number of patients using benzodiazepines is right at 10 percent of the total population. Those groups have 270-some-odd patients in them. It's a very small number.

DR. STANLEY: I just wanted to get a sense of, you

know, what percentage of this group that is being treated, had those signs of activation, or the nervousness or --

DR. ZERBE: Yes, that's another good way to look at it. We tried to look at the data in as many different ways as we could, in the time, but I think that is a valid way to look at it, too.

DR. LEE: But didn't you also use chloral hydrate? I mean, weren't there other sedatives given besides benzodiazepine?

DR. ZERBE: Benzodiazepine and chloral hydrate, but there was so little chloral hydrate, the N's are even smaller. I do have that data on inacetate. We can look at that, but --

DR. LEE: Could I ask you a question?

DR. ZERBE: Yes.

DR. LEE: In reviewing the studies, I noticed that the dosage range, the maintenance dosage range, was very narrow. It was usually 60 to 80 milligrams, and mostly 80 milligrams. I wondered how you determined your dosage range.

I was very concerned about it when I heard you say just now that one person got -- was given double the dosage and became psychotic.

DR. ZERBE: Well --

DR. LEE: I'm wondering what sort of information you have on people above 80 milligrams.

DR. ZERBE: Well, let me ask Dr. Chouinard to address

that point, because he has -- that was his patient, and he has more experience with higher doses.

DR. CHOUINARD: I am just writing up the report for publication. This is a patient that I have no previous history of, bipolar, 1 or 2, became manic after the dose was by accident increased. It was a double dose. He was supposed to get 70 milligram, and got 140, and he became manic.

The drug was discontinued. He was given clonazepam, or clonidine, and within two days, the mania disappeared. It was not other psychotic than mania -- there was no hallucination or delusions, and the mania disappeared two days after we discontinued the drug.

And the patient became depressed again without the drug. We reinstituted the treatment, and the patient had his depression relieved at a much lower dose.

So, just to comment on this specific issue of this patient that has been mentioned.

DR. HAYES: At what interval had the patient received the 140-milligram dose?

DR. CHOUINARD: Two weeks.

DR. THOMPSON: To sum up these data, we have asked Dr. Chouinard, whom you all know from his work in Montreal, to summarize his own work with fluoxetine. He also has been a consultant to Lilly, and therefore has reviewed all of our data on this drug.

DR. CHOUINARD: I thought the best way to present my experience, clinical experience, both as an investigator and a, shall we say, clinical psychopharmacologist prescribing the drug on a humanitarian basis, obviously, I thought the best way to proceed was to present our study, that we did, and the data are in the NDA, so it doesn't go into conflict with the present purpose of this meeting.

However, obviously, the N's are small, and it was designed initially to stand by itself. Having had, in previous studies using this sample type, enough power to detect differences between the two treatments, however, the power was not calculated in this particular study, because the statistical analysis was different than the one we used in our prior study.

So, in fact, I will comment about my own clinical experience in the presentation of the data. This study is a double-blind clinical trial, which has a sequential entry, and the patients are thus included as they become available, and it's a parallel study.

In fact, it has the same design as the previously presented data, with one single-blind washout placebo in the treatment phase, given under a double-blind condition.

It was a flexible-dose regimen, comparing amitryptilene and fluoxetine. In fact, here, the total number of patients included was 51. In fact, the sample size represents

a kind of normal distribution between having 20 to 30 percent of patients having not been treated previously for depression, and the rest of the patients had had some prior treatment.

Also, I forgot to mention that we had a stratification in the study. There was a stratification for sex, meaning that randomization took into account the sex distribution per treatment.

In fact, this is the dose that were given to our patients. Most patients went up to the 80 milligram per day dose. This is on fluoxetine treatment.

Now, on amitryptilene treatment, in fact, the maximum dose was given to very few patients, most patients receiving between 100 and 150 milligrams per day amitryptilene, and the other group, 150 to 200 milligrams per day. The N was 24.

In fact, here, one of the most important data is efficacy data from a single study. Less important is to look at the percentage of patients who completed the study. In fluoxetine, this percentage is higher than in amitryptilene, although not significantly so.

And, in fact, there were two patients who did not complete fluoxetine treatment. One patient, in fact, took only a single dose of the drug, and he felt anxious, restless, and in fact it was maybe more his fear to participate in the clinical trial; and there was also a patient who had the suicidal attempt on the eve of final evaluation, and this patient was

presented previously by Dr. Wernicke. He took 200 milligrams of fluoxetine, plus a bottle of rum.

In the amitryptilene group, in fact, the adverse experience is higher, and I think of interest is to know what led to discontinuation of treatment in this clinical trial. In fact, in fluoxetine, I already said that this patient took one dose and felt this way, and decided not to continue the clinical trial.

On amitryptilene, we encounter four patients who were terminated because of adverse experience, and these patients are -- were discontinued because of the well-known side effects associated with amitryptilene, published in the literature.

One patient was because of complications in serious cardiac arrhythmia. One patient was because of a manic episode. In fact, in this study, there were nine patients with bipolar illness, and one of them became manic during the amitryptilene treatment.

The other patient was discontinued because of epileptiform abnormality. We do this to prevent the obvious clinical manifestation of seizure, and this patient was so sensitive in reacting on the EEG, that we discontinued him, and the other patient, with orthostatic hypotension, was incurring severe dizziness.

So, in fact, these are the well-known side effects

associated with amitryptilene.

Interim efficacy -- I don't want to talk about this, because, as I said, I don't have the beta value here for our study, but we could say that both treatments were efficacious, as far as the evolution over time.

Now, in terms of adverse experience, I think I want to describe all of what is reported by the patients, whether it is drug-related or not, and recorded by the physician.

In fact, patients on fluoxetine reported more nausea than patients on amitryptilene, and it was the opposite for dizziness. There were more patients on fluoxetine. In fact, in orthostatic hypotension, as we measure it following our procedure, the incidence was higher with amitryptilene.

These are obviously only percentages. The number of cases was not presented, for just this -- because they are small numbers, but I just want to give us a profile here.

In terms of anticholinergic side effects, we just confirmed what is well known with the drug. A lot of patients have dry mouth, constipation, and vision disturbance, blurred vision, which was less prevalent in fluoxetine. Again, it is a profile of side effects, and doesn't intend to be statistically compared.

In terms of adverse CNS experience, anxiety was found to be more prevalent in fluoxetine as opposed to amitryptilene; and as regards tremor, drowsiness, and nervousness in this

particular case, here it is psychic anxiety. So it is not necessarily somatic anxiety or nervousness by the patient.

Overall, here, I just want to give you, after reviewing the data that Lilly provided to me -- I would say that my conclusions are very similar to what is presented by FDA. I would say, in just a couple more comments, I would say that fluoxetine is an effective antidepressant, although it is not efficacious in all patients, like all drugs available at this time, having used the drug open-labeled in patients on a humanitarian basis.

The anxiety is relieved with fluoxetine, as shown in double-blind placebo-controlled studies, but most probably it is only the anxiety which is associated originally and caused by the depression. So it relieves when the depression is relieved.

In fact, here, the drug was found efficacious in both agitated and retarded patients. However, here, I think, we are still looking for some group of patients responding specifically to an antidepressant, and at this time there is no evidence, for fluoxetine or for any other drug, that they may be better in any type of patients. In fact, most probably here we will have to wait for a kind of biological marker to be able to find subgroups.

The drug appears to be efficacious also in elderly patients. Once given daily, it is efficacious, and we followed

patients up to three years, and it seems that the maintenance effect, in our own experience, is maintained. And, I think, in the data provided by Lilly.

Overall, we could say that this drug has fewer anticholinergic side effects, that the effect on cardiac conduction would be minimal. There is less sedation, and psychomotor impairment, as far as I could see in the data.

A considerable concern in the tricyclic is the weight gain for female depressed patients. In fact, fluoxetine doesn't seem to have this effect, and the nausea is definitely present, especially at the beginning of treatment, but usually is mild and would respond to a decrease in dose.

In fact, our major issue is related to use of antidepressants, and I think it has been alluded several times, drug-induced psychosis, drug-induced mania.

In the published literature, there are two cases of fluoxetine inducing mania. We will be reporting a third one. It is very difficult to know the exact expected incidence with the tricyclic antidepressants. However, some of these drugs are well known to precipitate an induced mania in patients.

The other issue that, since one of our patients was also mentioned in regards of overdose -- in fact, we had a patient who overdosed on fluoxetine, and the EEG that was done showed an epileptiform abnormality that was not present before, and this was mentioned also by Dr. Wernicke, that an

overdose of the drug has a possibility to induce epileptiform changes, and maybe also clinical seizures.

Thank you.

DR. DETRE: Any questions? Dr. Preskorn?

DR. PRESKORN: Any data on tricyclic nonresponders and their response to fluoxetine, either historical data on tricyclic nonresponders or crossovers?

DR. CHOUINARD: I think Dr. Wernicke would be better to address this question.

DR. WERNICKE: Well, to use the term "data" loosely, I'll tell you what the experience we have is. The reason I don't talk about it -- because it's in open-label, compassionate use. We have a number of patients, and what we did is, I went through and at least, in my mind, tried to convince myself that these people had a fairly well-documented history of failure on other antidepressants.

I identified 28 such people, and as I remember, I think 13 did better on fluoxetine, three did worse, and another few were equivocal. So most of those patients did do better, but whether you can really call this treatment resistance, I don't want to pass that off as any kind of real data. It's anecdotal at best. That's really all we have on that.

DR. LEBER: I guess I made the point when we began, but I'll make it again, that I don't personally -- and I don't know if everyone else shares the concern -- accept an active-

controlled trial as evidence of antidepressant efficacy. You could even look at the six-treatment pooling, and 27, and recognize that even after the placebo washout of four to ten days, many patients randomized to treatment, and two placebos continued to improved significance.

Therefore, it is conceivable, even in Dr. Chouinard's sample, that the observed improvements had nothing to do with the administered drug. And that is why I find it difficult, in such circumstances, to do much more with that data than look at it as evidence of safe passage -- no catastrophic events that were life-threatening.

Whether it speaks to or against the efficacy issue is questionable. One thing, though, I think Dr. Lee wanted to go back to, and that's dosing, isn't it?

DR. LEE: Two things. First of all, in my review -- and I took this out of the company's sponsor (sic) -- on page 11, 111, and 117, 111 shows the outcome of patients who, at the completion of their six-week trial, were continued upon their drug, if they were doing well. You'll see -- that's on page 111. You will see that, out of 309 patients, there are possibly 30 who are moderately depressed in that -- this is when they completed their long-term trial.

If you compare that with page 11? these are the people that crossed over, because they weren't doing well, you will find that there were 94 people who were rated as markediy

depressed -- no, markedly depressed, and 29 markedly depressed again out of the 323 subjects who crossed over for failure.

Now, this was just a final, global evaluation that was made by the psychiatrist, but I think it suggests that it is not clear that it is effective, and -- well, this is a very large group.

Okay, my reading of this information, this data, is that if you don't do well on a tricyclic, I can't be sure you're going to do well on fluoxetine either. It seems that if they're resistant, they're resistant.

DR. WERNICKE: That may well be. We do have some people that did do better and some that didn't. We also did looked at -- in people that continued both imipramine and fluoxetine, looked at their relapse rate, and they were the same in both.

And if you looked at the efficacy of the people that stayed in treatment, there they seemed to be about the same. But I think the same caveats that Dr. Leber puts on it are true here, too. It's not blinded. It's open-label, mainly safety experience.

DR. LEE: But it compares two open-label conditions.

DR. WERNICKE: Yes, true.

DR. DETRE: Any other questions from members of the committee? Yes?

DR. LEE: May I have one more question?

DR. DETRE: Yes.

DR. LEE: I would like to find out how you arrived at the dosage range, and how many patients got dosages above 80 milligrams.

DR. THOMPSON: Virtually no patients in the pivotal studies got doses greater than 80 milligrams, because that was the maximum allowable dose.

If you would like to see dose-response data, we have, in fact, finished our analysis of a 700-patient trial, comparing, in a fixed-dose design, three doses of fluoxetine and placebo. This has not been written up finally, so it has not been submitted to you formally. We have, however, four carousels more of slides that we would love to show you and the audience, if you want to get into it.

DR. LEBER: Can I make a suggestion? I would prefer that we have a chance to review it, and if it bears on the determination of approval of the drug -- it will, in the sense of labeling, but if it were to be a major issue, I would prefer to return to the committee at the time we are prepared to deal with it, if the committee agrees.

I mean, unless there is something in it which speaks to a question we should be aware of, even now -- I mean, is there something surprising, a non-linear --

DR. THOMPSON: Very likely. In the same kind of design which you have seen, comparing 20, 40 and 60 milligrams

with placebo, the efficacy is better at 20 and 40 milligrams than at 60, and there is clear dose-dependency in some of the side effects. The side-effect profile is exactly the same, but if you track the frequency of some of the reported side effects, such as nausea, insomnia, et cetera, it is increased as you go progressively from 20 to 40 to 60, all the efficacy parameters we looked at, and the efficacy is best at 20 and 40 milligrams -- a quick synopsis.

DR. LEBER: Do you have any blood level data for norfluoxetine and fluoxetine in those studies?

DR. THOMPSON: Not in those studies, but we have data on fluoxetine and norfluoxetine concentrations in 13 patients who were treated for periods of 340 to more than 900 days, at doses of 40, 60 and 80 milligrams, so that that was a way of looking at the long-term effects.

If you would like to see those data, I would be delighted to show them to you. In essence, both the fluoxetine and the norfluoxetine plasma concentrations exactly overlap the concentrations seen after five weeks in other subjects.

So there is no evidence that there is a change after long intervals, one to three years, in terms of the plasma concentrations of those two drugs, for those doses.

DR. LEBER: Right. That doesn't deal with the issue of nonlinear pharmacokinetics, though.

DR. THOMPSON: No.

DR. LEBER: It simply deals with not accumulating more for those individuals.

DR. THOMPSON: Dr. Leber is exactly correct, and the area under the curve is greater for fluoxetine on the first dose than it is on chronic dosing. However, we do not believe that that will lead to any problems in terms of administration, because the dispersion of plasma levels at any dose is so great that that becomes a relatively small determinant of the plasma concentration of fluoxetine and norfluoxetine.

DR. LEBER: Again, one of the things that I'm doing -- we're sort of arguing with ourselves. I think we came here prepared to say that we think, from what we have seen, that fluoxetine is one effective antidepressant, and two, on the basis of what we have seen, seems reasonably safe. We didn't say we knew everything about it, but what I am trying to bring out is that we have to intensely candle this egg before we reach a final conclusion.

One thing is on the record that I would like to clear up, because it was introduced, and I had asked Dr. Karin Kook, who is in the Division of Biopharmaceutics, to be here in case a question arose about the evidence bearing on what we have analyzed so far, on the pharmacokinetic bioavailability and dose proportionality.

Is there anything you think we ought to clarify, where there is a disagreement with the agency, Karin? You'll

have to come up to the table.

DR. KOOK: The one thing that I would like to clarify is that I do not believe that it is a dose-proportional drug. The data that you have presented are based on single-dose results, where your control was dosed simultaneously with the test drug, if you will.

Also, what I would like to emphasize is that the half-lives that you presented are, again, based on single-dose data, and from my looking at your results, the half-life does appear to increase with dose, as well as increase by chronic administration. And by chronic administration, I would also like to emphasize that I mean at least 30 days.

DR. LEMBERGER: Yes, I agree with you. I did mention that the dose proportionality was single-dose. With the half-lives, I mentioned that the mean was two days with single-dose administration, and a mean of four days with chronic administration, although we have looked at dose administration up to 45 days, and clearly the half-life dosage increase.

There is nonlinearity of the fluoxetine, but the norfluoxetine metabolite, the metabolite form, is linear. So that is a question that -- and I agree with Dr. Leber, this is something that we'll have to get together with.

It is very complex data, in the sense that the agency and Lilly will have to sit down, because, although the fluoxetine itself is nonlinear, the metabolite is linear, and --

DR. KOOK: Right, but in fact, on multiple-dosing studies, the half-lives appear to be more on the order of six days for the parent drug, and up to as high as 18 days for the metabolite.

DR. LEMBERGER: With the data that we have, we find four days, but we can discuss this at some future date.

DR. KOOK: Yes, and the other thing, also, then -- in some of the drug studies that you mentioned, studies with elderly renal-impaired patients, et cetera, were also done on a single-dose basis, which it is very difficult to interpret such data. It is not representative, really, of the actual dosage situation; and also, you have referred to some multiple-dosing studies as being seven days, which, for a drug with half-lives like this, I think it is not fair to represent those as being multiple-dose studies.

DR. LEMBERGER: Well, as I -- normally, when drug interaction studies are done, they're usually done with single-dose studies. We elected a sophisticated study design, which would at least address the issue of buildup of metabolites.

True, they weren't in steady state, but clearly the study design was much better than what is normally presented in single doses. So I didn't want to give the impression that we didn't do our homework. We clearly did.

The other issue we -- I didn't mention, but we have

looked at patients who have received the drug for prolonged periods of time, and have taken other drugs concomitantly, and we have seen no indication of drug interaction there.

DR. KOOK: Okay. Again, it would be interesting to see long-term data where the patients are compared to their own early-on blood levels, if you have something like that. This group of 13 patients who were treated for at least a year were compared to a different group of patients, so it's difficult to draw very --

DR. LEMBERGER: We do have some individuals where we took random blood samples throughout the period, sort of like Dr. Temple's pharmacokinetic screen, and we have done this throughout. We do have that kind of data.

DR. KOOK: Thank you.

DR. DETRE: Ladies and gentlemen, it is my feeling that, by now, all civilized people have adjourned for lunch, and we should do the same, but let's make it for no more than 60 minutes, please.

(Whereupon, at 12:55 p.m., the conference was recessed, to reconvene at 1:58 p.m. this same day.)

AFTERNOON SESSION

1:58 p.m.

DR. DETRE: Let me call the meeting to order again, if I may, and Dr. Thompson asked to make a very brief statement, so labeled by him.

DR. THOMPSON: Thank you, Dr. Detre. In terms of the discussion that there are clearly more data now available on fluoxetine, than in the NDA at the time of submission, one thing I wanted to make perfectly clear was that all significant adverse events that have occurred worldwide, have in fact been reported promptly to the FDA, through the IND. And, in fact, Lilly's definition of "significant" includes not only the regulatory requirement of tests against hazardous warnings, side effects, and precautions, but in addition we use all of the definitions in the current NDA regulations of "serious," with one exception.

And that is, if an adverse event requires prescription drug therapy, and that's the only thing that would make that serious, and we don't include that in "significant."

So I think that, in fact, there would be no new news in the safety update, in terms of significant adverse events, that we haven't already talked about.

DR. DETRE: Thank you very much, Dr. Thompson.

DR. LEBER: That needs some clarification, too.

DR. DETRE: Dr. Leber?

DR. LEBER: That cannot stand hanging there like a slow pitch on a hot summer's evening.

(Laughter.)

DR. LEBER: Let me pcint out very clearly that the IND is a document that we look at primarily to evaluate whether or not clinical trials should be conducted. It is not looked at with a -- shall I put it, with the intensity and comprehensiveness that we would look at the NDA, prior to a drug approval.

So, technically, you are absolutely correct. The FDA, as an institution, has received, and I take your word for it, all the material necessary, and all the things you know or need to know about this drug.

That is not the same as to say that it has moved, in memory, from this particular address called the IND, for those of you who understand computer jargon, to the memory -- active memory, where we are going to work on it for the NDA.

All I can do is fess up, and say a small, beleaguered staff is doing its best to get this information. We will, and not only the fact that it's here -- it has to be organized, put into tables, and then statistically evaluated with pertinent questions, and that has yet to be done.

And in that ongoing, iterative process, we may learn things that neither of us yet understand or know. And so I am just putting that out as a caveat.

In no way, throughout any of this suggest, imply, or lead you to the inference has done anything wrong. I just want it very we have to be very certain. That's my job -- turned all stones over to look.

So that is my answer to your slow pitch, but I hope you take it in good spirits.

DR. DETRE: Well, with those semi-final comments, perhaps we could proceed to the committee's discussion. Everybody, any questions?

Dr. Chien?

DR. CHIEN: I'd like to bring up two points, just as my comment on the morning's exciting presentation. One, it's about how to analyze the data. We looked at the placebo-controlled studies that you have presented. Six investigators participated in protocol 27. Three of the six did not come up with really consistent, significant superiority of fluoxetine over placebo.

If those six investigators publish their own papers, the common practice now in psychiatry, who like to review the existing literature, may end up saying that 50 percent of the six studies show almost no difference with placebo.

The other two independent comparisons with tricyclic antidepressants -- one out of the two showed no difference at all. So, suppose all eight people publish their papers -- that

would end up like a disaster. Four out of the eight papers may not show, really, some striking difference between placebo and fluoxetine.

And I learned a good lesson from today's presentation, that we really need a kind of pooled data. And I think that Paul Leber is absolutely correct, that we should not really call them six different studies, but as a one pool of data. And I think this is really a good example to tell us, depending on how you look at the data, that the conclusion might be very misleading.

My second comment is about Dr. Chouinard's presentation. In his slide, the so-called clinical profile, I wish I could share his enthusiasm and optimism, in saying that this drug has less side effects, in terms of less sedation, and saying that nausea is existing but mild.

I feel a little uneasy about that. I would like to play a little bit devil's advocate. I got the impression that almost saying, when outside is a 100-degree heat wave, we are saying we don't have the snow.

What I'm trying to say is, when there is about 25 percent of nausea, one out of every four patients was experienced nausea, I don't feel like to see that in the drug company's submission, saying that nausea is present, but mild, and also saying that there is no side effect of sedation, like imipramine, which is correct.

On the other hand, we should say, although there is no sedation, but there is about 25 percent of so-called agitation or anxiety, which is not a small incidence. So I just want to be careful about how we are going to put that in a drug insert, about these side effects.

DR. THOMPSON: Let me try to address each issue. In regard to the number of studies, I agree with you completely, and we agree with Dr. Leber that that study was designed for pooling.

The reason that we presented the individual studies is we thought that made fluoxetine look worse, and we wanted to make a conservative presentation. We also, for that reason, excluded that one investigator. So it was not an intent not to pool that study, as originally designed. We submitted to the FDA both pooled data with and without that investigator, so I agree on the number of studies and the way it should be analyzed. We agree completely with Dr. Chi's approach.

In regard to the nausea, let me say two things. First of all, the total incidence of 25 percent, for number of events -- in other words, any patient who at any time said that they had nausea got counted in that big lump.

Now, we looked at severity in two ways. The first was, we asked the investigators to score each adverse event on a four-point scale, from zero to three. And the average scale for the severity of nausea was one, which was about the

same as the score of nausea reported with the other drugs.

Now, although nausea was reported more frequently with fluoxetine, another measure of intensity is how many people discontinued the study at the time they had nausea, and that rate was 3 percent with fluoxetine and 4 percent with imipramine.

So that is one of the reasons that we believe that it's fair to say that nausea was the most commonly-reported adverse event, but in fact it was mild.

In addition, as pointed out previously, vomiting was quite unusual. So I agree with you that -- and then the third point you made, which we agree with, is that the safety profile is different for this drug than the tricyclics. They tend to be more sedating, and this drug tends to be whatever you want to call it -- more alerting.

However, remember, as Dr. Wernicke showed you, that the number of patients who reported any adverse event was significantly less for this drug than imipramine -- I'm sorry, the three tricyclic comparators, and the number of people that discontinued for adverse events was significantly less for fluoxetine than with the tricyclics.

So, although the pattern of adverse events was clearly the same, overall, we believe that the adverse events in general are less severe than for the comparators which we chose to use.

Now, Dr. Wernicke can elaborate on that in detail, if you like.

DR. LEBER: Can I elaborate on something which I think is even more important? Since all people are not trained to the use of terminology, you have, throughout the body of the clinical data base, different physicians using their own language to describe events, which is subsequently recodified in some central place, and recategorized and re-expressed, perhaps with a glossary that people understand and perhaps not.

My own personal belief is that absolute incidences of side effects, as enumerated in the tabulation, is a bit like a phrase I once used to describe them -- the Emperor's Clothes. I'm not too sure what they really represent, or if they're really there.

As a matter of fact, it's sort of like coming up with an average size for all fruit. You can get a number, but I don't really think it has very much communicative value, and I suggest that everyone realize that drugs have different risks and different side effects.

The issue is how patients behave, and I agree with that. I think for you to say, for example, that a physician rates a patient as having nausea of grade 1, when in fact all the physician can deal with is the report of the nausea, and the patient is experiencing it, is, in itself, a very questionable enterprise.

If I were going to rate nausea, I would rely entirely on a patient-rated scale, because I would assume that the patient is experiencing the event, and not the physician. You want to talk about episodes of vomits, volume of vomits, and so on, that's a more objective scale, but it is very hard to talk about the number sensibly.

And I suggest we move on to the more important question, which -- and all of these are labeling issues, and I agree, too, with Dr. Chien, that it could turn, in a way, to advertising, but the real question for the agency, and for the committee, is, having heard what the drug is capable of doing or not doing, and having reached a conclusion, if you do, that it has efficacy as an antidepressant, is there anything in its distributed description of adverse reactions, that would lead you not to want to see this drug used in the treatment of depression, and if so, why?

And obviously, no drug is going to be free of risks. And I think the precise definition, in terms of, you know, confidence intervals and incidence of risk, is an enterprise that is doomed to failure, because we can probably float them up and down and all over the place.

The way I want to phrase the question is, this is an incomplete database. This NDA was submitted when? A couple of you probably remember.

DR. TALBOTT: September of '83.

DR. LEBER: Two years ago. In the interval between the time of submission, when the books closed on the data officially submitted, and the current time, the company has not stood still. They have continued to conduct clinical trials, they have continued to accumulate information, much the way the drugs once marketed have continued to accumulate information. You have to look at the evidence in your hand today.

Now, because we have been concerned about this interval of time, under current rewrite policy -- and before rewrite regulations, it was policy -- the company has to submit to us a safety update, but we haven't gotten that yet. And it's true, we could have waited another six months to come to the committee, but I felt we were close enough to looking at the preliminary stage of our judgment to get your view, because it's true -- if we decide there is a terrible risk that appears now, I promise we'll come back to the company -- to the company afterwards, and to the committee.

But if it is in fact no difference to the safety update, in rate, incidence, in display, in distribution of adverse risks, then I don't see why you couldn't make a judgment now on the question, as I've sort of organized it.

We're going to miss things. I guarantee, or at least I'm willing to place a bet with anyone, that fluoxetine, if marketed, will have reports of adverse events we have never seen. Some of them may be due to the drug, some of them may not

be due to the drug, but they're going to be out there. In fact, there may be something that turns up that's really caused by it, but below the detection power for the size of the databases we work with in the NDA's.

So, I mean, nobody has an absolute guarantee of safety, but on the basis of what you have seen, is this drug a reasonable antidepressant? And if it isn't, or if you're not sure, what are the questions you want to ask of the company and of us? What do you want to know before approval?

DR. DETRE: Dr. Preskorn?

DR. PRESKORN: One question. If the data that I didn't have the chance to see are presented, and that is, given its structure and also its side effects, is there any evidence, either in animals or in man, that the drug is self-administered, and how does this drug, in terms of a discriminative Q, is it distinguished from amphetamines, methlyphenadate, and other such drugs in animals, from fluoxetine?

DR. DETRE: Would somebody from the company like to respond to that question?

Would you kindly come to the microphone, please, and state your name?

DR. THOMPSON: Dr. David Wong is the discoverer of the drug.

DR. WONG: From all the animal behavior studies that we have studied so far, we have not seen a stimulation effect

with any resemblance of amphetamine, and also that we have not seen the evidence of dependency in animal behavioral studies.

DR. LEBER: What kind of tests have you done -- yeah, I think what we have to do, once again, answering questions with one-liners is difficult.

DR. WONG: Yes.

DR. LEBER: We need to know the type of testing in humans. Has this drug been used in any stable of amphetamine abusers, for example?

DR. WONG: I just addressed the animal studies.

DR. LEBER: I know, but I'm trying to give some concrete meaning to questions that get asked, and I think it's useful to have data to answer them. So it may be that we haven't done it.

DR. WONG: In the NDA, there is a study, and it's in animals supposedly to detect sedative activities, and the absence of activity, to produce activity in sacrificial animals, and also we also have study done of locomotor activity -- again, did not detect any stimulatory effect with fluoxetine up to 40 milligram per kilo, nor an inhibitory effect with fluoxetine at that dose.

DR. LEBER: Have there been, for example, in animal studies, any self-administration paradigms done, where animals are first habituated or addicted to a stimulant, and then

allowed free substitution for that, or that kind of design?

DR. WONG: Yes, the -- precisely design approach of paradigms have not been done, but in self-administration in the presethanol (ph.) intake, that study has been done at Indiana University. Up to seven days' administration did not demonstrate a self-administration with fluoxetine.

DR. LEBER: Different question. I think the point is, it's been a partial -- is that a fair statement, that there has not been a systematic assessment in animals at the preclinical level of self-reinforcement or habituation? That is a legitimate request to look at.

DR. DETRE: For the record, we know your name, but would you please state your name?

DR. LEMBERGER: Lemberger. In normal volunteers, when the drug is administered over periods as long as 45 days, and then individuals are followed through that period, post-drug, first of all, we haven't seen any stimulatory behavior comparable to that which one would see with an amphetamine-like drug, and there is no withdrawal-type symptoms after, nor is there any tolerance that seems to develop.

The drug itself, in normal volunteers, has very little pharmacologic activity of a behavioral type.

DR. LEBER: Lou, how many patients have actually been followed systematically in withdrawal studies?

DR. LEMBERGER: Well, these are not really studies

designed for withdrawal, per se, but questionnaires are given throughout the period of drug administration. Then they're followed post-drug, because, as you can imagine, in the kinds of metabolism studies that we do, with this long half-life, we have to follow people for a long period of cime after the drug, and we have seen no changes in behavicr, no marked changes that --

DR. LEBER: The reason that I'm doing this sort of dialogue with you is not that I know that you don't know it, but I think I want to make clear that people who have -- if we had had a concern, if this were benzodiazepine, the chances are that this would have had a fairly elaborate discontinuation series of studies done, which people would either have titrated down and off the drug, and there would have been a more formal assessment of dependency and use and so on, and probably -- and it's a consideration for the committee. Is this the kind of information you would want now, or before marketing or after marketing?

It's something that they should look at, but it is clear that there has not been a systematic assessment of this aspect of fluoxetine. Is that fair?

DR. LEMBERGER: Yes, but basically, in normal volunteers, the drug is without activity.

DR. DETRE: You have said that you follow patients for your metabolic studies after the drug was discontinued.

What was the longest period you followed normal volunteers?

DR. LEMBERGER: We have admitted patients to a greater than 90-day study, where we administered the drug for 30 days, and then followed the disappearance over the following 60 days. During that period, before discharge, for 60 days.

DR. DETRE: Thank you.

DR. WERNICKE: Could I make a comment about the potential for self-administration?

DR. DETRE: Certainly.

DR. WERNICKE: We haven't studied it that systematically, like Dr. Lemberger said. However, in the clinical trials, when people have been taken off, we haven't had any requests for reinitiation of the drug, except as judged by the psychiatrist as a recurrence of depression, and that has gone along with Ham.D.

I can't think of one single instance where there was any doubt as to why that patient wanted to go back on. That's, again, not real data, but that is in fact what happened.

DR. PRESKORN: Well, I would have to concur with Dr. Chien in terms of the efficacy, which, you know, is -- depending on the way you cut the study, it may either -- and some studies may not turn out better than placebo, and in most studies, not better than imipramine.

In addition, my other question is that these are all

acute studies. Do we have any maintenance data? In other words, you have controlled studies that look at relapse rates, because, in use of antidepressants, one not only thinks about acute efficacy, but also in terms of its ability to prevent recurrences of a depressive episode. And how much systematic data do we have on that?

DR. LEBER: Probably none. What you have very often is extensions of controlled trials in which patients who have presumably been successful -- their outcome is due to drug, are continued on drug.

However, a formal discontinuation design of the type we have talked about in various meetings has not been done, as far as I know, though the company may have done one after submission. But as far as I know, a re-randomization of patients to drug that they're on, and placebo or some controlled condition, to see whether or not they suffer a relapse under the two groups, which would be a fair test of this question, has not been done.

And it's one that we would be very interested in. But I point out, in fairness, it has not been done for any other antidepressants up to this time that I know of, not in schizophrenia.

DR. DETRE: Only now are there trials underway to determine the efficacy of the first generation of antidepressants. for the prevention of recurrent episodes. So this is a

new standard.

DR. LEBER: Speaking of new standards, there is no fixed requirement of law or regulation --

DR. DETRE: I know.

DR. LEBER: -- on -- and another thing, and that is this abuse potential issue. We do not have a fixed panel of ways of assessing, and I think that's fair too. There are circumstances where I think we have a high index of suspicion, and ask for a study of the drug for self-administration potential.

I think that more recently we have dealt with activating drugs, and we have been sorry we haven't asked. But there isn't one in existence, but that doesn't preclude you from enclosing one. It's just that we don't have a standard, pre-fixed one, and it's not the company's obligation to provide one, by the way, unless we ask for it now.

DR. LEMBERGER: I think, in your initial comment, you talked about the chemical structure possibly being close to amphetamine. Basically, the side chain is similar to those seen on the tricyclic antidepressants. It's a 3-carbon with nitrogen. But if one were to reverse the oxygen and the carbon on there, basically you'd have the benadryl structure.

In the literature, it was shown that benadryl prevented the uptake of amines into the heart, and one of our chemists reversed the carbon and the oxygen, and was able to

demonstrate that this series of compounds also could affect uptake of norepinephrine, and that was nisoxetine, which was the lead compound.

Then when fluoxetine was discovered, it was shown that it had no effect on catecholamines. But it basically is an antihistamine structure, rather than an amphetamine structure.

DR. LEBER: While you're talking about structure, Bob Temple, who left, had a question. He was very concerned because of zimelidine's history as a 5-H,D uptake blocker, and the introduction of Guillan-Barre-like syndromes -- whether or not there is any similarity between this drug, pharmacologically, and zimelidine structurally -- you can answer that into the record, and secondly, whether there has been a report of any syndrome mimicking or looking like the zimelidine?

DR. LEMBERGER: I could answer that, but I'll leave that to Dr. Wernicke. The structure -- there is no similarity of structure, but we have done a careful analysis of the zimelidine issue, and patients have been crossed over, and maybe --

DR. WONG: I can draw it on the board.

DR. LEMBERGER: There may be --

DR. LEBER: As long as somebody from there doesn't object.

DR. THOMPSON: There are two questions on the table. One is in regard to the long-term use of the drug. We can

show you the data that we have, but exactly, as Dr. Leber said, these are not patients that have been re-randomized to therapy, but those who have been continued on, either on fluoxetine or comparator, when we looked at the relapse rate.

The second question, in regard to zimelidine syndrome, on that, we have some very specific data. As you will recall with zimelidine, it was reported that a flu-like illness occurred in anywhere from 3 percent to 10 percent of the patients who were given zimelidine, largely occurring within the first six weeks of therapy, in addition to which there were, to my knowledge, between eight and thirteen patients who had a neuropathy similar to the Landre-Guillan-Barre neuropathy.

And we have looked at both of those, and Dr. Wernicke can address those issues.

DR. WERNICKE: We have been concerned about this exact issue, and we have looked at our database in a number of ways, and what -- let me just tell you some of the things we have done. Perhaps I could have the lights off?

We looked at the frequency of some of the phenomena that have been related to the zimelidine syndrome -- chills, fever, headache, myalgia, rash, malaise, arthralgia, liver dysfunction, and have not noted an increase in -- with regards to comparator.

Now, some of these will happen with any kind of viral illness, and of course there have been some with fluoxetine.

But we looked at relative incidences.

Then we looked for patients with a computer search, that had this specific complex, and could not find any. But I think the most telling evidence is that there are three patients, two in the U.K. and one in Canada, that have had zimelidine and had that syndrome, and also had fluoxetine and have not had it.

Now, we have done a little bit further analysis than that slide shows. Let me show you just some of the specific data, because the Swedish authorities asked that same very good question.

This is some of the actual data of some of the frequency of some of the cardinal features of this syncrome -- headache is seen with comparable frequencies in all of the groups, and so are the others. We looked at things -- reporting of influenza is probably none of these true influenza, but people use that for flu-like illness, and there just isn't any difference, statistically.

These are all the things that we have done. We have looked at the reports of flu-like illness, and as I've shown you -- well, actually, those were specific incidents, but then we just looked for flu, influenza, or flu-like illnesses, which were in codeable terms, and the same as in the comparator.

We looked at the patients who had some symptom and

also had some elevated liver functions at that time, and none of those had this syndrome, in the best way that we could determine.

We looked at the frequency of multiple symptoms, and basically did a computer search to list anybody that has had five symptoms, four symptoms, three symptoms, and then look at the comparators -- the number that had five, four, three or two, and was the same in all the groups, and I can show you that data in a second.

Then we looked at, as I just showed you, the individual symptoms in the comparative groups, and there was no increased frequency. And then we looked, because fever is sometimes associated with this syndrome, we looked at the people who had fever, and again found nobody that had that symptom.

And at the bottom, I listed again some of the features of that syndrome. Can I have the next -- this table shows -- what we asked here was, it is known that zimelidine is reported in the first two to three weeks. So we asked for the data, what is the frequency of any flu-like illness over time, compared to a pool of the tricyclics in week one, two, and so forth?

These are the frequencies of either the flu-like illness, influenza, or viral infection, and all of the numbers of course aren't exactly the same. There is no statistical difference.

Next on the slide is that we pooled the frequencies for the first three weeks, and again there was no significant difference. Next slide, please?

On this slide, as I showed you on the overall, we looked at the frequency of patients in all the groups who reported either zero, one, two, three, four, five of these symptoms -- chills, fever, and so forth, and what one sees is that fluoxetine -- first of all, none -- no patients on fluoxetine -- 78 percent of the patients on fluoxetine reported none, as opposed to almost 60 percent on imipramine.

And fluoxetine, other than doxipen, has the least frequency of reports of anything. Then as one goes down to one, two, and three symptoms, the same pattern holds true. That basically is that imipramine is associated with a lot of symptoms, and is followed by amitryptilene, and so forth. And, in fact, placebo -- one symptom was reported by more placebo-treated patients than by fluoxetine-treated patients. Next slide?

Here, I think this is the same slide, basically. It lists the frequency of individual adverse events in that three-celled study.

So, in summary, I feel we have looked at this, and detailed simply everything we could think -- every way we could think of looking at it, we did, and we have come to the conclusion that we don't have it.

Now, Dr. Chouinard, who unfortunately had to catch a plane, has treated patients with zimelidine. One of those crossover patients was his. We gave him all that data. He has seen the zimelidine syndrome, and he says there is absolutely no doubt in his mind that we don't have one case of that.

Now, again, we have had 3,000 patients.

DR. LEBER: I think one of the concerns I have -- I don't know, really, what the incidence background rate of zimelidine's flu-like syndrome really is. If it's a very, very low rate, and I don't think -- we certainly don't know here what its rate is, the number of patients you have looked at may not be enough to tell. In fact, you could be looking at the wrong kind of flu-like illness.

So, it may be, depending, as I think, on the base rate of zimelidine risk for this syndrome, the total number of patients, and the distribution in time of the zimelidine risk, and I don't know that, either.

I mean, you said that most of them have their onset within the first two weeks?

DR. WERNICKE: Yes.

DR. LEBER: I don't really personally -- I am not that familiar with the distribution of the syndrome, but I think it would be important to set an upper window, or an upper limit, on how much risk you can really exclude, and that would depend upon what the incidence of the zimelidine syndrome is.

DR. WERNICKE: Let me clarify. We did not look just in the first two weeks. We looked at all patients. Their incidence is, in the literature, estimated at between 1-1/2 and 10 percent of patients on zimelidine, having that syndrome.

That's what the literature has, and people from Sweden have assured us that there has actually been a -- that seems to be what it was. Now, why wasn't that seen earlier? I don't understand that either, but that is what people are saying.

DR. LEBER: It wasn't seen earlier? That is very interesting.

DR. WERNICKE: Well, I can't really comment on that.

DR. LEMBERGER: You're right that you may not see something in a small population, that may show up in 700,000 people or in 100,000 people. One of the things that gives us some degree of confidence is, being that the zimelidine syndrome was of an immunologic mechanism, in the crossover studies, we didn't see it.

So if the same factors were associated, maybe a part of the molecule, or serotonin -- not the mechanism, per se, of serotonin uptake, but something inherent in the molecule, then we might have expected that the zimelidine-reacting individuals might in fact react to fluoxetine, which was not the case.

So that crossover data gives us some degree of good

feeling, but you're right, you wouldn't know. It may be in a couple in a million patients, or something.

DR. WONG: Our colleague Dr. Wickstrom, a colleague of Dr. Everett Carlson, who initiated the project of synthesis of zimelidine with Astra, in Sweden, and showing that -- pointing out to me that the (inaudible) of zimelidine perhaps is due to the possibility that there is a double bond, and the possibility of forming an aldehyde in the mediate, and which might -- well, that is speculation, the covalent binding to some protein in the circulation, whereas it would not be possible with fluoxetine.

DR. DETRE: Any other questions from the committee? Yes, Dr. Steinbach?

DR. STEINBACH: You said that there was related anxiety associated with depression, and I wasn't real sure where that came from. I thought we were worried more about the side effects of anxiety from the medication.

DR. THOMPSON: That's a good question. You will recall that all the patients in those trials had their anxiety assessed with the Cobe anxiety scale at the beginning and throughout the study, and that, in fact, to exclude patients who had predominantly anxiety, the patients had to have a greater Raskin depression score than their Cobe anxiety score.

But the measurement by the Cobe anxiety score provided a means of assessing the improvement in anxiety,

associated with depression, during the treatment, and fluoxetine significantly decreases the anxiety score on the Cobe scale in these patients that have predominantly depression.

Now, there is a simpler issue in regard to anxiety as a side effect, and those are reported by the investigator as adverse events. We go to a lot of effort to point out to the investigators that we want them to tell us events -- everything that occurs.

Obviously, they have to select, in interviewing the patient, whether or not they're going to put anxiety down as an adverse event. We have no control over their following our instructions, so we have presented two different kinds of data.

There is relief of anxiety as measured by the Cobe anxiety scale, when it's associated with depression, and the report of anxiety as an adverse event in the trials.

So it seems paradoxical, but I think the data would suggest that both events occur -- that some people get anxiety as an adverse event, and that, overall, anxiety in association with depression is improved.

DR. DETRE: Any other questions?

I would like to ask one. I was wondering whether, indeed, early non-blind, non-controlled studies, doses higher than 80 milligrams were used or not?

DR. THOMPSON: Dr. Lemberger, I think, can address that, because you used higher doses in a few volunteers, didn't you?

DR. LEMBERGER: We haven't used doses higher than 80 milligrams in depressed patients voluntarily. I mean, some individuals, as in Dr. Chouinard's example, took more than was recommended, but in normal volunteers, in the initial dose ranging, we dosed up to 90 milligrams, single oral dose, and then in the dose proportionality study, with single doses, we gave -- the known cap, we'll say, 60 to 80 milligrams, plus we gave solutions of fluoxetine, and I think the total dose was 120 milligrams, to the case that was receiving the highest dose. But the solution, which also contains the material, was used as an internal marker to demonstrate absorption, and so on.

DR. DETRE: Thank you.

DR. LEBER: Can I clarify what your point is, Dr. Detre? What are you going after?

DR. DETRE: Well, I was interested to find out why the therapeutic dose was established between 20 and 80 milligrams.

DR. LEMBERGER: Perhaps Dr. Wernicke can address this issue after, but the point is that, when the dose -- when the initial clinical trials were carried out, the investigators were allowed to increase the dose, based upon increasing it 20 milligrams, until a maximum of 80.

The slide that I showed was one of the very early studies that we did. We looked at the uptake of serotonin into platelet, we selected a dose that would affect uptake in

the platelet as a model for the brain. So we started with 30 milligrams. We kinetically modeled that to try and give us a blood level which would be continuous through that period, and that was established by giving 30 milligrams for seven days, and then 20 milligrams for the remaining 23 days.

Herb Meltzer tested that specific dose regimen, and found, in the few patients that he looked at early on who were refractory to other drugs, because that was one of the first trials -- that it was ineffective, basically, in his patients.

So then what we did is, we decided that we would start at 20 milligrams, and allow the investigators to increase the dosage up to a maximum of 80, to try and demonstrate early on whether there was efficacy, because --

DR. LEBER: One thing. Why did you stop at 90 in the single-dose ranking tolerance study?

DR. LEMBERGER: Well, we stopped at 90 milligrams because we had written our initial protocol to do those studies up to 90 or 100, I forget.

DR. LEBER: But that was the protocol.

DR. LEMBERGER: That was the protocol, and then being that we did get significant effects -- and during that study, we harvested platelets, and being that we did get significant effects on the uptake of serotonin, we felt, using our, quote, "bioassay," that we were in the ballpark that we wanted to be, if we could demonstrate it, because there were

no -- basically no behavioral --

DR. LEBER: It's actually a generic one, that was going to use your behavior to discuss, to save the audience, but I think it's important. There is a great dispute about how you -- when you should stop rising dose-tolerance studies, particularly since we're in a situation now where the highest you have done in normal volunteers is dramatically close to the dose you want to use, basically overlapping.

And there is a group of people who like the idea of limiting early human pharmacology tox. testing to that. You run the dose up until you get into trouble, and it is important to determine whether the upper dose was limited by protocol or by toxicity.

And you're saying you didn't have toxicity at 90 milligrams. You could have gone higher, to where you could look at single-dose toxicity in normal volunteers.

DR. LEMBERGER: Basically, our philosophy is that if we do have a handle that we can attach, whether it is a biochemical effect or an antiarrhythmic, say, a blood level or something, then we will try to go through that range, and then we go through the clinical trial.

DR. LEBER: That's more for safety than it is for efficacy.

DR. WERNICKE: I'd like to add something to that. It is true that, in the clinical trials, 80 was the upper limit,

but just so -- to be complete, in the compassionate use patients, namely Dr. Chouinard's patients, he has several patients on 100 milligrams, and he feels that some people respond better. That, again, is not real data. That's just clinical perception, and he is quite satisfied with that response. So I believe there are four or five patients that are getting 100.

DR. DETRE: Any other questions? Yes?

DR. STANLEY: While Dr. Wernicke is up there, you had mentioned before that, with regard to the side effects of insomnia, that those people who displayed the side effect early on in the drug trial tended to -- their level of insomnia tended to persist throughout, and that was over quite a long period of time.

DR. WERNICKE: Yes.

DR. STANLEY: I was wondering two things. Is it also the case, or do you have data on that, for the symptoms of anxiety, and also for the nervousness? Is that a similar profile?

DR. WERNICKE: It goes down. Give me just a second and I'll get those out for you.

DR. STANLEY: Okay.

DR. LEBER: One of the things the committee is -- we need your help on is to advise us on what else we should ask of Eli Lilly before we would consider granting final approval?

It's not that we don't think the drug has evidence of efficacy. It seems reasonably safe, given that evidence.

But we would like to know, what are the things that we haven't been smart enough, that you, in your wisdom, think we ought to have, either as premarketing demands or post-marketing demands? Your advice on that issue -- and during this period, it doesn't have to be a formal motion, even. It can just be a discussion.

DR. WERNICKE: The only one I have is anxiety, but I've looked at the first reports, and it follows a similar pattern. You see that all reports tend to sort of dwindle down with time, not as much as the nausea. I remember that one went down by four weeks, pretty much, and insomnia was pretty consistent. Insomnia was sort of in between, but again, the first reports seemed to be mostly in the beginning, and then they dropped down.

Lest somebody think there is an increased frequency at the end, this is an artifact produced by the fact that there are less and less patients, and any one contributes a greater percentage. This is a percent report, so you really just have to take a trend.

DR. STANLEY: The other question I wanted to ask you, related to the side effects of anxiety -- I think that was reported with about a one in four or one in five incidence of patients -- 20 percent, something like that.

DR. WERNICKE: Right.

DR. STANLEY: And nervousness was similar.

DR. WERNICKE: Right.

DR. STANLEY: What would happen if you pooled them?

DR. WERNICKE: Pooled them? Can you just give me a second and I'll pull that out?

DR. STANLEY: Sure.

DR. FULLER: While Joe is looking for that acetate -- Ray Fuller. I just wanted to make one further comment about the comparison to zimelidine.

This is obviously a question we have thought about a great deal -- was there really a likelihood that fluoxetine would have the same kind of side effects as zimelidine, and the structural similarity, I think, is not any greater than -- I think the structural resemblance of fluoxetine is probably greater to other drugs than to zimelidine in general.

But the thing that they do share in common, of course, is their ability to inhibit serotonin uptake. So there could be zimelidine side effects, that could be related to inhibition of serotonin uptake, per se. I think one doesn't know that absolutely, but bear in mind that these are not the first two drugs to inhibit serotonin uptake. A lot of other drugs do that. They simply don't do it selectively, but drugs like imipramine, amitryptilene, et cetera, which have been used widely for a long time, do inhibit serotonin uptake in

humans, as evidenced by, for example, the reduction in serotonin levels in the blood platelets. And those particular side effects are not always associated with those drugs.

Now, one could always argue that possibly some other actions of those drugs, counteract the influence, but that seems somewhat unlikely, so that it would seem the best guess, at this point, that inhibition of serotonin uptake, per se, would not produce those symptoms.

DR. WERNICKE: In this acetate, what we have done is tried to anticipate all the things that could be put together, and just to be sure that we weren't missing something by listing them separately, anxiety, nervousness, in this case, includes the terms anxiety and nervousness.

Although fluoxetine -- well, we looked at the three-celled study, because that's where we have a comparison. It was 21 percent, with imipramine, 17, and placebo, 11, with fluoxetine being significantly more frequent than placebo, but there is no statistical difference between the others.

Likewise, we have pooled other things, nausea -- everything that could possibly be related, and we have done that for all the adverse events that we could conceive of.

DR. STANLEY: So in other words, you're saying, then, that those people who display the side effect of anxiety are the same people, more or less, that show nervousness?

DR. WERNICKE: Right. Some did one, some did both.

and some did -- a lot of them did both, because often what happened with anxiety and nervousness is that the patient would come and say, "Doctor, I'm nervous," and they would write that as an adverse event. And we'd have an adverse event, and then cause, so their physician would write in "anxiety," so that would get quoted in both places. So a lot of them do overlap.

So, just to be sure that -- we had that exact same question, for the same reasons you have -- we pooled everything that we could conceivably think of, that might be, really, the same thing, in those data.

DR. DETRE: Thank you.

Well, ladies and gentlemen, I suppose we could put an end to the extremely open discussion, and start a more limited and focused one, and I would like to ask members of the committee and others around the table, who would like to give additional ideas to Dr. Leber and the FDA about potential issues that need to be clarified, in the process by which this drug may move throughout approval, and perhaps we should start with Dr. Preskorn and go around.

DR. PRESKORN: Well, my looking at the data, in terms of antidepressant efficacy, shows a drug that does have antidepressant efficacy in comparison to placebo, in the majority of the studies -- perhaps less generalized efficacy than imipramine.

The major questions that I would have would be on

the safety side of the issue, in terms of this drug being marketed as an antidepressant, also specificity of action, such as whether the drug has any action in generalized anxiety disorders -- whether it has been tried in those conditions. What is its effect in patients with psychotic depression; and then particularly the issues of whether this drug, given the fact that I suspect the clustering of anxiety, nervousness, and a general stimulant effect -- is there any potential for this drug to be abused, self-administered, and is it discriminated from psychostimulants in animals?

DR. DETRE: Dr. Stanley?

DR. STANLEY: I would concur with Dr. Preskorn's assessment of the efficacy, and also, my concerns are, again, mostly in the area of safety. And I think that the representatives from Lilly have shown some data that kind of addresses some of the issues that I had in my mind when I came to the meeting, but I don't think these data were prepared in time for this meeting, in time for FDA review.

And I think that it would be important to include in their future submissions, the -- those side effects, and I was particularly interested in the activating one, and their time course, if this is available, and maybe, since this is -- has been identified, and things like insomnia tend to persist, whereas the anxiety seems to go down, maybe these should be looked at a little more systematically by the clinical

researchers in the field, and also I think Dr. Thompson had mentioned, just before we broke for lunch, that there have been some more recent studies which have looked at the efficacy of fluoxetine, and lower doses, 20 and 40 milligrams, and perhaps that data could also be incorporated in future submissions to the FDA, again with particular emphasis not only on the efficacy, but also to see if this in any way changes the overall incidence rate of occurrence of the side effects that have been noted for the compound.

That's all.

DR. LEBER: Mike, could you go into a more practical light, in one sense? Do you think these are issues that could prevent approval at this time?

DR. STANLEY: No.

DR. LEBER: Okay, and I would like to go back and ask Dr. Preskorn the same question. Do they preclude approval, or are these nice things to know? He can get it later, or he can work it out in the labeling?

DR. PRESKORN: Well, I think that the drug shows efficacy, and I think the only thing would be, if there is a significant abuse potential, then, that would be a concern that would have to be considered, in terms of probably the labeling of the drug for widespread use.

The other -- sort of following up on Stan's comment is that, at least in the trials that we primarily have, the

lower doses were not tested, because, given the long half-life of this compound, the acceleration of dose was rather rapid, and if, in fact, antidepressant efficacy is related to steady-state concentration of drug, those doses were not tested, at least in the data that was primarily presented.

DR. LEBER: Excuse me, I don't understand that. They got antidepressant efficacy at lower doses than -- at lower serum concentrations, than you would anticipate are possible to -- in other words, if they're running up this drug, and they had a lot of accumulation, and they looked at it early, and basically they found that the levels that are lower, are you concerned that they could get it at -- that we haven't looked at higher levels of serum concentrations, whether it retains its efficacy?

DR. PRESKORN: No, I think they're -- I think that I would stand on the fact that they have really escalated up to 60 to 80 milligrams within the first week, to 14 days, and one would expect to see attainment of steady-state concentrations on those doses.

So if one is advancing it, one is advancing it more on the absence of side effects than --

DR. LEBER: Absolutely, but is there anything in the data that you're talking about that would influence the conclusion about their study showing efficacy?

DR. PRESKORN: No.

DR. LEBER: Okay.

DR. DETRE: Dr. Steinbach?

DR. STEINBACH: I think the only point I'm a little uncomfortable about is the narrow dose range of the dose, and I've always sort of kicked the dose of an antidepressant up, and I want to know what happens if my patient doubles the dose that I put him on, because I've found that patients tend to do that. Maybe it's because I'm from Texas, and we think our depression is twice as bad, but what happens if the patient doubles the dose? And that would be a question I would want to know.

DR. DETRE: Couldn't the same question be raised about digitalis?

DR. STEINBACH: Yes, yes, but that --

DR. DETRE: This is really not a specific one.

DR. STEINBACH: And I would also want to know how it works with lithium, because that's a common clinical problem.

DR. DETRE: Dr. Carter?

DR. CARTER: I'm only capable of talking about the analysis of the data, and I agree with the analysis that Dr. Chi did, in addition to those done by the company, and I would concur with the inferences drawn from those. And that is just about all I can add.

DR. DETRE: Dr. Chien?

DR. CHIEN: I don't know whether it's an advantage or

a disadvantage to be the last in the committee, but most of the points have already been brought up by our distinguished committee members.

However, it seems like, since I come from Los Angeles, which cost the taxpayers most money, I like to say a few words.

I think this is a very interesting drug. I think, in the American psychiatric market, other than tricyclic, excluding amine inhibitors, I think this drug really presents some interesting challenge, and also usability for the clinician, who may fail to treat all the patients who have gone through almost all kinds of gamuts. So at least this should give ther a new horizon, I hope, to treat those so-called treatment-resistant patients.

In terms of the clinical efficacy, again, I have some kind of doubts in the beginning, depending on how you look at that. If John Davis came up with another literature review over the past ten years, and published a double-blind controlled study on (inaudible), your protocol 27 may end up 50-50. So, really,-it is important to analyze the data very carefully.

As I said before, I really am interested in our lesson this morning. Other than the different chemical structures, the lack of anticholinergic property also can provide some interesting opportunities for those who simply cannot

tolerate anticholinergic side effects. I guess this is also another indication for this drug.

I don't have much kind of concern or reservation, not to recommend approval of this drug at this time. However, I like to follow up a few points, that was not actively discussed in our previous discussion. That was the increased LDH and the decreased hemoglobin. I don't know what it means clinically in the long-term study.

Also, in terms of the issuance of side effects, such as anxiety or insomnia or nervousness, these are the common characteristics of the depression that we are treating with.

The way that the company came up to differentiate side effects versus primary or target symptoms to treat with, seems to be too simplistic at this point.

I would like to see how many so-called normal subject would suffer from this so-called unique stimulant effect. If we have a similar instance of insomnia or nausea or nervousness among non-depressive patients, then I would be much more convinced that this is indeed drug-related side effect, for FDA or a clinician to warn about their patient.

Lastly, I share the same concern with Dr. Steinbach about the relatively narrow range of so-called safety, to switch over to the manic side in the bipolar patient. We only heard one case from Dr. Chouinard, saying when he used 140 milligram a day, then he got it.

We have seen many other so-called switchover examples on other tricyclic antidepressants. On the other hand, I heard from Dr. Wong that in the animal study, he has used up to -- how many, 40 milligrams per kilogram, without causing any trouble. So I got the impression from the animal studies that this drug seems to have a very high range of safety.

However, when it comes to treat the depressive phase of the bipolar patient, I'm not so sure we have such a high index of safety, and I don't have that data to tell my resident or my family physician what to look for.

Therefore, I think even postmarket surveillance in that area would really help us a lot.

Thank you.

DR. KAPIT: I'd just like to say a couple of words about the hemoglobin and LDH questions that you brought up. Those were questions I raised before the statistical review of the NDA had been completed, and the hemoglobin question was raised as a result of a fairly small number of patients who participated in open trials early on in the study of the drug, and these relatively small studies -- there seems to be, for some reason, an unusually large number of patients whose hemoglobin declined between 1.5 and 2.5 grams, and we don't have any explanation for that.

However, when we looked at the controlled trials in the larger number of patients, this early suspicion was not

borne out. The LDH, we're talking about a laboratory value change. There was no question ever raised about any clinical changes in patients. There was some elevation in some patien in LDH between -- about 200 percent of normal value, the uppe limits of normal.

Again, this did not prove to be clinically significant -- statistically significant, when the review of the controlled studies was done. So we don't think either of tho appear to be a problem.

DR. LEBER: Again, I would just point out, remembe the issue of multiplicity? We usually think about it in con- trolled clinical trials, but it certainly applies to labora- tory tests as well. If you do enough, a few of them are goi to lie outside the normal range, and that is not unexpected.

We rely more, I think, on trying to find syndromic events, big-ticket items that happen to the patient to cause their death, discontinuation from clinical studies, or some- thing of major concern.

If you study any large body of patients with multi drugs and diseases, you will probably find outlyers, and the may drag the mean a bit, but we have no real way of dealing with that.

We use cross-tabs, by the way. Rich did a nice jo in displaying a lot of these, with the help of the firm, in which we tried to look at entry scores versus the highest

exit score, or the highest score obtained to look for outlyers, rather than just look at mean. And then we usually go back and look at the outlyers, and try to identify them on a case-by-case basis, to see whether or not they had anything.

Well, in going through that, we still haven't come up with anything. It doesn't mean that we won't in the next safety review, but the question I come back to the committee with, after everyone has their doubts -- the FDA always has its doubts, the firm always has its doubts.

But given the evidence presented, given the evidence of efficacy and the degree of risk seen, in your judgment, does this seem like a reasonable antidepressant drug product? It obviously is not going to be risk-free, and that is really the question I want the committee to say.

The other things that you've said are advice, about how to approach it, what questions we need to ask. But can we get a closure on that kind of question, Mr. Chairman?

DR. DETRE: Well, you just presented your statement --

DR. LEBER: Thank you.

DR. DETRE: -- what you had, asking us to determine whether there is any reason to prevent this process from moving forward.

That doesn't mean guarantee of approval, but whether or not there are any major concerns, or even not so major concerns, which would warrant further delay, or any specific

questions or advice we may give you. Well, we have already given you our best advice -- it may not have been very good.

Now, I suppose we should move on the question of reasonable safety, which is all we can move toward, and would the committee please -- somebody move, or do we need a formal motion for that?

DR. LEBER: Well, we had a question, I think, in the approach to the committee.

DR. DETRE: All right, why don't you read that?

DR. LEBER: Maybe I can restructure it, if you don't mind.

DR. DETRE: Not at all.

DR. LEBER: Well, we have really asked you to examine the basis for the conclusions, that is, that the product has antidepressant efficacy and appears safe, given that claimed use. Do you endorse our judgment? A simple yes or no, really will happen on that level, and if you don't endorse our judgment, tell us and the firm what to do.

So you can turn that into a motion any way you want, but the first part is --

DR. DETRE: All right. Hands up -- who endorses the judgment?

(A vote was taken.)

DR. DETRE: All right, that's unanimous.

Next question. Any more questions?