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CASET Associates, Ltd.
3927 Old Lee Highway
Fairfax, Virginia 22030
(703)352-0091

List of Participants:

Carol Ann Tamminga, M.D.

Javier I. Escobar, M.SC., M.D.

Robert Mark Hamer, Ph.D.

Ken-Ming Lin, M.D.

Regina Claire Casper, M.D.

Nina Rosenberg Schooler, Ph.D.

Larry Ereshefsy, Pharm. D.

Abby J. Fyer, M.D.

Dennis S. Charney, M.D.

Ellen Frank, Ph.D.

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P R O C E E D I N G S (8:39 a.m.)

DR. TAMMINGA: Welcome, everyone, to the 42nd meeting of the Psychopharmacologic Drugs Advisory Committee. My name is Carol Tamminga. I'm from the Maryland Psychiatric Research Center at the University of Maryland. I am the chairperson of this committee.

Next, I would like those of us seated around the table to introduce themselves.

(Whereupon, introductions were performed.)

DR. TAMMINGA: We have a couple more committee members who will introduce themselves when they come. Now Mr. Bernstein, who is the committee's executive secretary, has requested time to make several administrative announcements.

MR. BERNSTEIN: Thank you, Dr. Tamminga. I would like to welcome each of the committee members to this, the 42nd meeting of the Psychopharmacologic Drugs Advisory Committee. My name is Michael Bernstein, and I am the executive secretary of the committee, which functions within the Division of Pharmacological Drug Products. Please bear with me while I make a few administrative announcements.

On the table by the entry are handouts of the agenda, question list and roster of committee membership. I hope that everyone has picked up a copy. We ask that all speakers speak directly into a microphone. Individuals from

the audience, following recognition by the Chair, should come forward to a mike. Unless one speaks directly into the mike, comments cannot be heard by our transcriptionist nor by those sitting in the rear of the room. If anyone in the audience desires to make any comments in the open public hearing, we ask that you wait until you have been recognized by the Chair before coming forth to a microphone. Please identify yourself and your affiliation before beginning your statement. Statements made in the open public hearing must relate to the issue being considered at this meeting, and be of general interest to the committee members.

A lunch break will be determined according to the time frames allotted for presentations, and we will make an announcement a little later. As this is an open meeting, a reminder that the proceedings may be tape recorded, and that the recording is considered to be unofficial until it has been approved by the Commissioner of Food and Drugs.

The following announcement addresses the conflict of interest and is made part of the record to preclude even the appearance of such at this portion of the meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interested firms regulated by the Center for Drug Evaluation and Research, which had been reported by the participants, present no potential for

the appearance of conflict of interest at this meeting, with the following exceptions. Two of the committee participants or their employing institutions have previously been involved in research relating to Deracyn that we believe should be disclosed. FDA believes that it is important to acknowledge these participants' involvement, so that their participation can be objectively evaluated.

Dr. Lin was previously involved in a pharmacokinetic study of Deracyn. In addition, while he was at the University of California-Los Angles, Dr. Escobar collaborated with a colleague who was an investigator in a trial on Deracyn. Dr. Escobar is also aware that in the past, some colleagues at the University of Connecticut had conducted a study of Deracyn. However, Dr. Escobar had no personal involvement in this activity. Since neither Dr. Lin nor Dr. Escobar have a current financial interest in Upjohn's Deracyn, they do not have a financial interest as defined by 18 USC 208.a. Further, since these past studies are not included in the material that the committee will be reviewing, the agency has determined that Drs. Lin and Escobar may participate fully in the committee's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the

participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Lastly, NDA 20-158, Deracyn, will be the only issue discussed by the committee at this meeting.

Thank you for your attention, and this concludes my comments, Dr. Tamminga.

DR. TAMMINGA: The open public hearing is now in progress. Does anyone from the audience have any comments or statements to be made during the open portion of this meeting? If so, please come forward to a microphone, identify yourself, and proceed.

If there are no comments to be made in the open meeting, we will move on. The topic for today's meeting is NDA 20-158, Deracyn. Dr. Tom Laughren, who is the group leader, division of neuropsychopharmacology, has the opening comments on this NDA.

DR. LAUGHREN: Good morning. I would like to welcome you to this 42nd meeting of the Psychopharmacologic Drugs Advisory Committee. The topic for today is an application for Deracyn SR in the treatment of panic disorder.

Deracyn SR is an extended release formulation of adinazolam, which is a triazolo benzodiazepine. At the present time, as you are aware, there is only one drug approved for the treatment of panic disorder in the U.S. market, and that is of course alprazolam.

Because the FDA has not had a lot of experience reviewing applications for panic disorder, I thought it might be useful for the committee to address not only the data pertinent to adinazolam, but also perhaps talk about some generic issues related to developing drugs for panic disorder.

From the standpoint of adinazolam, for efficacy we're going to be focusing on three short term trials of adinazolam in panic disorder. Dr. Lee from FDA will be presenting the details of the effectiveness data. In the package that you received from FDA, you received reviews from Dr. Lee, the clinical reviewer, and Dr. Taneja, the biometrics reviewer, focusing on two of those three studies. Those two studies were 7400, which is a four-week flexible dose study looking at adinazolam in a dose range of 15 to 120 milligrams compared to placebo, and then 7450, which is also a four-week study, in this case a fixed dose study, looking at three doses, 30, 60 and 90 milligrams compared to placebo.

You have not received any information on study 90,

the third study. This is an eight-week study. It is a three-way study comparing adinazolam up to 90 milligrams per day, imipramine up to 150 and placebo. The reason that you didn't receive any data is that we didn't receive a preliminary report on this study until after we had mailed the package to you, and we still haven't received the complete data on this study. But we thought that it is of considerable relevance, so we're going to try to present you at least a preliminary look on the data for this study.

From the standpoint of safety, there are two databases for adinazolam that we're going to be looking at. There are two development programs. An immediate release form of adinazolam was conducted a number of years ago in a depressed population. We have roughly 3,000 patients exposed to the immediate release form of adinazolam. Then the sustained release development program in anxiety disorders includes roughly 1300 patients exposed. So the total database is roughly 4300 patients. Dr. Knudsen from FDA will be presenting his safety findings.

There is only one safety issue that I'm going to spend time focusing on in my comments, and that is the general issue of dependence and withdrawal that I think is important for any benzodiazepine.

One other point I want to emphasize is that although our focus today is going to be exclusively on

clinical data, there are many other parts of an application that we need to look at very carefully before the agency can take an action. As one example of that, I want to focus a few minutes on an animal toxicology issue. This has to do with lifetime carcinogenicity studies. To understand the issue, you have to understand that humans who are exposed to adinazolam make a metabolite, N-demethyl adinazolam, which turns out to be the major circulating active species for this drug.

The lifetime carcinogenicity studies for adinazolam were done in rats and mice, as is standard. So it is important to know that those animal species also make the metabolite that is the important metabolite in man. Several weeks ago, a question was raised as to whether those species make that metabolite. If they didn't make the metabolite, the lifetime carcinogenicity studies would not be relevant. So regardless of the committee's recommendation on the clinical data, the agency would not ordinarily take an action on a product for which there were not adequate lifetime carcinogenicity studies.

Now, as it turns out, as recently as last Friday we got some additional data suggesting that at least in rats, the metabolite is prominent. We haven't completely resolved the issue. We still have to get a complete report for rats, and we have to find out what happens in mice. But

it appears at this point that the issue is resolvable. I am raising this not so much as an issue that needs your input, but to caution you about the complexity of the decision that the agency has to make.

After you have heard the data presentations, and after you have had a chance to discuss the data, we would like you to vote on the usual questions about safety and effectiveness that we always ask you to vote on. But as I pointed out before, I think it would be useful for the committee also to look at some of the generic issues involved in developing and evaluating drugs in this area.

I have some transparencies that Mike Bernstein has agreed to show for me. You also have a hard copy of some of the questions and issues that we handed out.

The first issue that I would like to focus on is the question of what are the critical outcome variables that should be looked at in panic disorder studies. As you are aware, there has been a lot of interest in recent years in trying to figure out what the best measures are. NIH has had several workshops and meetings, and other groups have had meetings.

I think one critical question is how important is the number of panic attacks as an outcome variable in this disorder. There has been some controversy about this. From a positive standpoint, number of panic attacks has face

validity as an issue. After all, if panic disorder isn't panic attacks, what is it? On the other hand, it has been noted that there is an awful lot of instability in that measure. Some have argued that there is so much instability that in short-term trials, number of panic attacks is not a particularly good measure. Also, number of panic attacks appears not to correlate very well with some other measures that are used in studying patients with panic disorder, such as phobic anxiety, avoidance and so forth. So that is one question that we would like your thoughts on, how important is panic attacks. This variable and its importance is particularly important for this NDA.

A second issue is a general one of the measures that we have looked at in these studies: what are your thoughts on our selection? You will hear more about this, but basically, we have looked at number of panic attacks. We have also looked at phobic state score from the Marks-Sheehan phobia scale, phobic anxiety score from the SCL-90, an anticipatory anxiety measure, and the CGI, both severity and improvement. Those are the six measures that we have chosen to focus on, and we would like your thoughts about that selection.

Could I have the next transparency? A second issue that I would like to focus on is the issue of long term efficacy data and how important an assessment of long

term efficacy is in an evaluation of a drug for panic disorder. In particular, how important a deficiency is that the lack of having long term data in this development program? We're looking at short term trials.

Like most of the disorders that we bring to this committee, panic disorder is a chronic condition. As is often the case, we have only short term data for this NDA. It is true that in study 7400, a subset of patients were examined for 22 weeks. However, it was a relatively small sample. That extension design is not the correct design to assess that issue. In fact, we don't even have any statistical analyses on those data. So we're dealing with a short term program, and the question is, how important a deficiency is that for this disorder.

A related question is, how important a benefit is effectiveness for short term treatment. Again, it is true that for many of the chronic disorders that we deal with, we don't have long term data, depression being an example. However, it may not be an entirely parallel situation. For one thing, there are long term data for some antidepressants, and I suppose one might argue that you can take some comfort in that fact, and perhaps generalize to other antidepressants in the general class. I am not aware that there are any long term data for drugs that are used in treating panic disorder.

A second issue has to do with what I feel is a general belief that there is benefit in depression for treatment of an acute episode. Patients have considerable dysphoria and truly benefit from a resolution of symptoms in an acute episode. My question to you is, can panic disorder be thought of in same sense, as a chronic disorder that has episodes for which there is a benefit from short term resolution of symptoms.

If you believe that long term data are important, it would be helpful if you could comment on what would be optimal study designs for evaluating long term efficacy. Finally, if you were to recommend the approval of Deracyn for panic disorder, what advice would you give clinicians in labelling with regard to how long responding patients should be continued?

Could I have the next transparency? Another issue that I would like you to think about is the issue of dose response. In general, how important is it to have dose response information in evaluating a claim for panic disorder? In particular, is this program adequate from the standpoint of providing information on dose response for effectiveness. Again, if this drug were to be approved for panic disorder, what dosing instructions would be appropriate for clinicians in labelling?

Finally, I want to make a few comments on the

general issue of dependence and withdrawal for benzodiazepines as a class. For any benzodiazepine, one would like to be able to answer these questions. First of all, with regard to withdrawal, is there a physiological withdrawal syndrome associated with discontinuation of the drug? If so, how is it characterized, what is the incidence? What is the range of severity of withdrawal symptoms? Do patients have seizures when they come off the drug? At what incidence? Can one separate psychological from physiological from physiological withdrawal? Are there any predicters of withdrawal, for example, dose or duration? What is an optimal discontinuation schedule to minimize withdrawal symptoms?

Could I have the next transparency? A parallel set of questions has to do with return of illness. When a patient has been treated with a benzodiazepine and treatment is stopped, do symptoms of panic disorder return after discontinuation? What is the incidence, what is the time course? Are the symptoms worse following discontinuation than they were at baseline, in other words, rebound? Can one distinguish relapse from withdrawal?

I think a very important question is, do patients have great difficulty in stopping a particular benzodiazepine after they have been taking it for some time? Another question that some have asked is, could a particular

drug actually alter the course of illness, in the sense that there is an increase in the likelihood of panic attacks over what might have been seen without treatment?

Those are general questions that I think one would like to ask. Obviously, they are very often difficult questions to answer. I am not suggesting that all of these questions would need to be answered prior to the approval of a product.

Could I have the next transparency? I would like to get some input on what the committee thinks would be the minimum set of data that one would like to have in regard to these questions. If you believe they are important questions, what study designs and analytical approaches do you think would be useful in addressing them? Specifically with regard to this program, how does this program stack up with regard to questions about dependence, withdrawal and so forth?

What actually has been done in this program in the way of looking at dependence and withdrawal? As I mentioned earlier, there are two parts to the program, the database. There is the immediate release program that was done in patients with depression, and as far as I can tell, there was very little attention paid to discontinuation symptoms in that program, other than seizures, and we will provide those data for you. In the sustained release program, there

was a lot more attention paid to the whole notion of what happens when you stop treatment.

As I understand it, the taper and discontinuation approach involved an unblinded discontinuation at a rate of roughly 50 percent per week, down to a dose of seven and a half, and then a two-week follow-up period, unblinded in the sense that patients knew they were being withdrawn. I don't believe they knew what they were being withdrawn from, so the blind wasn't broken, but everybody knew they were being withdrawn during that period.

From my standpoint, that is probably not the best design for trying to tease out a withdrawal syndrome. I think for one thing, the groups are not comparable. One is comparing placebo patients who made it to the end of a four-week trial with drug patients who made it to the end of the trial. Those groups may not be identical. Placebo patients who survived that long may be different in some sense from the drug patients. The other part of it is, it's not blinded, so everybody knows they're being withdrawn.

The other potential problem from that type of evaluation is that patients were seen only every week. If one wanted to get a very specific picture of what is happening day to day, which one might want to have if one is trying to sort out re-emergence of symptoms from withdrawal, one can't get it from that design.

Dr. Knudsen is going to present the data pertinent to discontinuation. As I mentioned, he is going to look at seizures as one measure of serious withdrawal. He is also going to look at the emergence of new symptoms from studies 7400 and 7450. I think in our view, that reveals that this drug has a fairly typical benzodiazepine withdrawal syndrome. He has also looked at the need to use adjunctive medication, in particular other benzodiazepines, during discontinuation and withdrawal. He has looked across the entire database to look for other serious events other than seizure that might be suggestive of important withdrawal.

The sponsor has also done some analyses looking at relapse and withdrawal, using a very interesting approach, but with definitions that are quite arbitrary and I think somewhat difficult to interpret clinically. We're not going to present those data, but I'm sure the company would be happy to present them or answer questions about them.

At this point, I would like to introduce the first FDA speaker, Mohammad Hossain, who is going to give a brief summary of the pharmacokinetics of adinazolam. We thought this would be useful as background information for the effectiveness and safety data you will hear later. He will be followed by Dr. Lee, who is going to present the efficacy data. The biometrics reviewer, Dr. Taneja, is not going to make a presentation, but he is here and can respond to

questions about analysis and so forth. Finally, Dr. Knudsen will present the safety data.

DR. HOSSAIN: Thank you, Dr. Laughren. As you mentioned earlier, I will be briefly presenting the human pharmacokinetics of adinazolam mesylate sustained release tablets.

Following oral administration, adinazolam is essentially complete absorbed. The absolute bioavailability from the sustained release dosage form is about 40 percent due to extensive first-pass metabolism. Relative bioavailability compared to an oral solution is about a hundred percent. Food has been shown to affect the rate, but not the extent of absorption. No evidence of dose dumping was observed when the sustained release formulation was given with food.

Being a very lipophilic compound, adinazolam is widely distributed throughout the body. However, a steady state volume of distribution following intravenous administration was about a hundred liters. In vitro plasma protein binding studies show that adinazolam is about 70 percent bound over the therapeutic concentration range of adinazolam, and the major metabolite, N-monodemethyladinazolam, is about 40 percent bound.

Both the parent and the major metabolite demonstrate linear pharmacokinetics over the dosage range of

10 to 60 milligrams with predictable accumulation. The major metabolite, N-monodemethyladinazolam, has been shown to possess pharmacological activity comparable to the parent compound adinazolam, and also has higher affinity for benzodiazepine receptors compared to adinazolam.

This slide shows the linear relationship between area under the curve and dose of the major metabolite, N-monodemethyladinazolam, which is represented by this upper curve, and that of adinazolam, represented by the lower curve. In this slide, I wanted to point out that exposure to the major metabolite is about fourfold to that of the parent compound.

Following oral administration, adinazolam is primarily eliminated by demethylation to the major metabolite, N-monodemethyladinazolam. The contribution of the various isozymes of cytochrome P450 to the metabolism of adinazolam has not yet been characterized. However, since the preparation of this slide, preliminary reports of in vitro metabolism studies conducted by the sponsor have been made available to the agency, and I will discuss those preliminary results under the drug interaction section.

Ninety-five percent of a radiolabelled dose of adinazolam was recovered in the urine. Of that, 50 percent is the major metabolite N-monodemethyladinazolam. N-monodemethyladinazolam also undergoes metabolic oxidation to

various metabolites, five of which are as minor metabolites, each representing less than five percent of the dose. These minor metabolites, while active pharmacologically, do not accumulate in plasma even after multiple dosing. Less than two percent is recovered in the urine as intact adinazolam with about 20 to 30 percent that has not been identified. Four percent of the radioactive dose was recovered in the feces. Therefore, the overall recovery was about a hundred percent.

Elimination half life is about three to five hours for adinazolam and six to seven hours for N-monodemethyladinazolam. Therefore, steady state should be achieved within two to three days.

Based on a pharmacokinetic drug interaction study, cimetidine has been shown to decrease the clearance of adinazolam by about 30 percent. Cimetidine is also known to be a moderate inhibitor of cytochrome P451A2, and a strong inhibitor of both 2D6 and 3A4. Also, it has been known in the literature that alprazolam and triazolam, which are structurally similar to adinazolam, are metabolized by cytochrome P453A4.

The preliminary in vitro metabolism studies conducted using human liver microsomes show that low concentrations of cetoconizol, which is a selective inhibitor of CYP3A4, inhibits the conversion of adinazolam

to form N-demethyladinazolam. In the same study, preliminary reports suggest that alpha naftaflavon and fufloralin, which are selective inhibitors of CYP1A2, and also quinidine, which is a selective inhibitor of 2D6 but itself is not a substrate for that isozyme, do not inhibit the metabolism of adinazolam.

Based on these findings, it can be concluded that adinazolam is primarily metabolized by cytochrome P453A4. Also, in the same in vitro study, it was shown that adinazolam does not inhibit cytochrome P453A4 itself.

The following factors have been identified to affect adinazolam disposition in humans: decrease in clearance of adinazolam was observed in renal impairment, hepatic impairment and with age. Clearance was reduced by 30 to 40 percent with a corresponding prolongation of half life of both the parent and the major active metabolite, N-monodemethyladinazolam.

Gender effects were found not to be significant. No specific pharmacokinetic study was conducted to investigate race effects. However, retrospective analysis of pharmacokinetic data shows that the clearance of adinazolam is increased by about 20 to 30 percent in African-Americans, compared to Caucasians. Therefore, African-Americans have a higher metabolic capacity for adinazolam. Based on these findings, appropriate

precautions and labelling recommendations will be incorporated.

Finally, I would like to conclude my presentation by introducing other members of the pharmacokinetic review team: Dr. Safaa Ibrahim, Dr. Vijay Tammara and Dr. Raymond Miller. All members of the pharmacokinetic group are currently attending this session and will be available to provide any additional information regarding human pharmacokinetics of adinazolam.

Thank you.

DR. TAMMINGA: Now we will hear from Dr. Hillary Lee on the clinical review.

DR. LEE: The efficacy of adinazolam in panic disorder was assessed in three placebo controlled studies. My presentation today will focus primarily on the fixed dose and the dose titration studies. The third study, which included imipramine as an active control, was submitted only recently and will be discussed following the main section.

Protocols 7450 and 7400 were randomized, double-blind trials in which parallel groups were treated for four weeks. Both trials were multi-centered. Entry criteria were the same in both trials. Subjects were required to be physically healthy adults with a diagnosis of panic disorder with agoraphobia.

Subjects were ineligible if they met DSM-III-R

criteria for a concurrent episode of any major psychiatric condition, for example, major depressive episode, generalized anxiety disorder, or obsessive compulsive disorder. Historical evidence for certain psychiatric diagnoses were also exclusionary, as were seizure disorders. Subjects were not permitted to receive any other concurrent treatment for their psychiatric condition.

Here are the medication schedules for the two trials. The table gives total daily dosages. Note that medications were administered BID. In both studies, dosing began at one tablet, 15 milligrams, in the evening for three days, and was increased by adding one tablet in the morning for four days. Subsequent increases were by one tablet every three or four days. In protocol 7450, those escalations ceased when the specified dosage was reached. In protocol 7400, escalations ceased when the patient responded or reached 120 milligrams or developed intolerable side effects. Chlorohydrate was allowed up to three times a week for insomnia. If the patient was taking an alpha or a beta blocker for non-panic reasons, the dose had to be stabilized for at least three months. No other concurrent medications were permitted.

Each study began with a drug-free interval of one to two weeks followed by a single blind placebo phase of one week. This in turn was followed by a four-week double-blind

treatment phase. The studies ended with a taper, lasting up to four weeks, and a two-week post-taper phase. Protocol 7400 allowed patients who were classified as responders to enter a double-blind 22-week extension at week four. For these subjects, the taper and post-taper phase followed the extension.

There were six primary efficacy variables: total number of panic attacks from the patient's diary, anticipatory anxiety -- this was the mean percent of waking hours spent worrying about panic attacks, a patient assessment of overall phobic state, the SCL-90 score on the phobic anxiety cluster, CGI severity of illness and the CGI improvement score. The results will be presented as a change from baseline for the first five variables, and as the actual means for the sixth variable.

I will begin with protocol 7450, the fixed dose study. First, the study conduct. There were approximately 80 subjects in each treatment arm, and more than 80 percent of the subjects in each group completed the trial. Mean maintenance doses were equal to or close to proposed doses. The mean age in all treatment groups was around 37 and a half years. Approximately 62 percent of patients in all treatment groups were women, and more than 85 percent of all patients enrolled were white.

Now the results for protocol 7450. All the data

presentations for protocol 7450 are based on the last observation carried forward analyses for the all-patient sample. These are the patients who had a baseline evaluation, at least one double-blind dose and at least one set of follow-up observations. There were essentially no differences in outcome between the LOCF and observed cases analyses of data. Treatment duration is shown on the X axis and change from baseline on the Y axis. A negative change indicates improvement over baseline. An asterisk signifies a P value equal to or less than .05 two-tailed versus placebo. The lowest adinazolam dose, the 30 milligrams, is in the lightest color, and the highest, 90 milligrams, is in the darkest color.

As you can see, adinazolam 60 milligrams produced significantly more improvement than placebo in the number of panic attacks at weeks one, two and four. The 90-milligram dose produced more improvement than placebo at week four. Adinazolam 90 milligrams was more effective than placebo in reducing anticipatory anxiety at weeks one, two and four. At week one, adinazolam 30 milligrams was also significantly better than placebo.

All three doses of adinazolam were significantly more effective than placebo in reducing the overall state of phobias at weeks one and four. The two higher doses were also significantly more effective at week two.

On the phobic anxiety cluster, the effects of the three doses of adinazolam did not differ from that of placebo. Only 30 milligrams was shown to be different from placebo, and only in the first week.

Adinazolam 90 milligrams produced significantly more improvement than placebo on the severity of illness item at weeks two and four. The 60 milligrams dose was also superior at week two. Adinazolam 90 milligrams produced significantly better scores than placebo on global improvement at all weeks. The 60 milligram group was significant at weeks one and two, and the 30 milligram group at week one.

This slide shows the percent of completers for each treatment in each category of change on global improvement at week four. Here, there appears to be a shift to the right for adinazolam, particularly to the much-improved category. This is what you would expect to see when the drug works.

To summarize, this was a positive study. Adinazolam produced significantly more improvement than placebo at week four on five of the six variables. Jonquier's(?) test was carried out on the number of panic attacks, change from baseline, and when placebo was excluded from the analysis, it approached significance, suggesting a weak dose response.

Now the results for protocol 7400. You will recall that protocol 7400 was a dose titration study with treatment beginning at 15 milligrams and rising in 15 milligram increments every three or four days to a possible daily maximum of 120 milligrams. A total of 221 patients entered the trial and 87 percent completed the four-week trial. Sixty-six percent of the completers entered the 22-week extension, and 69 percent of this group, that is, 88 subjects, completed the extension.

In the following, the results of the four-week trial alone will be presented. The mean maintenance dose, 84 milligrams, was similar to the high dose in protocol 7450. The demographic characteristics were also similar to protocol 7450.

In this study, there was no difference in the amount of improvement produced by adinazolam and placebo on the number of panic attacks at any of the evaluations.

Here, adinazolam produced more improvement than placebo on anticipatory anxiety at weeks two and four. There was no difference between the effects of adinazolam and placebo on overall phobic state at any time point. Adinazolam produced more improvement than placebo at week four on the phobic anxiety cluster.

On severity of illness, adinazolam produced more improvement than placebo at week four. On global

improvement, adinazolam produced significantly more improvement at all time points.

In this bar graph of percent completers, we see the same pattern as in protocol 7450, with a shift in the distribution to the right for adinazolam, particularly to the much and very much improved categories.

In summary, in protocol 7400, adinazolam was more effective than placebo on four of the six variables. The panic attack item was not significant, although this may have been because of the larger placebo response in 7400 than 7450. The mean change from baseline for placebo was 1.2 panic attacks in 7450 and 2.0 attacks in 7400. It should also be noted that the extension cannot by design be used for evidence of long term efficacy. The extension sample began with only 57 percent of the randomized subjects, and only responders were allowed to participate. The sponsor did not do any statistics on the extension efficacy variable.

The sponsor has recently submitted a report of a third study of adinazolam in panic disorder. This is protocol 90. This was a comparison of adinazolam with imipramine and placebo, using the same end points as those employed in protocols 7450 and 7400.

We have not had an opportunity to review these data. They are presented here so the committee can see all

available data pertaining to the efficacy of adinazolam in panic. This study by design should be capable of providing evidence of efficacy.

Protocol 90 differs from the other studies in three ways. First, the double-blind treatment duration was eight weeks, not four. Second, there were three treatment arms with adinazolam, imipramine and placebo, with a total daily dosage increased to 90 milligrams for adinazolam and 150 milligrams for imipramine. Third, subjects were required to have some depression secondary to panic disorder. The minimum entry depression score was six or greater on the retardation factor HAM-D or eight or greater on the depressive scale of the SCL-90.

There were 86 adinazolam subjects with 79 percent completing, 83 imipramine subjects with 72 percent completing, and 80 placebo with 78 percent completing.

All the slides from here forward were prepared by the sponsor. The next two slides compare the baseline scores of the subjects in the three studies. These are on page 26 and 27 of my handout, if you would like to see them there. The first slide includes mean baseline scores on the efficacy measures for the three studies: 7400, 7450 and 90. Descriptively, it appears that in protocol 90, there were more panic attacks, higher scores on the SCL-90 phobic anxiety, and higher scores on the SCL depression.

The second slide shows HAM-D scores at baseline. Here, it also appears that protocol 90 had higher baseline depression scores.

Now, the results. The first slide shows the mean change from baseline and total number of panic attacks. For weeks one to eight, the data are the observed cases analyses of the all-patient sample. The week eight LOCS analysis is also included. There are no statistically significant comparisons at any time point for this variable.

Anticipatory anxiety. No significant comparisons, except for adinazolam at week two. Overall phobic state, no significant comparisons. Phobic anxiety cluster, imipramine produced more improvement than placebo at week six. Severity of illness, adinazolam is superior to placebo at weeks one, two and eight; imipramine is superior to placebo at weeks two, four, six and eight, and imipramine is superior to adinazolam at weeks one, four, six and eight.

Global improvement by week. Both adinazolam and imipramine produced significantly more improvement than placebo at weeks two, three, four, six and eight. Imipramine was superior to adinazolam at weeks one, four, six and eight.

Here we have the week eight percent of completers on the improvement scale. The shift to the right is not very marked for either treatment, except in the very much

improved category.

Protocol 90 appears to be a failed study. It was only on the CGI that either drug appeared effective, and this was in the absence of any effect on panic attacks.

This overhead shows the efficacy variables on the left with significant outcomes for the three studies, 7450, 7400 and 90, based on the LOCF results. Protocol 7450 was the most positive and was the only study where adinazolam significantly changed panic attacks. Protocol 7400 had four significant outcomes, and protocol 90, one.

Thank you very much.

DR. TAMMINGA: Questions for Dr. Lee?

DR. HAMER: What statistical tests were used to test all these various hypotheses?

DR. LEE: Dr. Taneja is here to answer those questions.

DR. TANEJA: Good morning. In order to answer your question, the sponsor has used Koswalie's(?) test and Wilcoxen test, and as an alternative analysis I have used Van Alderin(?) test.

DR. HAMER: But in terms of the decision that Dr. Lee presented here, where she said something was statistically significantly different from placebo or not, which of those three tests was used to make that statement?

DR. LEE: I used Dr. Taneja's scores, his P

values.

DR. HAMER: Which were?

DR. TANEJA: Van Alderin test. It is also known as block Wilcoxen test.

DR. HAMER: So these P values that were just presented were all the Van Alderin's test?

DR. TANEJA: Yes.

DR. TAMMINGA: Is it correct to say that the FDA has not yet analyzed study 90, and the data that you presented was the data that was given to you by the company?

DR. TANEJA: That is correct.

DR. CASPER: We just had a discussion on what we thought might be a discrepancy in your discussion of the data. Wehn you said that either imipramine or adinazolam was more effective at week one, two, three or so, these were comparisons by week and the overall slope -- do I understand you right? -- is not significant? Because you said, for instance, for severity of illness or anticipatory anxiety, the week by week comparisons sometimes are significant, but the overall slope is not significant?

DR. LEE: Is this for protocol 90?

DR. CASPER: Yes.

DR. LEE: These are the sponsor's tables. They compared the drug at each week. I don't know about the overall tests. Those were the paired comparisons at each

week. Whether the overall test was significant, I don't know. They might know, but I don't know.

DR. FYER: Because that is the only eight week data that we have. I don't know if this is the appropriate place, or maybe we should come back it.

DR. TAMMINGA: We can ask any questions of the FDA presentations that we want to now, and we'll have discussions about the points later on.

DR. FYER: I would like some additional information about 90, but maybe you should do that during the sponsor's presentation.

DR. TAMMINGA: You can ask for whatever information you want, and if Dr. Lee can answer it, she can, and then the company will get a little fore warning about what your questions are, so they can prepare.

DR. FYER: I'm not sure I understand your presentation of protocol 90, in terms of why you consider it a failed study, even though I think some of the findings are a little unusual, given previous imipramine trials in panic. If there is a significantly greater decrease in panic at week eight, why that is different than the 7450. It seems to me what you were saying was, these aren't your tables.

DR. LEE: Tom?

DR. LANG: The tables that Dr. Lee showed did not show any statistically significance for number of panic

attacks for imipramine or Deracyn, compared to placebo.

DR. FYER: I understand that, but in the global improvement, they did. I was wondering about the difference between her analysis of that graph and the similar graphs that were shown for the 7400 and the 7450. It seemed to me that what Dr. Lee was saying was that these weren't her tables.

DR. LANG: In the 7400 and 7450, in both of those trials, the comparisons were significant for most of the variables, including CGI improvement in severity. In 90, according to these tables, the only variables that made it prominently were CGI. The panic attacks didn't make it, anticipatory anxiety didn't make it, overall phobic state didn't make it. Almost nothing made it other than CGI. A question I have for the company is, how was the CGI administered? What was the focus of the CGI? Was it on panic disorder or depression? What were the instructions to the clinicians who were administering that?

DR. JONAS: It was based on response to panic disorder and response to panic. Not depression, panic, when it was administered.

DR. CHARNEY: What were the anchor points? When you were instructing the clinician to rate the global improvement, were you saying that they would be asking about the number of panic attacks and the degree of phobias?

DR. JONAS: Yes, it was on the symptoms of panic.

DR. CHARNEY: How do you understand the discrepancy between no change in panic, no change in phobias, but a change in global improvement?

DR. JONAS: I'm not certain I understand, frankly, looking at the data. The patients do say they were better, but there were no responses. There is some trending, as you can see, but no significance. So I don't have the answer to that. I don't know.

DR. LEBER: I have a question I would like to ask. It is also intended to draw attention to the design of global instructions. I'm a bit surprised that anyone is told how to do a global, because generally, the global is an experienced clinician's evaluation of whatever they choose to evaluate, and then they are asked to measure it on a particular categorical assessment that is usually four equals no change, seven is getting much worse and one is getting much better, and you see that. It usually is not anchored. It usually doesn't provide many instructions, and the intent is to get an overall sense of what is going on.

The domain content, that is, the features that makes something panic disorder, are usually picked up on the domain specific rating scales that supposedly focus on the items that make the entity what it is. So I'm ever a bit surprised that any instructions were given at all, and I

wondered if they were consistently given, or whether the protocols called for them, or whether there is any such. It is quite possible that every clinician uses his own idiosyncratic assessment for the global. We have found that in other areas, and I wonder if that isn't true here.

DR. JONAS: We will review that, just to be certain about that.

DR. TAMMINGA: I think the committee has not seen any of the data on study 90 in our packets, so we haven't had a chance to pre-review any of that.

DR. LANG: I just want to emphasize that FDA has seen precious little as well. Up until the middle of last week, I was feeling fairly confident that the slides that Dr. Lee presented fairly represented the situation. But then over the weekend, I was looking at an additional bit of information we received late last week from the company that seems contrary to what was presented in the slides.

I have some transparencies that I would be happy to show, mostly as a question to the company, to explain what appears to me to be a discrepancy, if I could do that.

DR. TAMMINGA: Why don't we go ahead and look at those right now?

DR. LANG: This is one of the slides that Dr. Lee showed. This is for study 90, total panic attacks, looking at mean change from baseline, the observed cases analyses,

weeks one through eight and then LOCF.

As you can see here -- this is imipramine, the solid circles -- it appears that at almost all time points, imipramine is doing less well than the other two groups. The squares are Deracyn and the solid squares are placebo. So it appears that imipramine is doing less well in terms of change in baseline in number of panic attacks at all time points, with no statistically significance indicated between either active drug and placebo on this slide.

Could I have the next transparency? This was a table that was included in a fax that we received late Thursday afternoon -- I looked at it this weekend -- summarizing P values, again for study 90, the observed cases data at weeks one through eight, imipramine versus placebo and adinazolam versus placebo. Number of panic attacks, mean change from baseline. If you look across this row, you see an indication of statistically significance at weeks four, six and eight versus placebo for imipramine, not for adinazolam versus placebo, using the Kruskall-Wallace test, which I assume was the same test used in the data presented in the slide.

If you look across some of the other variables, you find other discrepancies. Overall, if you look at the P values in this slide, it suggests that there is more statistically significance for imipramine compared to

placebo than there is for adinazolam compared to placebo. It seems inconsistent with the slide that Dr. Lee showed.

So that is a question for the company.

DR. SCHOOLER: One question for the company regarding the CGI. It would be useful to have the exact wording of the question as it appears in the case report form, which would be what people would be seeing and what they would be responding to.

The second question I have is a more general one. I'm just confused about how we're supposed to deal with the results of study 90 when we haven't had an opportunity to review this in advance, and when our colleagues at the FDA, who we tend to rely upon, have not had an opportunity to review the data in advance. I'm wondering what the ground rules are for presentation of a study in this way to us.

I personally feel uncomfortable adding it into the mix, and I feel equally uncomfortable about ignoring it.

DR. TAMMINGA: Do either Dr. Leber or Dr. Laughren have some information to give?

DR. LEBER: Yes. It was our decision to share this with you. As you know, it has been recent policy to schedule meetings of this advisory committee several months in advance, in fact, a year in advance. A particular item comes to the agenda in a fairly fixed way. We are in the same position as anyone else is, that there is a stream of

data appearing about an application; reports are made sooner or later.

The original filing of this application did not contain reports of study 90. It was only in the last few weeks that we became aware of study 90. Our first read of study 90 was that it wasn't a failed study, but a negative one. It appeared to show that imipramine did produce a significant effect on panic in a general sort of way, whereas adinazolam did not. That made it have assay sensitivity. We use this three-way design often to document the population response, and we treat studies that fail to find a difference between the new drug and placebo in that setting quite differently than when all treatments fail to show a difference.

Accordingly, we told the firm that -- and I think this study was completed sometime in 1991. I cannot explain, nor is it our obligation to find out necessarily, why the amount of time elapsed that did before they provided a report. When they did, we had this meeting scheduled, and accordingly, just as Dr. Schooler has said, we were at a loss to ignore it, and at the same time felt we had to present it in the way it actually exists. That is the mix of the data stream. You have to look at it that way as well as we do.

Remember, our final advice from you doesn't

necessarily have to come today. What we are interested in knowing is, given the information available to you, could you as experts on the basis of the evidence deduced in controlled trials, reach a conclusion about the safety and effectiveness of this product, primarily the efficacy, in controlled trials. That is what you have, that is what you get, in a way.

DR. TAMMINGA: Has the FDA called this either a failed study or a negative study? Dr. Lee suggested that it was a failed study.

DR. LEBER: She was calling it failed, but I think it is fair to say that represents her current judgment of the evidence she has in hand. Were new evidence to be adduced, were we to look at the results that Dr. Laughren has just presented, you might change your mind and call it a negative study. It depends very much on how you weight the imipramine response.

Again, for all the vagaries involved here, our rules are idiosyncratic, too. It is nowhere written in stone that this is how you do it. We have just found it a convenient internal way to look at studies that fail to find differences.

DR. LAUGHREN: I can just add that I don't think I am anywhere close to feeling comfortable coming to a conclusion about study 90, based on what we have seen.

DR. HAMER: Can I ask Dr. Lee, when you used the word failed study, what went into your thoughts about the choice of that word? What appears to me to be a placebo response versus the somewhat imipramine response compared to the lack of an active drug response?

DR. LEE: It was more in contrast to when we saw the original data maybe three weeks ago, where they didn't use change from baseline, they used the actual scores, and imipramine at that point was significantly better than placebo, and there was no difference between placebo and Deracyn. At that point, we were thinking that this could be a negative study. So we asked the firm to send in the change from baseline results, and seeing those, which is what I showed you today, I decided that this was a failed study in comparison to being a negative study. That is where I was coming from.

What it really is, I don't know. We don't have any more data. We haven't had a review.

DR. FYER: In general about the 90, as I understand it, it is a study where the patients had depression plus panic? Okay. I think in terms of imipramine studies of panic disorder, of which there have been a fair number now, the results in the CGI severity of illness are somewhat peculiar. This is a 150 dose limit, and you see significant placebo-imipramine differences much

earlier than you usually do in panic studies, and usually not until six weeks.

DR. LEBER: Technical point. The fact that you find between group difference has little to do with the size of the effect, but has to do with local phenomena related to the amount of variation and so forth. So I don't think it is a fair test to say that.

DR. FYER: I understand that. The point I'm making is that I think the confounding of depression and panic may affect the interpretation of this data. This doesn't look like a typical imipramine panic response. I think considering the efficacy of each of these drugs with panic needs to take into account that 90 is not the same kind of study. Imipramine is an effective antidepressant as well as an anti-panic agent. It is not clear that adinazolam is.

So it's a complicated thing. I'm not even sure I would suggest that this kind of study even be appropriately considered as a panic efficacy study.

DR. LEBER: I would like to ask a question. We understand that depression is a very common comorbidity, to use the current language, with panic and with panic disorder and with panic agoraphobia. As a matter of fact, once this drug were to be marketed, it would be widely used in patients that present with panic, many of whom will have

depression.

This particular study happened to have high HAM-D scores, but there are other people who would have had less. The entry criteria I think was considerably less than that. So the product will be used in patients in whom there is a fair amount of depressive affect. The question comes up for us, and it is for you to answer, given a representative sample of patients in a study which by design should be capable of finding a difference, how do you interpret the failure to find that difference? The only reason we care about imipramine is not because we're interested in a comparative statement, but we're interested in whether or not the population that is randomized in this study is capable of responding to a pharmacological treatment in some manner.

It turns out that if you get no differences in a study, we usually throw it out and say it is failed, in the sense that we can't interpret it. But if you do find a difference, whatever the difference is caused by in that study, if it is due to drug or one of the two treatments, you're stuck with the population being sensitive in some way to a pharmacological treatment, and you add that to your mix of reasoning about whether you can conclude from all the data adduced that this drug is going to have the effects claimed for it.

Part of the risk/benefit ought to be consideration. You can't do it in terms of pure effectiveness, but how well will this drug work if marketed under the recommended conditions for use? Would you recommend it not be recommended for use in patients with depression? That is part of the inference base we are interested in.

So you may say this study doesn't apply typically, but then if that is the case, you might want to change your recommendations.

DR. ESCOBAR: I just want to go back to Dr. Schooler's question. The problem is now, before we debate the 0090, are we going to include it, or are we going to decide to ignore it?

DR. TAMMINGA: I would suggest that it is already included. We've already been presented, as the FDA has. I would suspect that the company should take some clues that we're in the dark about a lot of the aspects of study 90, and whatever kind of detail you can present when you get to your presentation would be very helpful. Even in contrasting study 90 with the other studies would be useful.

DR. CHARNEY: Does the company have Hamilton depression scores on 7400 and 7450? Maybe when you present, you can contrast the degree of depression in the various studies.

DR. LANG: That is in Dr. Lee's slides. She did show a slide comparing patients at baseline on HAM-D totals.

DR. LEE: 7400 did not have the HAM-D, only 7450 and 90 had the HAM-D. The first slide I showed you was all the efficacy variables using the SCL-90 depression.

DR. PEACE: Carl Peace from Biopharmaceutical Research Consultants in Ann Arbor, a consultant to Upjohn. I could perhaps add something that hasn't been added before that offers a bit of an explanation. When you compare the treatment groups at baseline, in terms of factors that are related to the disease under study, such as duration of current episode, it appears that the randomization was a failure to balance the treatment groups out. For many of such factors, it is always that imipramine is the least severe and Deracyn is the most severe. There are some acetates available that can be shown later on that reflect that.

Now, one other bit is that the analyses that were done and that Dr. Lee presented focused on mean change from baseline, but I think the inferential basis did not adjust for any factors. When you determine analyses which adjust for factors, such as investigational site differences, as well as the baseline value of the response variable, if it were measured, such as total number of panic attacks, then you do get a P value of .05, for what it is worth, for the

comparison of Deracyn and placebo at week two.

DR. CHARNEY: Which study?

DR. PEACE: The 90 study that was under discussion.

DR. FRANK: At this point, I am finding myself extremely confused, because I think what we're doing is trying to back our way into an understanding of study 90 rather than having a systematic presentation of what the study really looked like. I am trying hard to incorporate what you are saying, but I don't have a clear picture of the design of the study into which to incorporate it.

DR. TAMMINGA: The only presentation we have had so far is the presentation from the FDA. I think the usefulness of the discussion is that the company will know what some of our questions are, so that you might focus on them to what extent you can.

DR. HAMER: Although it winds up being more useful to wait for the company's presentation before going really deeply into this particular study. Although, let me hint that perhaps part of my source of confusion with this study as well as the other studies has to do with the multiplicity of dependent variables and the multiplicity and choice of the statistical hypothesis tests that were done on them. The variables are fairly different from each other in terms of distribution and categorization, ranging from number of

panic attacks, which I presume was per day, which is a count variable with relatively low numbers, to other dependent variables like scores on phobia sub-scales or anxiety sub-scales or those types of variables for which linear models analyses of some sort might have been more appropriate.

It looks like they pretty much did the same three or four tests on every one of the variables, categorized in three ways furthermore as responders and non-responders, plus the mean score analyses. I'm having a great deal of difficulty trying to figure out how to interpret all the asterisks and cross hatches and everything else, and come out with any sort of a global evaluation.

Then the additional complication of the fact that apparently, some of the analyses were done taking center into account and some of them weren't, so there is that problem as well.

I would also like to ask the sponsor, did they at any point attempt to come up with a single measure, perhaps a first principle component or some sort of measure which took into account all five or six of the aspects of the disease, and then do the analysis on that.

DR. TAMMINGA: I would like to focus our current questions on questions to Dr. Lee, and the questions that we have of the company, if they would just take note of and incorporate into your presentation.

DR. CASPER: Dr. Lee, my question refers to the data which Dr. Laughren also presented. You did not present the data on the imipramine response in your presentation, which is a little confusing to me. Why did you decide to present the data from the company, or was this just a sequential presentation of the data, that you got the printout on imipramine too late? Your presentation would have been much more of a negative study rather than a failed study if you had had Dr. Laughren's data.

DR. LEE: This was a matter of timing. I think we have already said we got the results of this study, some very preliminary results, after you had received your mailing. We looked at that, we asked the company to do certain kinds of things because it looked like imipramine was effective, and that Deracyn was not, that is, that it might have been a negative study.

After that, I got the slides. I'm sure I didn't get them more than a week ago, and some of them in the middle of last week. Then on Thursday afternoon we got a fax with these data in them, which Dr. Laughren got to read this weekend, so he is presenting them here to show you that we weren't confident when we began, but now we can point out a complete discrepancy that we don't understand.

DR. CASPER: Thank you. We have another question to the company. Why did the data drop in the way they

dropped in just shortly before the meeting? Why did the company wait to inform the agency and give full data disclosure earlier? So there is another question I would like the company to answer.

But there is an issue which Dr. Fyer has brought up, namely, the diagnostic heterogeneity of the samples. The two first studies were based on patients who apparently did not have an anxiety disorder nor depression. They had presumably a disorder of pure panic attacks. I would like the company to describe those two samples a little better in comparison to the sample in 90.

DR. LEBER: Can I make a suggestion that I hope will be a constructive one? We seem to be already launched into a discussion of efficacy. Ordinarily, we would go through the FDA's presentation next of safety. This is just a suggestion to the committee. Perhaps it would be useful to continue the discussion on effectiveness by asking that we break the usual mold, go right to the firm's discussion of the trials, so that we can have a discussion of substance, rather than going through this series of pre-fixed issues.

DR. TAMMINGA: Then the company would present their total presentation, including 7400 and 7450?

DR. LEBER: Yes, just go right to their efficacy presentations. You have the right, Dr. Chairman, to

determine how this meeting is run. It seems to me that one part of the issue is to facilitate discussion of the studies that are before us. If it suited you, you could ask them to present the effectiveness data now. They can still make their summary presentations, but it is your choice. It might be useful.

DR. TAMMINGA: Is the company prepared now to present some efficacy discussion of 7400 and 7450 and 90?

DR. JONAS: We're ready.

DR. CHARNEY: Just to be fair to the company, shouldn't we give them some time to prepare?

DR. TAMMINGA: I think we ought to take our coffee break now.

(Brief recess.)

DR. TAMMINGA: I would like to call the meeting to order again after the coffee break. We have one more introduction for the advisory board.

DR. FRANK: Ellen Frank, University of Pittsburgh.

DR. TAMMINGA: Thank you. I would like to ask the company people, when they get up, would you please introduce yourself? Just say your name and your business. We decided to alter the presentation order for the morning because of our discussions about efficacy, and go ahead and talk about the sponsor's discussion of efficacy, for all of the three studies that Dr. Lee presented, studies 7400, 7450 and 90,

and from the previous discussion, the company understands a number of the questions.

DR. JONAS: Good morning. Let me just begin by addressing some -- I'm sorry, I'm Jeff Jonas, and I am a psychiatrist with the Upjohn Company. Obviously, I am here to discuss adinazolam MSR with you today.

Let me begin by addressing some brief comments about the general questions that were raised. I'm going to give a talk on 7400 and 7450, and then turn over the discussion of the details of 0090 to Dr. Janet Fawcett, who is the chairman of our department of psychiatry at Rush Presbyterian.

There are a couple of brief corrections I would like to make first. One is that, on the CGI, that was administered as a standard CGI, as a global scale. I wasn't accurate in that regard. Relatively to 90, this was designed as a phase 3B product support study, and it was not intended at its inception to be a part of the original application. As a work load issue, it was not given high priority. When it was finished and it crossed my desk, which was a number of weeks ago, I only had two choices. One was to not submit it, or to submit in its current TR form. So we felt that in the interest of full disclosure, we had to send it in to the FDA for analysis, albeit late, and to discuss it at that point.

The other correction I would like to make is, reflecting the new analyses that we did because we were requested to do full analyses than this study had been in its initial design, one of the tables that Dr. Laughren showed was incorrect, Dr. Lee's slide was correct. That is the mean change from baseline for panic attacks was not significant. The mean values were, but the mean change from baseline was not significant. So those bottom three stars should not have been there in that table.

I now go back to my planned talk. We are in general agreement with the efficacy presentation given by Dr. Lee today, and as a result we do not plan to repeat the data from the presentation nor from the brochure. Instead, we would like to take this opportunity to expand on some selected topics. Our original agenda was that I would be speaking about efficacy, some issues about dosage and a brief comment about safety. You can decide if you would like me to add that nor or not. Then we're going to turn to Dr. Jonathan Davidson, who is professor of psychiatry at Duke University Medical School and director of the anxiety program, to discuss topics relative to discontinuation issues, quality of life and risk/benefit. This obviously will be delayed until after Dr. Knudsen's presentation. I have only one brief safety slide, so I will show that in the interest of parsimony.

The protocols prospectively define three methods of analysis that are seen here. Dr. Lee has presented our efficacy data from the adequate and well controlled trials looking at either analyses based on mean change from baseline or mean values. We are in agreement with her findings.

We would like to add to this discussion the clinical perspective, based on examining the patients who responded to each of the efficacy measures. That is, looking at responder analyses. Responder analyses can give you a sense of how the patient is doing and whether he benefits from treatment, and the protocols prospectively define criteria for responders. As a result, additional and perhaps more clinically relevant insight can be gained about a compound by looking at responders rather than mean values alone. So I would like to begin by reviewing the primary efficacy variables that we analyzed in the program.

Here are the efficacy variables that we assessed in the adequate and well controlled trials. They are seen on the top of the slide. At the time these studies were designed and initiated in 1988 to 1990, many investigators felt that response of panic attacks to treatment was the gold standard for response. But even at that time, the importance of other features of this disorder were still being debated.

Thinking about panic disorder has now evolved, and three domains of symptoms are recognized in panic, and these are highlighted in color in the upper portion of the slide: panic attacks, measures of phobic anxiety and phobic avoidance, and anticipatory anxiety. There is still disagreement whether one must eliminate panic attacks to achieve clinical benefit from a treatment, or whether behavioral and cognitive features of the disorder are more disabling than the panic attack itself.

Regardless, there is agreement that panic, phobic avoidance and anticipatory anxiety are the three major domains of symptoms. For this reason, we obtained measures of these in our trials.

The CGI, the clinical global impression, is used as a global measure that in effect assesses the integrated effect on a patient that combined improvement on all of the domains may have. We have seen data from Dr. Lee for these efficacy measures, as well as in our brochure dealing with mean change from baseline and mean values.

So I'm going to focus today on looking at responder analyses for the following reasons. As I mentioned, responder analysis has clinical relevance. You know the patient has improved on the measure in question. Secondly, it is not driven by outliers. A large percentage change that may or may not be clinically relevant can drive

the result. Thirdly, they were defined prospectively, so it is appropriate to deal with this today. The details of what I will present now can also be found summarized in your brochure on page five, and in more detail in the efficacy section of our brochure.

These are the protocol definitions of responder that we prospectively established. We had prospective definitions for total panic attacks, the SCL-90 phobic anxiety cluster, the overall phobia scale, which is based on the modified Marks-Sheehan, and the global improvement on the CGI.

There were no prospective definitions for either CGI severity or anticipatory anxiety. However, both showed significant improvement in both studies as described earlier.

I'm going to begin by reviewing the data for total panic attacks. Here we used a reasonably stringent criteria of zero panic attacks in the week prior to rating. Let me just review the slide formats we will use. The vertical axis will represent the percent of responders according to the definition used. The horizontal axis will show the week of measurement, week one, week two and week four observed values, and then the week four last observation carried forward, LOCF value. Significant measures are starred at all points, and these are comparisons with placebo.

Measures greater than .05 but less than .1 are noted by daggers, but only at the week four observed or LOCF end point.

Turning now to total panic attacks from Dr. Lee's presentation, you may recall that on a measure of mean change from baseline on panic attacks, the presentation of our data showed no significant change in the flexible dose study. However, in looking at responders in both of our trials, there is a clear effect on panic attacks.

Here is the data from the flex dose study. Let me remind you that our response parameter here was zero panic attacks. We do see good separation for adinazolam both at week four and at the week four LOCF end point.

This slides shows the results from our fixed dose study. Once again, you can see good separation for the 90 milligram dose of adinazolam, beginning at week two through week four and again significant at the week four LOCF end point. So as you have seen in both the flexible and fixed dose studies, when looking at the percent of patients who were panic attack free at week four, there was significant improvement for adinazolam.

Let me turn now to the SCL-90, seen here in yellow. The protocol definition for response was a 50 percent or greater decrease from baseline. This is data again from the flexible dose study. Again, you can see good

separation for adinazolam, both at week four and the week four LOCF end point.

These are the data for the fixed dose study. There is a trend in the expected direction, but no significance for adinazolam at any dose.

Third, let me turn to overall phobia. This is another measure of phobic avoidance and anxiety. In this, we use the definition of a decrease of two or more from baseline to define response. These are the data from the flexible dose study. Again, there is a trend in the expected direction, but no significance.

The data in the fixed dose study on this measure are more robust. For 90 milligrams, you see significance beginning at week two, at week four and at the week four LOCF end point. For 60 milligrams of adinazolam, there is significance throughout, and some early significance for the 30 milligrams here.

I also should note that the titration used in this study was such that all groups were receiving 30 milligrams at week one. So in a sense, these reflect 30 milligram findings.

Now I would like to look at the fourth variable, the CGI global improvement. Here we see the responder definition is one that is consistent with a clinically meaningful response. That is, a rating of either very much

improved or much improved. The CGI can be viewed as an overall measure of improvement that taps efficacy on all variables.

Here we see the data from the flex dose study on the CGI global improvement. There is improvement beginning at week one and maintained at each time point, including the week four LOCF end point.

These are data from the fixed dose study. Once again, we can see significance for the 90 milligram dose beginning at week two, maintained at week four and at the week four LOCF end point. There is an error on this slide. This value is not 50, but should be 60. It is not significant, but I just want to point that out.

DR. FRANK: Is that for both, 60 and placebo?

DR. JONAS: No. I'm sorry, you couldn't possibly know. Just for the 60 milligram, not for placebo.

Now, another important parameter that should be shown is the impact of adinazolam during long term treatment, so I would like to turn briefly to maintenance of efficacy. We obtained long term data for each of the four variables we have just reviewed, where we had prospectively defined what constitutes a response.

Looking at this slide, the vertical axis shows percent responders on each of the primary efficacy measures where we had defined response. The week of measurement is

seen here, and measurements were done at week four, eight, 12, 18 and 26. The number of patients at each time point are seen here. All responders were eligible for inclusion in the extension. This is the extension of the flexible dose study. About two-thirds of the adinazolam subjects and a little less than half of the placebo patients were included in an extension. This slide shows only the data for the adinazolam subjects.

So if you look at these data, the first impression that one has is that there is sustained improvement over time.

DR. FRANK: Were these responders defined according to these response criteria?

DR. JONAS: These were responders defined by the CGI improvement at either week two or week four could qualify for inclusion. So it was a CGI response. It is just the CGI responders, to get a sense of that.

I would like to comment briefly on dose. All the subjects in the flexible dose study --

DR. CASPER: I have a question. Here you say in the flexible dose study, on the CGI improvement you have virtually 95 percent, much improved. If you go back two slides and you look at your CGI improvement, you do not come as high. I think your response rate has --

DR. FRANK: That is because only those who

responded by CGI were included in the ongoing protocol.

DR. JONAS: Right, only responders were included. So this is all the people at the outset of the study.

DR. CASPER: It should have been a hundred percent.

DR. JONAS: It should have been a hundred, or close to. But since it was week two and week four, there would have been some people who didn't.

DR. CHARNEY: Do you know what happened with the dropouts?

DR. JONAS: The next slide. I'll comment briefly on dose and then I will go to that.

I wanted to make one brief point about dose, and that is to recall that you could titrate to 120 milligrams through the flex dose study. The mean dose in the short term portion of the flex dose study was 84. Throughout this extension, the overall mean dose was 86. If you go to the 55 subjects who completed the extension, the mean dose was 82 milligrams.

DR. HAMER: Can I ask a question also? With respect to the flexible dose study, you started them out at 15 milligrams, right?

DR. JONAS: Correct.

DR. HAMER: And then they could every three or four days go up by 15 milligrams?

DR. JONAS: Correct.

DR. HAMER: In terms of the four week acute phase part, that doesn't leave them very much room to be at 120 or anything close to it, right? It takes them most of the study to get there.

DR. JONAS: No. I don't have the figure in front of me but I can give you the distribution of the individuals who were at the 120 by the end of the acute and at the end of the flex.

DR. HAMER: What I mean is, in the acute phase there weren't very many subjects, couldn't have been by definition very many subjects near 120 for very long, because it would have taken them a long time to get there.

DR. JONAS: I think I have week four. I don't have the number with me. I have week eight and week 26, but that is correct. But there was time to get to 120. Can I just get the data, so I'll answer that question?

DR. SCHWARTZ: There were 39 patients who had greater than or equal to 90 milligrams by week four.

DR. HAMER: But it took them most of the four weeks to get there, right? So they weren't at greater than 90 for very long, isn't that right? Or am I misunderstanding it?

DR. JONAS: By day 17, you could have been on 90 milligrams, so from day 17 to day 28 would have been the

opportunity to increase to 120. So depending on how you view 11 days, that would have been the time period that that increase could have occurred, according to the titration schedule.

DR. FYER: Could I ask just one question, clarification about the slide? I'm trying to understand how the different lines fit together. You took everyone who was a responder according to CGI improvement?

DR. JONAS: That is correct.

DR. FYER: Say the line about total panic attacks. Does that mean that 70 percent of the people who responded on improvement had zero panic attacks?

DR. JONAS: At that point, that would be correct.

DR. FYER: So those lines could be interpreted as what the overlap was between the different responder categories.

DR. JONAS: Yes. That is a good point. This is the one that should have been driven to one hundred. These would have been independent, reflective of the patient's state at the time of inclusion into the long term protocol.

This was the disposition of dropouts. The take-home point we think from this is, if one looks at the -- there is no major differential dropout rate between the placebo group and the adinazolam group. That would tend to validate the conclusion of some maintenance of efficacy

throughout the treatment period. These are the dropouts throughout the entire extension, from week four through week 26.

DR. LEBER: Jeff, do you have a slide comparable to the one you showed for the adinazolam patients, for those who improved on placebo? Or were they all converted to adinazolam at the 22 week extension?

DR. JONAS: No, we don't have a slide. We could make a hard copy of one. But the placebo patients were not converted. They were allowed to maintain throughout the extension. But since we did no statistics, we didn't present them in this format.

DR. LEBER: It is a sort of latent comparison hanging there. I just wondered how they did compared to the slide which shows these relatively positive or non-changing results.

DR. JONAS: I think we can make an overhead for the committee, so you can look at that in the question and answer.

Our conclusions then are that these data show that adinazolam SR is effective in the treatment of panic disorder, that efficacy is maintained over six months without dose escalation, and that overall, adinazolam SR is superior in the domains of panic disorder on measures of panic, phobia, anticipatory anxiety and clinical global

improvement.

Now, as part of this presentation, I did want to go into dosing, which is related. I just want to review what we feel the dosing recommendations should be, based on our clinical studies.

First, 30 milligrams is an appropriate starting dose. Considering that in the fixed dose studies, all subjects received 30 milligrams in week one, if you look at the observed values in those studies, you do see improvements on some measures in both the 60 and the 90 milligram arms. The dose range of 60 to 90 milligrams is supported by data from the fixed dose study, where the optimal dose was 90 milligrams, with some efficacy at 60, the flexible dose study where drug was titrated by tolerance and efficacy and where the mean short term dose was 84 and the dose in the extension was 86 milligrams.

Finally, I want to turn now to another way to evaluate dosage, and that is using concentration response data. This slide summarizes data from our concentration response analysis in the fixed dose study, where subjects were sampled at weeks one, two and four. Here, the data are being presented for their LOCF values. We did look at response not only to panic attacks, but also for the CGI and SCL phobia. All showed a concentration response, but I will present now the data for the panic, both for adinazolam and

N-desmethyl adinazolam.

Let me just describe the slide format. First for panic attacks, we looked at zero panic attacks as a response measure. The vertical axis displays the percent of subjects who have a response. The horizontal axis groups patients on the basis of their concentrations of adinazolam. In the next slide they will be grouped on the basis of their concentration of N-desmethyl adinazolam. The number on top of the bars show the Ns in each concentration range, so we're seeing what percent of subjects at a given concentration had a defined response.

As can be seen here, the slide does show a good relationship between the concentration and response as defined as zero panic attacks. Just note that the 50 percent response is roughly equivalent to the 26 to 50 nanogram per milliliter concentration range. I will relate this to dosing in a moment.

On the next slide we see a similar concentration response relationship for N-desmethyl adinazolam. Here, just note that the 50 percent corresponds to the 141 to 210 nanogram per milliliter concentration range. So we need to consider how these concentration levels relate to dosing, and this is seen on the next slide.

Here we see the relationship of plasma concentration of adinazolam and N-desmethyl adinazolam at

week four dose. For adinazolam, if you recall the 50 percent response concentration of 26 to 50 nanograms per ml, that corresponds to a 60 milligram dose at week four. The same is true for N-desmethyl adinazolam, considering the concentration of 141 to 150, which also corresponds to the 60 milligram dose. We see then that these data do support the use of a 60 to 90 milligram dose range in panic disorder.

The dosing data then can be summarized as follows. First, there is a concentration response demonstrated for adinazolam and N-desmethyl adinazolam. Second, I should point out as is clear from the slides that the plasma adinazolam and N-desmethyl adinazolam concentrations are highly correlated. They are fairly well behaved. Third, the concentration response relationships confirm a dose range of 60 to 90 milligrams, and this is similar to the clinical studies which are themselves consistent with the 60 to 90 milligram dose range.

I had a brief comment on safety, but I think maybe I should wait.

DR. CHARNEY: Can I ask you a question about those?

DR. JONAS: Sure.

DR. CHARNEY: Maybe this is going to get discussed in another presentation, but what is the affinity to the

receptor of the N-desmethyl adinazolam and adinazolam in comparison to alprazolam? The question behind the question is, what does 90 milligrams of adinazolam equal -- what is it equal to in relation to alprazolam, which we have a good feel for what doses are required for treatment of panic versus generalized anxiety?

DR. JONAS: Dr. von Voigtlander can answer that question for you.

DR. TAMMINGA: I think your part of the presentation on 7400 and 7450 is finished, so we could address questions to you right now, on your whole presentation.

DR. JONAS: Unless you want the 90, and Dr. Fawcett.

DR. TAMMINGA: I think we need to have an opportunity ask whatever questions on these slides that we want.

DR. VON VOIGTLANDER: Phil von Voigtlander from the Upjohn Company and Discovery Research. The question was raised on the relative affinity of adinazolam and the desmethyl metabolite for benzodiazepine receptors.

This slide shows five subtypes of benzodiazepine receptors and their relative affinities for the 41-123, which is adinazolam and 42-352, which is desmethyl adinazolam. As is rather clear from the slide, the affinity

of the desmethyl metabolite is considerably higher, being on the order of, depending upon the receptor you're looking at, up to 70 times the affinity. So at equal concentrations, one would expect most of the GABA related pharmacology to arise from interactions of the desmethyl metabolite.

This speaks to affinity, and I think your question really refers probably to efficacy as well. The next slide will show you that both compounds are full agonists, this receptor. These are three subtypes of benzodiazepine receptors, and we are looking at the intrinsic activity of adinazolam versus desmethyl adinazolam. These are at saturating concentrations in the case of both compounds, and you can see that both compounds, by the definition of the efficacy ratio here, which is a comparison to diazepam, are full agonists.

DR. CHARNEY: How does this compare to alprazolam?

DR. VON VOIGTLANDER: Alprazolam is also a full agonist at these receptors. The affinity for the desmethyl compound approaches that of alprazolam, but doesn't quite get to it. It is more in the range of diazepam.

DR. CHARNEY: So you are saying that the affinity of alprazolam and the metabolite are about the same, correct?

DR. VON VOIGTLANDER: No, the metabolite has a somewhat lower affinity than alprazolam.

DR. CHARNEY: How much lower? An order of magnitude?

DR. VON VOIGTLANDER: Less than an order of magnitude.

DR. CHARNEY: What I'm getting at is -- and this will relate to safety and withdrawal issues, but is 90 milligrams of adinazolam, in terms of what you would predict from your preclinical work, -- would be equal to how much alprazolam in terms of efficacy at the benzodiazepine receptor subtypes? This has been helpful to us in understanding relative doses of other benzodiazepines to a standard.

DR. VON VOIGTLANDER: I think Dr. Fleishaker has some data that are relevant at this point.

DR. FLEISHAKER: Dr. Fleishaker from Clinical Pharmacokinetics. This is a summary slide on pharmacodynamic properties of the N-demethyl metabolite in man. We have done a fair amount of studies looking at things like psychomotor performance decrements and whether they are due to the parent compound or the metabolite. We found that most of those types of effects are due to the metabolite.

The one thing I would point to on this slide is the third bullet down, comparison of EC 50 values for decrements in DSST versus alprazolam and triazolam. In a

couple of studies, we found EC 50 values of 325 nanograms per ml for N-demethyladinazolam, versus 25.6 nanograms per ml for alprazolam and 4.6 nanograms per ml for triazolam. So this should give you some feel for the in vivo potencies of these benzodiazepine agonists in man.

DR. ESCOBAR: If I understood correctly, it is the same as diazepam? So 90 milligrams of adinazolam is about the same as 90 milligrams of diazepam, according to your side there?

DR. FLEISHAKER: I probably wouldn't --

DR. ESCOBAR: The other one, the one they showed before.

DR. VON VOIGTLANDER: We weren't making direct comparisons of the affinity to diazepam. We were showing that the intrinsic activity is similar.

DR. TAMMINGA: Could you try to make an estimate according to your best opinion from your animal studies?

DR. VON VOIGTLANDER: On which question?

DR. TAMMINGA: On Dr. Charney's question, what would be the relative -- how you might make an approximation at the dose of your current drug compared to alprazolam.

DR. VON VOIGTLANDER: Again, it would be less potent than alprazolam. Just based on affinity, which bypasses a lot of other things, I would guess it would be less than an order of magnitude, but significantly less potent.

DR. CHARNEY: The reason we are trying to pin you down, this is helpful for two reasons. One is, we don't know what the most effective dose is. At 90 you're better than 60, but we don't know about 120. So it is conceivable that you may be at too low a dose, but on the other hand, we need to evaluate that issue from the point of view of safety and dependence and withdrawal. That is why we're trying to get you to give us a ratio that is very useful in comparison to other diazepines.

DR. JONAS: You want a number?

DR. CHARNEY: Right.

DR. JONAS: We'll give you a number. We were interested in doing some comparison studies between adinazolam SR and alprazolam. One of the problems that you have is picking relevant doses to make a comparison. The way that we chose the doses here was to look at relative response rates for panic attacks in the 90 trial versus response rates in a fixed dose trial with alprazolam, where it appeared that the response rates for six milligrams of alprazolam were close to those that we saw with 90 milligrams of adinazolam.

So for this single dose trial, what we did was look at placebo, .5 milligrams of alprazolam and 1.5 milligrams of alprazolam, versus zero, 15 and 45 milligrams of adinazolam SR. If you look at percent change in DSST

scores for these two particular treatments, the orange bars being the high dose treatments, on the left, alprazolam and on the right, adinazolam, you can see that pretty much we have achieved similar decrements in psychomotor performance with these two treatments, suggesting that that dose selection wasn't all that bad. So the one to 15 ratio of alprazolam to adinazolam SR is about what you would --

DR. CHARNEY: It was 30.

DR. JONAS: Excuse me, 30.

DR. CHARNEY: Then that would suggest that your 90 milligrams is equal to three milligrams of alprazolam, right?

DR. JONAS: No, no, no. Sorry, let me take into account dosing differences. You are administering alprazolam one and a half milligrams in a six milligram per day trial, four times a day. So if you extrapolated that multiple dosing, what we were trying to do was choose single doses that represented what we would give on multiple dosing. So the alprazolam dose there is a single dose out of a multiple dose regimen, six milligrams per day; adinazolam you only get twice daily, so that is a single dose out of a 90 milligram per day regimen.

DR. CASPER: Maybe there is a danger in insisting too much, but it is conceivable that you could have looked a the alprazolam data in comparison to your own data, namely,

the clinical data. For instance, taking the cart before the horse, have you looked at efficacy data in relation to dosing of alprazolam, and looked how they compared to your 90 milligram dose? If you look at clinical studies of alprazolam, have you compared them to the relative efficacy which you achieve with your drug? Do you have any data on this?

I have more questions. Would you like my next question?

DR. JONAS: Please. I'll write them.

DR. CASPER: My next question relates to your presentation of the data, and you're not mentioning either the duration of illness nor the severity. From your data, one cannot figure out which range of panic attacks patients had before they received drugs. So we don't know whether you are treating a mildly disturbed or mildly ill population, or whether you are treating the full range of the population, because a mildly ill population responds much faster, generally, to any drug and placebo, as we know.

I had one more question. Could you lead us in the flexible dose study through your sample numbers? Give us an idea of how many you started, how many dropped out when. When you say about 28 percent dropped out due to adverse effects, is this the total? How many dropped out throughout the study and how many arrived at week four or six,

whichever you take as your starting point for the long term study? How many do we have left there as responders from the original data? Whom are we seeing in the long term study who are basically maintaining the gains they have made with continued dosing?

Thank you.

DR. JONAS: In your first question, you are interested in clinical efficacy in comparison of adinazolam to alprazolam. We have data that are not from head to head trials, but which give you a sense of that, and we can present that. We'll put that together now for you as an overhead.

The second question, in terms of severity and duration, we can also present some data relative to baseline differences, characteristics at baseline. There are a number of ways to look at that, and we will also put that together now.

In terms of the flex dose study, those numbers I have on hand. I can tell you verbally, if this is helpful to you. In the flex dose study overall, in the acute phase, there is a dropout of 13.2 percent versus 8.3 percent for adinazolam, overall dropout.

DR. CASPER: Can you just give the numbers?

DR. JONAS: At baseline, they were 114 for placebo, 108 for adinazolam, for a total of 222. At week

four, there were 99 for placebo, 99 for adinazolam. At the extension, there were 52 entering for placebo, versus 76 for adinazolam. Completing the extension, there were 34 for placebo and 55 for adinazolam. That was at week 26.

DR. CASPER: Let me ask you one more question in relation to the comment you made about presenting the data on your 90 study. You said they were not of a high priority. I would like to disagree with you. I think they are.

DR. TAMMINGA: We're going to hold the questions for the 90 study until we hear it presented.

DR. CASPER: No, this is more in a way a political question. Why would you say they are not of a high priority?

DR. JONAS: In the work flow of Upjohn at the time, it wasn't an NDA submission study; it was a phase three and a half product support study. So in the preparation for the meeting, that was not an essential priority. We were preparing for this. But there was work continuing on it, so I was left with that decision of what to do, and I just sent it as soon as I had it.

DR. TAMMINGA: Any more questions for Dr. Jonas?

DR. FYER: This is just a clarification of some of the results from one of the 700 studies.

I think in the slide that you showed, there were

about 60 percent of patients who at week four were panic free. Yet I think it is on page 24 in your booklet -- this is in 7400, it seemed to me that these patients start out with a little more than four panic attacks a week, and they went down to two or three panic attacks a week. Since 60 percent of the patients were well, had zero panic attacks, I was interested in the distribution at the end. I wondered if you had data about that.

DR. JONAS: We have distribution data at baseline. I'm not sure if we have it at the end. We can generate it for you. But we can show you the baseline. I don't have that at the end, but we will generate that.

DR. FYER: It was hard for me to understand how that came about. Also, if a considerable number of patients are -- two or three panic attacks a week is a fair amount of morbidity, given epidemiologic data about panic attack associated morbidity in the population. I was wondering if maybe you were identifying a subgroup of non-adinazolam response patients, or there was some --

DR. TAMMINGA: Are you going to present data in response to that?

DR. JONAS: We will try to generate data now for the distribution, to answer your question. We do have the distribution at baseline, which shows the skew, and there is a leftward skew, from zero to 21.

DR. FYER: Do you have additional data for the previous question?

DR. CORRIGAN: Hi. I'm Mark Corrigan from psychopharmacology, the Upjohn Company. As Dr. Jonas mentioned, we do not have any head to head data on panic disorder between adinazolam and alprazolam. However, we did make an effort to compare both the flexible dose and fixed dose trials of the two compounds retrospectively.

There are some important differences between the trials. For alprazolam, the 4412 short term treatment was a flexible dose trial, and we compared two flexible dose studies here, that with the controlled adinazolam 7400 trial. The alprazolam trial was one to ten milligrams a day QID dosing; the adinazolam was 15 to 120 BID. The alprazolam short term treatment was eight weeks and the adinazolam was four weeks with a 22 week extension. There were 526 intent to treat patients in the alprazolam and 222 in the adinazolam arm.

I'm not going to present some of the differences in efficacy measures that represent the evolution of thinking about panic disorder. However, on this next very busy slide, what is depicted is the end point week in the left column, alprazolam in the first column and adinazolam in the second. The significance of the yellow highlighting is that these are the efficacy variables that may be

comparable. For the purposes of inclusion, all efficacy variables for both studies are included in the leftward column, but I think we should focus our attention on those that we can compare between the two trials. They are for mean number of total panic attacks, both compounds showed significance. The mean dose at that time for alprazolam was 4.9 milligrams per day and for adinazolam was 84 milligrams.

On mean change from baseline, as Dr. Lee has presented, it is not significant for adinazolam, was significant for alprazolam. For the overall phobia score, mean change significant for alprazolam, not significant for adinazolam. For CGI, mean score improvement at the .05 level for both compounds.

DR. HAMER: These P values are comparisons for -- these are two different studies, so the P values are comparisons each within their own study?

DR. CORRIGAN: Yes.

DR. HAMER: Of gain score versus placebo?

DR. CORRIGAN: Yes, exactly.

DR. HAMER: With center in the analysis?

DR. CORRIGAN: We'll have to check that. I'm not sure.

DR. HAMER: Thanks.

DR. CHARNEY: You have percent zero panic attacks

under the adinazolam 7400 study as non-applicable?

DR. CORRIGAN: Non-applicable, yes. The N/A refers that that was not a prospectively defined efficacy variable. In the adinazolam trial, we used percentage responders in which we included percentage zero panic attacks as a primary efficacy variable, as part of the definition of the responder. But it was not in itself a primary efficacy measure.

DR. FRANK: Before we look at any more of these data, could you say something about the inclusion and exclusion criteria for these two trials? Are we looking at comparable patient populations?

DR. CORRIGAN: This depicts the comparisons of subjects' entry criteria between Deracyn and Xanex pivotal studies. They had the same exclusion of all axis one disorders, concomitant comorbid disorders.

Some of the differences there are somewhat more stringent exclusion disorders for the Deracyn protocol. However, they were both conducted in adults. I think they are roughly comparable.

DR. FRANK: Can you say anything about baseline severity and duration of illness in these two protocols? Actual observed baseline severity and duration?

DR. CORRIGAN: I'm not sure I have those data immediately available, I can check. I'll have to check.

DR. FRANK: Do you have an impression as to whether these patient populations were comparable or not?

DR. CORRIGAN: My belief is that they would be, but that clearly at the time of -- but I would need to check to be sure about that.

DR. FYER: I guess it must be correct that the Xanex people were DSM-III, so they had to have the panic disorder criteria, while the Deracyn people could include some less frequently panicking people because of the DSM-III-R. It would seem to me that is an analysis you probably could do. You could find out how many of your Deracyn people met the DSM-III.

DR. CORRIGAN: As I mentioned, there are a number of difficulties between comparing two different studies not head to head. Clearly that is one of them. At the time the panic attack scale used for alprazolam had three or more symptoms for an attack, and adinazolam had four more symptoms. There were some differences even in the CGI scales used and the method of obtaining that data.

DR. CHARNEY: This is relevant to the questions that Dr. Laughren mentioned earlier. In your analysis, did you see any relationship between a response on the panic attack symptoms, the phobias and the CGI? Were there correlated?

DR. JONAS: We did not do that analysis. We

treated each one independently. We tended to view the CGI as the integrating function in looking at overall patient response.

DR. LEBER: I just want to remind you that we had asked the question about the extension of 22 weeks in 7400 regarding the placebo group, because you are leaving the impression that you have sustained effectiveness.

DR. JONAS: I have a list of things that we will be producing while Dr. Fawcett is done. Also, you had a question about baseline.

DR. CASPER: This is the same question asking about the patient population. Who are you treating and for whom are you trying to show effectiveness, for what kind of clinical population?

DR. FRANK: This one last issue that comes back to the question of change from baseline on number of panic attacks and the disparity that Dr. Fyer pointed out, I think there are a couple of possibilities. One is that there is a subset of patients who have a very severe disorder who don't improve at all. The other possibility is that there is a group that gets worse. I think it would be very important to see the distributions.

DR. TAMMINGA: Perhaps we ought to go on with your presentation, and then you will be able to prepare these things for us.

DR. JONAS: Very good. Let me turn this over now to Dr. Fawcett.

DR. FAWCETT: Good morning. I was asked as a consultant to Upjohn to look at the 90 study and to critique it. If we could have the first slide, which will show you the design of the study?

This is the basic design of the study. You will notice that one of the criteria for entry was a HAM-D retardation cluster of six or more for the entry criteria. There was no other depression criteria, although the SKID was done on all these patients. And 25 percent of these patients in the adinazolam group met major depression on the SKID, but that was not the entry criteria. The entry criteria was this retardation cluster.

If you look at the next slide, which reminds you, as I needed reminding, what the retardation cluster was, when I saw this, my first question was, why did they do this study. This to me looked like an endogenous severity rating rather than a retardation rating. You see the impairment item, then there is an increased libido item on here, so you're looking at a very endogenous item. I wondered why you would want to use a benzodiazepine in a sample of patients that were high in these items. It seemed to me a masochistic study to do in the first place.

The answer I got to the question was that they

wanted to assure that the patients -- by the way, these would not be alprazolam or adinazolam driven symptoms ordinarily in treatment, we all know that. Ordinarily we would expect them not to be driven by that treatment. So the answer that I got was that they wanted to be sure they had some patients with comorbid depression, because everybody knows that around 60 percent of panic patients have either past or current major depression. From my review of the literature, it looks like about 20 to 30 percent have concurrent depression, immediate depression, not including past or lifetime.

So that was the reason. They wanted to look for clinical efficacy comparing to imipramine. So it looked to me like a tough study for them to do in the first place.

Then we looked at the slide which you have already seen in terms of the outcome. I am only showing you total panic attacks here as an outcome. We can just see that the results shown one of the treatments better than placebo at the end, whether you look at an end point or the last end point carried forward. So you have a fairly uninteresting outcome in the study. The question is, what kind of a study was this.

My next question was, what about the randomization in this study and the severity of various aspects of both panic and depression. First I will show you the outcomes.

Here is a graph that caused the discrepancy. I've been told that this was an error, that this is not significant on this slide. There was no significant difference, and that accounts for the discrepancy between what you see on the graph and what you see on the chart here, in terms of panic attacks.

DR. TAMMINGA: Could you be clear about what is the discrepancy?

DR. FAWCETT: This says significant difference in terms of panic attacks at weeks four, six and eight for mean change, whereas this doesn't show -- looking at this you wouldn't expect a significant difference.

DR. CHARNEY: When does that reflect that the minus three point something at week eight is a significant change from baseline within that group? Do you understand what I mean?

DR. FAWCETT: From baseline?

DR. CHARNEY: Yes. It looks like you're going down three panic attacks from baseline within the imipramine group, but you're only going down -- so that shows you're getting a response of two plus panic attacks within one week, a huge placebo response.

DR. FAWCETT: Right, very high placebo response.

DR. FRANK: I am still confused about what the reality is. You're telling us that this is an incorrect

slide?

DR. FAWCETT: Yes. I'm showing it to you because it raised the discrepancy between the two.

DR. FRANK: Are the other values still significant? That is, percent responder is significant?

DR. FAWCETT: My understanding is that these are all as shown.

DR. FRANK: I'm up in the panic attacks.

DR. FAWCETT: Are none of those values correct?

DR. JONAS: Those are correct. The only error was mean change.

DR. FAWCETT: The mean change is the only error.

DR. FRANK: So for percent responder and for absolute mean number of panic attacks, imipramine was different from placebo.

DR. FAWCETT: Yes.

DR. HAMER: Can I make a remark about the previous slide? You said that at week eight, the three lines looked relatively close together. You wouldn't expect to find significant differences without error bars or something like that. I can't look at that graph. I have no idea whether or not the differences would be significant.

DR. FAWCETT: That is accepted.

DR. TAMMINGA: If you look at this slide in comparison with your previous significance graph, it looks

like placebo is better than imipramine. Is that correct? You have demonstrated here that placebo is a better drug than imipramine? That is the direction we're talking about of the significant change, right?

DR. CHARNEY: Is that true? The percent responders was more in placebo? In the other slide, you were saying it was still correct that placebo versus imipramine --

DR. FAWCETT: Placebo is lower at the last end point carried forward.

DR. CASPER: Could you tell us again what we are looking at? We are looking at the number of total panic attacks per week, correct?

DR. FAWCETT: Number of panic attacks per week.

DR. CASPER: And mean change --

DR. FAWCETT: Mean change in total panic attacks, right.

DR. CASPER: Right. But what does the mean change mean? Number of panic attacks per week?

DR. FAWCETT: Decreased.

DR. CASPER: So where are we coming from and where is the standard deviation, if we're talking about mean panic attacks?

DR. FAWCETT: These don't have the standard deviation on them.

DR. HAMER: The distribution of those things are going to be non-normal enough so that the error bars wouldn't necessary have the same meaning, anyway.

DR. LEBER: Do you have a table that displays for each of these three treatments by week the count of panic attacks at baseline in each successive week, just the numbers with perhaps some measure of the range or dispersion, so we can look at the numbers rather than these derived figures?

DR. SCHOOLER: Again, trying to read this slide, the most differences that you see between the treatments are at baseline.

DR. FAWCETT: That is week one.

DR. SCHOOLER: I'm sorry. So that means that we don't know what the baseline is. These are changes, and the changes get smaller and smaller. One of my questions would be, is baseline covaried in these analyses? Was that controlled? So this is the residual change, or are these raw change?

DR. TAMMINGA: One question at a time. There is a question on the floor to the company. Can you answer it now, or can you find these data? You can find these data. Next question, Dr. Frank.

DR. FRANK: This was a question to Dr. Schooler. I know how you covaried for an absolute score with the

baseline value, but you can't covary for a changed score, is that right, Dr. Hamer?

DR. HAMER: Actually, you can. It is an analysis that is done frequently. I have philosophical questions about the meaning of an analysis, but it is not uncommon for the dependent variable to be the difference between baseline and whatever gained score we're talking about, and also to include baseline in the analysis as a covariate. If you do that, that will not change the P value for the difference between the groups. It turns out that in that analysis, the P value for the group differences is invariant to whether or not you have subtracted off baseline in the dependent variable. What it will do is decrease the model sum of the squares or total sum of the squares or something like that, I don't remember, by the same amount. What it will do is, it will change the value of the coefficient on the covariate and usually make the covariate non-significant.

DR. TAMMINGA: Let's see what the company present us, and then we can comment on what we think of their analysis.

DR. ESCOBAR: A technical question. I am wondering, does the agency accept imipramine as the standard for panic? If not, maybe the debate is not going to be taking us anywhere. It is clear that if the sample is a depressed sample, that the results are in the expected

direction. But here we are talking about panic symptoms an the treatment of panic. Even though the clinical lore seems to suggest that imipramine is effective, do we accept it as the standard?

DR. TAMMINGA: I think that is a point for discussion, and I would suggest that we get all of the data presented to us first, and then take up that point in the discussion.

DR. CASPER: I have one more question to you, Dr. Fawcett, namely about this HAM depression or retardation score. Can you flip back to the slide? The score was over six, correct?

DR. FAWCETT: Right. It had to be six or more.

DR. CASPER: Which means, if you really look at this, this does not mean much of a depression, as far as I am concerned. You have four items, and you can easily reach a score of six without having much of a depression.

DR. FAWCETT: The average Hamilton in the study was around 16 in these patients.

DR. CASPER: Right, but you implied initially that this was a depression study, but I don't think this would indicate that someone needs to be depressed. This is a mild depression.

DR. FAWCETT: It is a secondary depression.

DR. TAMMINGA: Perhaps the company has some of the

-- you may want to go ahead.

DR. FAWCETT: I just want to show you one other question I had of the data, and that was the randomization, was the randomization good in terms of prior severity of the illness, since there is a lot of evidence that severity of panic disorder and severity of depression do affect the outcome of treatment. That has been shown by a number of authors. So I asked that they look to see if the groups at baseline were the same in terms of severity.

What came out of that analysis was a difference -- and I think this was a significant difference, in terms of there being more total months of panic disorder in the last five years in Deracyn versus imipramine. This is the number of previous episodes of panic disorder. This is Deracyn versus imipramine. You have some evidence of more severe panic disorder in your Deracyn group versus imipramine, not placebo. Then you have a difference which I also believe was significant of the duration of -- current episode of depression was longer in the Deracyn assignees, as was the total months of major depression in the last five years.

So it looks to me like the randomization failed in this study to provide a group of equal severity in both the panic and the depression, with more severity in the adinazolam group versus imipramine

DR. LANG: I just want to make sure that you're

keeping this in perspective. If you compare patients at baseline across the three groups with regard to number of panic attacks and severity of depression, my understanding was that there were no differences between treatment groups at baseline. Here you're talking about historical data, but in terms of baseline measures, they were roughly equal.

DR. LEBER: There is another question that I have. You have found four items in which you have done a contrast between these groups, two of the three groups, in which you have found something that is of interest to the case you want to make. How many total contrasts were actually examined? I don't know how many attributes these patients were examined on. It may be that some are actually in a different direction.

The second question I have is, what does it mean to say randomization failed? Randomization minimizes differences, it doesn't guarantee to erase them all, and it only minimizes them in the expected sense. In any particular trial, the randomization could wind up producing groups that might be different.

DR. FAWCETT: These items were all SKID items, of course; that is where the data came from. I eyeballed the differences, and asked that those be run. We didn't run eery comparison.

DR. FRANK: This is just a clarification of what

Dr. Fawcett just said. Are you saying that you did a scan of the SKID items you saw that looked like they might be different, and these were the four? One was actually significant and one was at a trend level?

DR. FAWCETT: I thought these were all significant. These are all significant items. They are not all starred on this slide.

DR. FRANK: What is the meaning of the asterisk and the cross then?

DR. FAWCETT: The asterisk is supposed to be a .05 level of significance. My understanding was that this was also significant.

DR. PEACE: That is correct. Those figures are 38 months for imipramine and 46 months for Deracyn, and there should have been an asterisk on that slide. The question about the difference between the asterisk and -- if you could go back to the previous slide -- for the third bullet point, the plus, that means that the P value was less than .10. There should be an asterisk on the fourth bullet point as well.

DR. CHARNEY: What about the placebo group?

DR. PEACE: They were relatively the same. There were no statistical differences between the placebo group and the Deracyn group, in terms of these measures.

DR. HAMER: Consider previous episodes of panic

disorder. Forgetting all the difficulty of how many items are there on the scale and picking out these four and so on, that says that the adinazolam group had a lot more previous episodes of panic disorder than did the imipramine group, right?

DR. FAWCETT: Yes.

DR. HAMER: If adinazolam is a drug that addresses panic disorder, then one would expect, if there is a group of subjects that have a lot more panic disorder, it would help them get well. In that case, the group that previously had a lot more episodes of panic disorder should improve more than the group that didn't have a lot more episodes of panic disorder. But isn't that the opposite of what you found? If there were a regression towards the mean phenomenon, something like that, then it would be consistent with this, and this is just an example. It would be that the adinazolam group should have improved more than the imipramine, and isn't that the opposite of what happened?

DR. CHARNEY: First, it is not correct to speak of episodes of panic disorder. It is generally a chronic condition. What that data really reflects is probably age of onset of the illness. If it is only a difference of eight months, it is a trivial item. It has no meaning, in terms of the clinical characteristics of the disorder or as a predictor one way or the other to treatment response.

DR. FRANK: I'm not sure what an episode of panic disorder means, because I don't think that is a clinically relevant concept. But assuming that somehow the SKID extracts that information, what this could actually mean is that one group had a more episodic form of the disorder and the other form had a very chronic form of the disorder, which might have been going on for years and years and years.

DR. FAWCETT: You have more total months of panic disorder in the past five years also as a measure here, though.

DR. LAUGHREN: I want to follow up on Dr. Charney's comment. I think you have to look at the numbers here. For total months of panic disorder in the past five years, for imipramine it is 38 months, for Deracyn it is 46 months. It is true that is a statistically significant difference, but I think you have to ask whether or not that difference is of any clinical importance. In the context of at baseline, these groups are equal with regard to the number of panic attacks and level of depression.

DR. TAMMINGA: We haven't seen those data yet, have we?

DR. LAUGHREN: We have in passing. We have seen a lot of data. Hopefully we can see them again.

DR. CORRIGAN: We didn't exactly scan a whole list

of SKID variables and choose those which were significant. From the literature, a number of studies have shown -- for instance, Keller et al. have shown that in a group of patients who have concurrent major depression, he found no treatment improvement for either adinazolam or imipramine.

The other point is, I think the concept that a sicker group of folks may show better improvement is not borne out by previous studies. In fact, these patients are often treatment resistant to a number of medications.

Secondly, there are a number of studies that have looked at previous episodes of panic. That is a separate discussion, about whether this is episodic, but that as an identified variable is having an impact on treatment outcome. Typically, patients who have more previous episodes of panic disorder, whatever that is, have less good outcomes in response to treatment.

Secondly, the bottom two points only refer to the subset of 25 percent of patients who presented with current major depression. I think it is important to bear that in mind, that this isn't the entire sample. The reason that Dr. Fawcett stressed the first point is, that applies to all the patients that are coming into the trial, and perhaps the panic variable is the more important one to look at.

DR. TAMMINGA: Do we have data to look at that would show us the numbers of the three different groups at

baseline and over time? Perhaps we could take a look at those data right now.

DR. FAWCETT: I think this goes along with Noyes' review of the literature pretty much in terms of severity variables, in terms of severity of both depression and panic predicting poor outcomes in these samples.

DR. CORRIGAN: There are a number of slides that look at these variables. This one tries to compare it across the various protocols here. There are some interesting findings. The column headings on the left, the variable and the statistic, then the 90 trial in comparison with the flexible dose study and the fixed dose study.

The first row is one thing that we looked at which was previously treated with other psychiatric drugs, and then the prior episodes of panic. There are similar slides that look at past panic, current major depression and past episodes of major depression, which is what we identified as potentially affecting the outcome and randomization that might be maldistributed in this study.

The percentage of patients is roughly similarly distributed in the flexible dose and fixed dose studies for the variable previously treated with other psychiatric drugs. Interestingly, the adinazolam group had received less treatment than the other two arms.

In terms of prior episodes of panic, once again

focusing on the flexible dose and fixed dose distribution of patients, there was equal distribution in terms of the previous episodes of panic across all arms of the study. If you focus however on 90, there is clearly a significant difference in terms of prior episodes of panic. Once again, I think the clinical relevance of that is subject to discussion.

DR. CHARNEY: Could it be that if the patient received less treatment, less exposure to psychiatric drugs, that is why you had more episodes of panic, because they were untreated?

DR. CORRIGAN: I clearly think that could be a conclusion one could draw from this data.

DR. FYER: How did you define episodes of panic? What was the definition between somebody having chronic panic disorder versus, this is one episode, that is the next?

DR. FAWCETT: This is an item from the SKID.

DR. LEBER: This is just a procedural point, but I find it odd that we're discussing the covariates and explanatory variables before we have gotten a definitive presentation of the evidence of this study by week, from baseline forward, of the evidence that is relevant.

I understand and take your point. This trial, if it shows an effect for imipramine and not for adinazolam, is

in fact a negative study and speaks against the effectiveness of your product. It is understandable that Upjohn Company would want to therefore undermine that conclusion. But why don't we get the evidence first? I'm not taking exception to your attempts, but why don't you deal with the evidence first?

DR. FAWCETT: What further evidence do you want? We've gone through the outcome variables.

DR. TAMMINGA: We haven't ever seen the numbers.

DR. FAWCETT: You want the numbers. Mark, can you put those numbers up?

DR. CASPER: We have never seen the age range, the severity range. We have never seen the baseline sample data.

DR. TAMMINGA: I think you're seeing reflected that the committee is used to reading over all of these characteristics of the study before we come and see the data presented. We're seeing the justification of the outcome without having seen the actual data, and it leaves everybody in a bit of confusion.

DR. CORRIGAN: I understand and appreciate the committee's concern over that. What we have in the slide presentation and what we're preparing is -- we have mean change from baseline data.

DR. TAMMINGA: We want to see baseline data, too.

We want to see the raw numbers over time in addition to the change from baseline. We want to see both of them.

DR. ESCOBAR: Is the company viewing this as a negative study? Are you viewing it as a positive study? Given the caveats that the global scale -- that was the only one that seemed to be of benefit here, was used the usual way? Are we looking at this from your perspective as a positive study?

DR. FAWCETT: I would feel that the study is not an adequate study for a number of reasons, which I have tried to illustrate. I think the study is just not a useful study to use as a comparison, especially since the imipramine also did not show much effect against placebo. Some, but not much.

DR. TAMMINGA: I would like to know if the company needs some extra time to get things prepared in response to the questions that the committee is asking. I don't want us to sit here and dredge up questions that get more and more off the point.

DR. JONAS: It sounds like you would like a full presentation of all the numbers, so we are preparing that now with as many numbers as we can put together for that.

DR. TAMMINGA: Are we talking five minutes or are we talking 15 or 20 minutes? I would suggest that we finish up with the current presentation now. Then we'll take a

lunch break and hear a full presentation of the data of 0090 after lunch.

DR. FAWCETT: I didn't show the efficacy outcomes, but that was all. Those are all the slides I brought up here to show. I knew you might want basic data slides, so we will have to prepare those for you.

DR. TAMMINGA: We can take any questions for Dr. Fawcett now that don't have to do with what does the data look like, anyway. We'll hear those after lunch.

Why don't we just take a summary of what we have already heard, and what we expect to hear after lunch? We have already heard the efficacy data presented by the FDA for 7400 and for 7450, and the FDA's read of the 0090 study. We have heard the company's presentation of 7400 and 7450, and we expect to get after lunch a presentation of the data, including the actual scores and the change from baseline. Now would be the time to raise additional things. And, of course, we have safety to cover after lunch.

Since there is no additional comments, I would suggest that we break for lunch now and be back at quarter to one sharp.

(The meeting adjourned for lunch at 11:45 a.m., to reconvene at 12:45 p.m.)

A F T E R N O O N S E S S I O N (12:43 p.m.)

DR. TAMMINGA: We're going to begin talking again about the drug under discussion today. We're going to continue with the company's presentation. The first thing in their presentation will be the placebo responder 26-week data. They are in the process now of copying for us what they have available for study 90, and as soon as that is finished, we will go on to take a look at that.

DR. JONAS: Thank you. Let me just comment briefly, we are in the process of making copies of all of the appendices from the technical report that address the raw data, so as soon as the copier becomes available, we will circulate that about to you for your examination.

Relative to 90, I just want to make two points. We acknowledge that there are two alternative explanations. The company feels that the differences in baseline can account for differential findings between the two, but we acknowledge that that may not be accepted by the committee, in which case, one issue that we agree will have to be addressed is whether the definition of the population in that study as it was defined leads Deracyn to have less efficacy than it does in the pivotal trials.

So with that brief introduction, I wanted to show you the numbers that you asked for relative to the extension phase. These are the responders from 7400, the percent

responders. These are the observed values with the LOCF value at week 26. This is for the total number of panic attacks. For placebo, we see at adjusted week four -- the N on top is the number of patients. Then you have the number of responders at that week, remembering that you are selecting for the CGI, which was the other comment that Dr. Fyer had made. Then we're going to week eight for placebo. The N is 52 at adjusted week four. At week eight of the placebo, you have an N of 44, 35, 35 and then down to 32, which is what I had mentioned earlier. Then what you see here are the percent responders in parentheses with the N of responders. This is for total panic attacks. I have one of these for each of the variables.

DR. SCHOOLER: But the Ns will of course remain constant.

DR. JONAS: No, the Ns diminish as people drop --

DR. SCHOOLER: I'm saying the N in each of the tables will be the same.

DR. JONAS: Yes.

DR. LEBER: A couple of clarifying questions, if I may. Adjusted week four means what? Presumably, a responder entering is a hundred percent. What have you done with that? Adjusted for what?

DR. JONAS: These are for the people who were entered into the extension.

DR. FRANK: With the responder being defined on the basis of CGI.

DR. JONAS: Right.

DR. FRANK: And we are now defining -- of those who were defined as responders on the basis of the CGI, the proportion of those patients who would be called a responder using the definition of zero panic attacks, is that right?

DR. JONAS: Yes. That is the format of each of these, which is that each of them will be the percent responder using the responder criteria.

DR. HAMER: So the fact that that says total number of panic attacks on the top really does not indicate what is in the slide?

DR. JONAS: That is the variable, and the responder is the analysis on the variable. So the variable is the total number of panic attacks, and this slide looks at percent responders. We took this from the table, in answer to the question.

DR. CASPER: Do you consider the differences between the placebo responders and the adinazolam responders, the slow release capsules, to be significant in any way?

DR. SCHWARTZ: We decided not to do statistical testing on such a small subgroup of patients. The idea here is that you've got patients who were selected for being

responders, so they are not randomized. Also, there is such a few number of patients in the placebo group, it didn't seem like it would be appropriate to do anything more than just descriptively present the data.

DR. LEBER: I'm still confused. I thought earlier today you were talking about responder analyses giving you some sense of how well the drug worked during the 22 weeks of the extension phase. Does that apply equally to adinazolam and placebo, or differentially apply?

DR. JONAS: Again, I think the real question comes down to, what is a placebo responder and what does it mean to be a spontaneous remitter. So I don't know that I would compare the two qualitatively. Our point was simply that if someone remains blinded on adinazolam through the extension, if you look at the observed values for percent response, those are maintained.

DR. LEBER: I realize the inference is cloudy here, but it dawns on me that you wouldn't have presented this unless you had a message. The message appears to be that one could assume that patients continued on adinazolam SR were in fact enjoying sustained effectiveness. However, you have the placebo group, albeit smaller, that appears to have the same percentage of dropouts over the course of the remaining weeks, and to show you how variable it is, the percent of those obtaining freedom from panic attacks could

even be higher as you select out the responders. So what are we to do with this mess? What would be your take-home point?

DR. JONAS: The numbers are the numbers here. I think the only take-home point is that, since we have not tested this statistically, and there is a smaller number of placebo responders entered, that those who go through the extension do have maintenance of efficacy.

DR. CHARNEY: Would it be fair to say then that no matter -- a responder tends to remain a responder, but that is whether or not they respond to placebo or adinazolam.

DR. JONAS: That is what these data would seem to show.

DR. LAUGHREN: Another take-home point might be that this is not the correct design to look at the question of long term efficacy. I would hope that that would be one of the things that the committee could talk to us later about, appropriate designs for looking at long term efficacy, relapse, prevention and so forth.

DR. FRANK: In fact, the first point that your colleague made is the relevant one. It is not appropriate to do statistical comparisons between these two groups because they don't represent randomly drawn subsets of a single population. They represent patients who got to, quote, response by different routes.

DR. JONAS: Right.

DR. TAMMINGA: I think we have additional study 90 data, is that right?

DR. JONAS: Yes. Do you want to see the other parameters for this? I'm not sure it will add more. At this point then, I would like to turn it over to Dr. Mark Corrigan, who will comment further on 90.

DR. CORRIGAN: While you are receiving the handouts, the handouts are directly drawn from the technical report. It is all of the raw data that we have at this point. I will be presenting the raw data here. As I discuss it, we do have calculations based on mean value, because that was the format requested by the FDA, which we could look at in graphic form, if so desired.

DR. JONAS: Mean change.

DR. CORRIGAN: I'm sorry, mean change, thank you. To start with depressive symptoms, it was a fixed dose randomized double-blind parallel active comparator study. Dr. Fawcett has gone over the entry criteria, which included the score in HAM-D, retardation cluster. The treatment regimen included a maximum of adinazolam of 90 milligrams a day and imipramine, 150 milligrams a day. It was an eight-week study with a four-week discontinuation and two-week post discontinuation, and the Ns are described at the bottom.

DR. CASPER: Obviously there is a line missing. I noticed this when Dr. Fawcett was presenting. At least one panic attack per week for what? How many weeks?

DR. CORRIGAN: For at least the four weeks prior to baseline. The primary efficacy measures defined prospectively are the total number of panic attacks, the phobic anxiety dimension of the SCL-90, global improvement score and the CGI. The safety variables were also considered in this study. Additional secondary efficacy measures were anticipatory anxiety.

This overhead depicts some of the sample characteristics, the variables on the left: sex, race, and some other summary of patient history and physical characteristics.

This further describes the sample characteristics. The pertinent one may be the age variable, which is the top row, and the second sub-row gives you the mean age for the three groups. No difference between the three arms.

DR. ESCOBAR: Is the mean age here different from the other studies?

DR. PEACE: From the pivotal studies, my recollection is that the mean age is about 37.16, something like that, as opposed to, in this study it is near 38 and a half and 39.

DR. CORRIGAN: Here are the descriptive statistics

of efficacy measures at baseline. These are going to be included on the summary data slides showing the mean for all the primary efficacy variables, but we thought you might be interested in comparison with the two adequate and well-controlled trials in pure panic disorder.

As you can see, the flexible dose study is the first two columns. The central four represent the three doses of Deracyn and placebo for the fixed dose study, and this column over here represents the 0090 three arms of it here. For total number of panic attacks, these patients have greater numbers of panic attacks. The severity of illnesses are comparable. Measures of anticipatory anxiety perhaps slightly lower. Once again, we don't have the testing between groups for these measures. Overall phobia state, phobic anxiety and the SCL generating depression scores.

DR. TAMMINGA: Did you say that you had or had not tested whether these groups are different from each other at baseline?

DR. CORRIGAN: Only the anticipatory anxiety I believe was tested. No? Excuse me, anticipatory anxiety is the only one that is marginally different.

This represents the comparison between the fixed dose study in the 0090. The Hamilton depression scores are baseline. Each of the groups was represented for each

study. As you can see, because this study selected for by entry criteria, scores on the retardation cluster in the second column, it is higher, as is the total Hamilton-D.

DR. CHARNEY: It didn't have to be six, the retardation cluster?

DR. CORRIGAN: It had to be six or more.

DR. LEE: As I recall reading it, you started out before you did the study requiring the retardation score of six or greater, and then you switched to the SCL-90 depression scale, which is on the previous slide, as the entry criteria. I'm not sure of the time course of these things, but if you look at the previous slide, the SCL-90 depression is much higher.

DR. TAMMINGA: Is there a clarification from the company about what actually -- why don't you go on, and as the clarification becomes available, you can give it to us.

DR. CORRIGAN: I know you have seen this slide before, but I think it will be helpful for us to review, since it has the significance testing, which does not accompany the raw data tables which I will be presenting further. This slide has been corrected, with one change on the mean change. The mean change here has been deleted as significant.

To walk through it, these are the comparisons versus placebo and the methods of analysis that were

prospectively described. For panic attacks, there were no measures that were significant for Deracyn, with the exception of the week two percentage responder, which was a trend. On the other hand, for imipramine at weeks four, six and eight, there was a significant improvement, percentage responder and mean. For CGI global improvement, focusing on week eight data, there is comparable results between imipramine and Deracyn, as is CGI severity of illness. There was no significant difference between Deracyn and placebo on the phobic anxiety measure for any of the analyses. On the other hand, for overall phobia, for the mean there was a significant change for Deracyn. I think you can review the rest of them, but as we go through them we can refer back to this if you get interested in the comparisons.

These are included in your handout. This represents an appendix to the technical report and the sum of the raw data for this measure that we have. This describes in the first column baseline weeks one through eight, and last observation carried forward for week eight for the three comparisons, placebo, imipramine and Deracyn. For each row, we will have the N, mean and standard deviation.

If one compares the three groups baseline to last observation carried forward week eight, there is a decrease

in the mean for placebo from 8.64 to 4.41, for imipramine from 7.59 to 4.29 and for Deracyn from 7.65 to 4.15. If one looks at the median number of panic attacks at baseline, the median for imipramine is somewhat less at three, and the Deracyn and four placebo arms, which are four.

DR. TAMMINGA: I have a question. Do you have for this the reason for the dropouts over the eight weeks? Or have you already shown them to us? I can't recall if we have seen those.

DR. CORRIGAN: I don't think we have shown dropout data for 90. It is included in the report.

DR. TAMMINGA: I think the committee needs a few minutes to look at this.

DR. CHARNEY: I may have this wrong, but the slide we were shown this morning changed from baseline on panic attacks. All three treatment groups converged.

DR. CORRIGAN: Mean change. That included baseline. It is a mean change from baseline.

DR. CHARNEY: They are converged at week eight, correct?

DR. CORRIGAN: Correct.

DR. TAMMINGA: But weren't those data number of responders? These data are total number of panic attacks.

DR. CHARNEY: It was mean change from baseline, right? You subtracted out baseline and they all converged

at week eight, is that correct?

DR. CORRIGAN: That is correct.

DR. CHARNEY: Looking at this appendix, the mean with imipramine at baseline is 7.59.

DR. CORRIGAN: Correct.

DR. CHARNEY: At week eight, it is 0.8.

DR. CORRIGAN: That has got to be a typo.

DR. CHARNEY: I am looking at week eight. Is that a correct number?

DR. CORRIGAN: It looks like it would be reasonable, considering it is moving down to 1.1, to 1.21, to .8. So I think it makes sense.

DR. CHARNEY: So there, you see a very large difference between imipramine and the other two treatment groups.

DR. CORRIGAN: That is correct.

DR. FYER: Maybe this is an unintelligent question, but the LOCF for week eight for imipramine is essentially equivalent to that for the other two treatment conditions. Yet, as Dr. Charney just observed, there is a striking difference between the completer analysis in imipramine and the other two drugs. I wonder if the company could comment on --

DR. CHARNEY: You've got a large dropout rate at week one, which is common with imipramine.

DR. PEACE: One possible explanation is, if you're looking at mean change, then across times from baseline you're looking at within-patient controlled, whereas if you just looked at the means by week, you might have some patients who had a smaller number at one week, a greater number at another week. So this is not controlling within the patient.

DR. CORRIGAN: Dr. Charney, you are also correct. There were 12 patients that dropped out of the imipramine group in week one, compared to two patients in the placebo arm and three in the Deracyn arm.

DR. CHARNEY: How did you dose that week with imipramine? If you dose the way you would dose with depressed patients who don't have panic, you do get that high dropout rate.

DR. CORRIGAN: That's right.

DR. LEBER: We struggle with the issue of the differences between observed case and last observation carried forward all the time. Generally speaking, if there is a trend toward improvement, a regression to the mean or whatever you want to attribute it to, the group differentially losing patients early generally suffers the penalty in an LOCF analysis. That is because in the time trend you are carrying forward more negative scores, even though they might have improved with the passage of time.

How do you get out of this bind? You have seen analyses that we have presented to you in the past that actually examined using various estimating techniques what is happening to the people that are leaving. That is one way to look at it, what is the pattern of dropouts.

Also, to complicate matters, when you compare week eight observed cases with baseline, you are comparing different groups of people because of the losses. If you did an analysis of covariants which only looks at people that have a baseline value and the eight-week for that period of time, you would probably have the same set of people looked at, and therefore you might get a different number out of that.

In short, the way you analyze this data set is going to give you different estimates of the size of the drop across the span of the eight weeks, which makes it exceedingly difficult to decide which is the right analysis, unless you know who is dropping out and why. But I don't think you can simply assert, because of some pattern, that that is the explanation of the results. This is not the kind of thing you do on the fly easily, is my point.

DR. CORRIGAN: Would the committee like to see the mean change data again, just to compare?

DR. TAMMINGA: We would like to see it, if you have it available, since several people have asked about the

reason for dropouts.

DR. FRANK: Could someone respond to Dr. Charney's question first, about the dosing of imipramine?

DR. DENAHAN: Angie Denahan. Both adinazolam and imipramine reached their max dose on day 18.

DR. FRANK: Day 18?

DR. DENAHAN: Day 18.

DR. CHARNEY: The issue is how fast you start it in the first week with imipramine.

DR. DENAHAN: With imipramine? We started with 50 milligrams. The second week, a hundred.

DR. CHARNEY: The first day would be 50 milligrams? Because that is a high dose to start.

DR. DENAHAN: The first three days, we started with 25 in the evening. On day four to day seven, it was 50.

DR. HAMER: Before this transparency goes away, I noticed that the medians are quite a bit lower than the means here. That means these data are pretty highly skewed. There is a big pile-up of very low values, and then a fewer number -- it would be nice to look at the distributions at each time point, but there is a big pile-up of low values, and a smaller number of higher values. As you watch those means decline, possibly the higher value is getting smaller.

If you look at the pattern among the medians, they

have gone down fairly quickly in all three groups, and then stayed down fairly solidly, which would indicate to me that in all three groups, most of the patients wound up with fairly low numbers of panic attacks.

DR. TAMMINGA: Would you comment on what your thoughts are about between the groups, looking at medians? Do your remarks suggest that there is no difference between placebo?

DR. HAMER: Certainly, if you look at the LOCF, you have a median of one panic attack in the placebo and adinazolam groups, and zero in the imipramine group. That is a median, which means that in the imipramine group, at least half the patients had zero panic attacks. I'm not sure about -- I can't do an on-the-fly statistically significance test in my head, and I am not a clinician, so I'm not going to try and interpret that difference. But it doesn't look like a whole lot of difference between the three groups to me.

I don't know, maybe half the patients having less than one panic attack per week is different than at least half the patients having no panic attacks per week. If you're a clinician, that may be a valuable piece of information to know, in which case the imipramine comes out better than either placebo or adinazolam.

DR. CHARNEY: One way of looking at it, that is

how you meet criteria for the disorder. You have one panic attack per week for six weeks.

DR. HAMER: So what you're saying is that in terms of the LOCF analyses or for that matter, the week eight scores, the imipramine group, at least half the patients no longer meet the criteria, and in the other two groups they did, or at least half the patients do.

DR. TAMMINGA: It seems to me that one would reach different conclusions, based on looking at these different pieces of outcome data, if you look at the raw scores at eight weeks or at the LOCF or the change from baseline.

DR. PEACE: Prior to lunch, there was a question about the distribution of panic attacks, and then Dr. Hamer just raised a question about the distribution as well.

The top is the placebo group, the middle, Deracyn, and the bottom, the imipramine group. These are actual counts of patients plotted on the vertical axis versus the number of panic attacks plotted horizontally, and understand, the number of panic attacks to get it on the page has been truncated to 21. So you can draw what you will about those distributions.

DR. FRANK: Total number for what time period?

DR. PEACE: This is at baseline.

DR. FRANK: No, one week, one month?

DR. PEACE: It was for the week prior to entry,

the average of it, yes.

DR. HAMER: And to correspond to this transparency that we had earlier, the median for that top graph is going to be about four, and the median for the imipramine, the middle plot, is going to be about three, and the median for the placebo is going to be about four again. Those medians have declined over the course of the -- if you have a transparency that shows either LOCF or week eight or something --

DR. PEACE: I'm not sure at what weeks, but here is the distribution at week two.

DR. HAMER: You can see they are piling up towards the lower end in all three groups.

DR. SCHOOLER: I would also like to comment that it appears as though those median figures are rounded to the nearest whole number, as opposed to the means, which are carried out to two significant decimal points, which may be what accounts for the differences between zero and one. Instead of zero, it could be 0.7, and one could be 1.2.

DR. PEACE: Yes, that is true.

DR. SCHOOLER: So what would this come out for the median at week four?

DR. PEACE: Is there a table that shows those descriptions?

DR. LEBER: Can I ask one other thing? The

scaling of the Y axis doesn't exactly appear to be the same in all these. Is it?

DR. PEACE: That is correct.

DR. LEBER: That is an important point. This is a frequency distribution. If you look at imipramine, it is 50 patients, and if you look at placebo, it is 35. So comparing across these histograms, it is a little deceptive to the eye.

DR. PEACE: This is a high of about 30 patients, this seems to be 32, and this seems to be 43.

DR. LEBER: The importance of visual presentations is to provide a gestalt of what the effect is, and this does just the opposite.

DR. PEACE: There was a question about seeing these, and I believe these are the only slides that were available.

DR. SCHOOLER: Could we just calculate the medians from these?

DR. HAMER: She means to more than a whole number, which is hard, because at that point there are at least five different definitions of a median.

DR. CORRIGAN: Would the committee like me to go through the other --

DR. TAMMINGA: I think we need to know what all the data are like.

DR. CORRIGAN: This is the similar table construct for the variable overall phobia state. And the final table, which is also one you have is for the efficacy measure, CGI severity of illness.

DR. CHARNEY: It may be useful to have a little bit of a debate here, but my looking at the data is that imipramine looks superior to Deracyn. When you look at the week eight data, you have to be careful in the LOCF analysis with imipramine. If those 12 dropouts during the first week were primarily the jittery syndrome that you get, and week eight is more of a true efficacy comparison --

DR. CORRIGAN: That is certainly one conclusion you could draw in this population, looking at the mean values that are presented here.

DR. CASPER: Maybe I'll ask you whether you did statistics on the --

DR. TAMMINGA: The statistics as I understand it for all of the data that you're presenting now are summarized on the initial sheet.

DR. CORRIGAN: Yes, they are, Dr. Tamminga.

DR. CASPER: No, I was wondering whether you did statistics on adinazolam versus imipramine.

DR. CHARNEY: The table that we have been referring to as the summary, is that all LOCF data?

DR. TAMMINGA: No, observed data.

DR. SCHWARTZ: Is there a particular question on the analysis?

DR. CHARNEY: For week eight, that is just the sixty --

DR. SCHWARTZ: For which variable?

DR. CHARNEY: All of them.

DR. SCHWARTZ: For panic attack variable?

DR. CHARNEY: I'm not addressing any one particular point. I am just clarifying that the week eight comparison -- is that the LOCF analysis, or is that the --

DR. SCHWARTZ: That is based on observed data.

DR. TAMMINGA: I think we're still waiting to hear whether there were statistical comparisons of adinazolam and imipramine similar to these comparisons that we're looking at right now.

DR. SCHWARTZ: Yes. We don't have an overhead of that. I have some tables that we have been putting together. I can show you any particular comparison that you're interested in.

DR. TAMMINGA: Dr. Casper was asking you about the adinazolam-imipramine comparisons.

DR. CASPER: Yes, but how are you going to show it if you don't have an overhead? Maybe you can make an overhead.

DR. SCHWARTZ: Okay, I can make an overhead of

these tables.

DR. TAMMINGA: Why don't you just describe it?

DR. SCHWARTZ: Okay. You're interested in at week eight the comparison of Deracyn versus imipramine for each variable? For the panic attack variable, we have percent responder, mean and mean change from baseline. Is there one in particular you want me to --

DR. TAMMINGA: Mean, unless Dr. Casper wants to hear another one.

DR. CASPER: Mean sounds fine.

DR. SCHWARTZ: Would it be better if I had this blown up into an overhead? We will be going through several test results. Read it? Okay, for week eight, for total panic attack, percent responder, Deracyn versus imipramine, the result was significant for observed data.

DR. CASPER: Significant for what?

DR. SCHWARTZ: A significant comparison of Deracyn versus imipramine. I would assume it is in favor of imipramine. I don't have the descriptive statistics or the plots in front of me, but I think from the plot, if I recall correctly --

DR. TAMMINGA: I think we're not going to do this by reading it. I think we need to have it blown up.

DR. FYER: I don't think it is appropriate. Taking these LOCF -- those little graphs, Dr. Jonas gave me

the week eight, and it looks like 67 percent of the imipramine patients had zero panic attacks as compared to the 30 percent of the placebo and 44 percent of the Deracyn. I wondered if I did that right or not. But that is a typical imipramine panic-free response.

DR. TAMMINGA: One of the difficulties is -- you will have to bear with the committee a little bit, because this is the first time we have had a chance to look at the data, so we haven't seen it ourselves or heard it presented or seen it analyzed by the FDA in a way that we usually see these data come through. So our questions are perhaps detailed.

DR. CORRIGAN: No, there is no problem. I think that the point that you and Dr. Charney made earlier in terms of -- that one can draw different conclusions looking from different modes of analysis from this, but certainly if one looks at the mean at week eight, one concludes that imipramine is superior on at least a couple of the measures here. That would be a different mode of analysis that was used to interpret the 7400 or the 7450 data.

DR. TAMMINGA: I think we have all the data that the company has to give us on the 0090 study.

DR. CORRIGAN: Let me just ask, obviously that is one interpretation of the study. If the committee is interested, we have got the variables that we discussed from

the SKID that speak to current panic attacks, past history of panic episodes, major depressive symptoms and past history of major depression, with the caveat pointed out by Dr. Leber that Hamilton-Ds at entry were not different between groups. If the committee is interested, I would be happy to go through those. It is in your packet.

The conclusions that the company has drawn is that there were from the examination of those patient characteristics an unequal distribution of patients based on psychiatric history, which may explain some of the differential effects of the medications. Patients with history of more panic or depressive symptoms showed less response to either treatment. Improvement in panic followed the traditional temporal pattern for benzodiazepines and tricyclic, that is, that the week two data favored Deracyn, whereas the improvement in imipramine was seen more strongly towards the end of the treatment period.

On mean change from baseline for total number of panic attacks, imipramine, adinazolam and placebo are not statistically different, and this study is not sufficient to establish differential efficacy between the compounds.

DR. FRANK: So if I take your meaning correctly, the sponsor is characterizing this as a failed study, not a negative study.

DR. JONAS: We believe that it fails to

demonstrate efficacy for Deracyn, yes. Although we do think on the observed values there is a suggestion of activity.

DR. FRANK: I'm using the failed and negative study in the sense that we have come to talk about them here. That is, a failed study is one that fails to show a difference between active compound and placebo or between a test drug and the experimental drug. In this case, I think what we're seeing -- as I extract everything and pick the kinds of analyses that I prefer and the kinds of data that I prefer, the meaning I take from this study is that there is a statistically significant difference between imipramine and placebo, suggesting that there was a drug responsive group in this study, but there is not a statistically significant difference between Deracyn and placebo.

DR. JONAS: Yes, overall, yes. For CGI, Deracyn did show superiority to placebo, but overall, yes.

DR. TAMMINGA: Additional questions? We still have a lot more to hear from the company, all of their discontinuation data, and we still have to do our safety review. So unless anybody else has any additional questions about the material presented, we will go on.

DR. CHARNEY: Do you know what percentage of patients in this last study met criteria for current major depression?

DR. FOSTER: About 25 percent of the sample.

DR. CHARNEY: That was 25 percent in each of the three groups?

DR. FOSTER: Roughly. It wasn't exactly, but it was roughly equally distributed.

DR. CHARNEY: Was it a 17 item Hamilton or a 24? Because 16 has different meaning, depending on the number of items.

DR. TAMMINGA: I would suggest that we go on now and finish with the company's presentation. I think that Dr. Davidson was to continue on.

DR. DAVIDSON: Thank you, and good afternoon. I have been asked to present the results of the discontinuation data from the two pivotal trials, and also to talk about the effect of adinazolam on quality of life, and to discuss some risk/benefit issues.

When we consider the important improvement of discontinuation of benzodiazepines, there are three aspects that have to be addressed. One of them is the issue of relapse and rebound, the second is the issue of withdrawal, and the third is a general issue of which particular symptoms are likely to get worse during the course of the drug taper. I will talk about each of these three things.

Firstly, relapse and rebound refers to the reappearance of the original symptoms of anxiety that were present at the beginning of treatment. Relapse refers to

the return of these symptoms approximately to the level that they were to start with, whereas rebound refers to the occurrence of symptoms at a level considerably in excess of their original intensity. So we will address both the duration and the frequency of these.

I should also remind the committee of the protocols that we're addressing, which are the fixed and the flexible dose studies. Both employed a four week taper at approximately 50 percent of the dose per week, and then a two-week post-taper period.

In order to be judged as a responder, patients had to have met criteria on any one of these three measures of panic or phobia. In this instance, we were looking at a reduction of panic attacks by at least 50 percent from baseline, so this was not the rigorous definition that Dr. Jonas had presented earlier, where it had to be zero panic attacks. These two definitions were both the same as those used in the responder analysis. In other words, a drop of at least two points on the overall phobia score, and then a drop of at least 50 percent on the SCL-90.

Reviewing the results, we looked first at the long term flexible dose study. This is what happens during discontinuation after people have been on treatment for several months. Forty-nine percent of the patient sample on adinazolam did not experience either relapse or rebound, and

51 percent therefore did experience relapse or rebound. We looked at the question of duration, and find that 23 percent had a brief period of only one week in the relapsed state, and then they recovered, and five percent more had a somewhat longer period of relapse or rebound, lasting up to four weeks. There were also eight percent who had a more prolonged state at the end of the tapering period; they were still judged to be in relapse. Then there was a group of 15 percent who were relapsers for one week and then no further data was obtained.

In the placebo control, there is very little relapse. You see only 70 percent of the placebo group after long term treatment had relapsed.

In the fixed dose study, which you recall was a four week treatment period, if you pull the data from each of the three dose groups, the 30, the 60 and the 90 milligram groups, you find that the relapse rate is approximately the same as it is here, with 46 percent of the sample who did not relapse, and 54 percent therefore who went through relapse or rebound after four weeks of treatment with adinazolam. In many cases, the relapse was relatively brief and followed by recovery, but there were a number of patients, 13 percent, who left the study after prolonged relapse, and then 21 percent who had one week of known relapse, and then there was no further data.

In interpreting these results, I think we should not lose sight of the fact that discontinuation of placebo after four weeks was associated with a 34 percent relapse or rebound rate, which in some cases led ultimately to recovery, but in other cases was not known to lead to recovery. So not everything that happens to people on an active drug is necessarily related to the discontinuation of the drug pharmacologically.

Moving from relapse and rebound to the second important question, which is benzodiazepine withdrawal, we examined frequency and duration. During a tapering of benzodiazepine, many symptoms can appear which might represent recurrence of the illness, or they might represent the specific effects of withdrawing from the drug. It is not always easy to tell the difference between the two. I think the point was made earlier this morning by Dr. Laughren that there is no official or unanimous definition which we use in order to come up with a measurement of withdrawal.

What was done here derived from methodology that was developed in the alprazolam trials by Dr. Peckrald and Dr. Clareman. The intent of this particular algorithm is to pick symptoms that are thought to maximize the likelihood that if they occur, they are due to withdrawal and not recurrence of illness. What was done to do this was, in the

whole population, all the withdrawal or discontinuation symptoms were tallied up, and those that occurred more frequently during the withdrawal as opposed to having been present at baseline were considered to more likely reflect withdrawal. There were I think about ten or eleven of those withdrawal clustered symptoms, and if anybody on the committee wants to see what they are, I do have an overhead.

Out of these symptoms, if at least three was present at any one time for a patient, then they were considered to manifest a withdrawal cluster at that time. So using that definition, what we see with the flexible dose study after longer term use of adinazolam was that withdrawal did not occur in 71 percent and it did therefore occur in 29 percent. The rate of withdrawal symptoms, in other words, in this population was 29 percent. It was relatively brief, and then led to recovery in many of those 29 percent. It was more prolonged, last several weeks, in about four and a half percent, and then in seven and a half percent it lasted for one to two weeks, and then there was no further data.

DR. HAMER: Excuse me. Without placebo, I don't know what to compare these numbers to.

DR. DAVIDSON: Well, let me tell you what the placebo was. The rate of placebo withdrawal in this population was zero percent after long term administration.

In this group, the rate associated with discontinuation of placebo was nine percent, as opposed to 17 percent of the pooled patients on adinazolam.

DR. CHARNEY: What was the mean duration of treatment in the flexible dose?

DR. DAVIDSON: The mean duration in the flexible dose was four weeks. Oh, in the flexible dose? I'm sorry, it was up to 26 weeks altogether. Because some people dropped out, I don't know what the mean was. Maybe we have placebo analysis, I don't know.

DR. CHARNEY: Was there any relationship between the duration and the group that had the more significant withdrawal?

DR. DAVIDSON: I tend to think that duration was a factor, because you have a higher level of withdrawal symptoms in this group than you do in this group. The mean dose here was about 82 milligrams a day. Here, of course, you've got three different doses, but we have separately analyzed the impact of dose on withdrawal after four weeks, and there is no relationship.

DR. HAMER: These Ns in the flexible dose study, do they include people who dropped out?

DR. DAVIDSON: You have 66, which is not every single person who entered into the extension, but it does include dropouts.

DR. HAMER: Were the dropouts discontinued according to the same regimen as the people who lasted all the way through? Didn't you say they were tapered over --

DR. DAVIDSON: Tapering occurred at the same rate, whenever they dropped out.

DR. HAMER: So if someone decided that he didn't want to come anymore, you managed to convince him to taper over some period of time?

DR. DAVIDSON: To the best of my knowledge, and I guess I probably need to have that confirmed, every single person in this analysis went through the four weeks of tapering.

Moving away from withdrawal per se to just simply looking at individual symptoms that got worse during the tapering period, we referred to this as discontinuation emergent symptoms, or DES. We are looking at frequency and severity. The criterion we used in these slides that follow are a difference of ten percent between the drug group and the placebo group. In other words, each of these symptoms had to occur at least ten percent more often in a larger number in the drug than in the placebo group. We're assuming after the short term fixed dose study, and also people who dropped out from the flexible dose study did not go into the extension. We're seeing these symptoms: sleep disorders, irritability, sensory disturbance,

lightheadedness, nervousness and depersonalization.

I should add, because I think I forgot to mention, that how we compute the discontinuation emergent symptoms is that they were worse at some point during the taper than they were either at baseline or during treatment. They are arranged in order to diminishing frequency in the drug group.

There were some non-CNS events. Again, the only ones that occurred ten percent greater in drug than placebo group was decreased appetite and nasal congestion.

From the long term study, there are many more DES. Sleep disorders appears as the most common, lightheadedness, tremor, paresthesia, sensory disturbances, headache, muscle twitching, nervousness, concentration difficulty, anxiety and coordination, depression, disorientation and fatigue. All of those are considered to be either CNS or psychiatric in nature. Then there were some non-CNS events: sweating, nasal congestion, weight loss, dry mouth, nausea, chills, muscle cramps, tinnitus, blurred vision and palpitations. It is a relatively long list, but they are symptoms that are very characteristic of discontinuation of benzodiazepines.

DR. LAUGHREN: I see that you are now moving on to quality of life. Before you leave discontinuation symptoms, I wanted to ask a question. I had the impression when I was reading your materials that your look at relapse and

withdrawal and so forth was done on a subset of the total patients. I had the impression that the patients who had to be treated with adjunctive medication during taper and post taper, most of which were benzodiazepines, were thrown out of the analysis. Is that true? So you're confirming my suspicions.

It seems to me that probably the most important patients who you're looking at during discontinuation, during taper and post taper are those whose symptoms are so significant that they need to be treated with another medication. You have excluded those patients from your analysis. It seems curious.

DR. DAVIDSON: I think a number of the patients, where they dropped out, where there was no further data available, that could well have been the case.

DR. LAUGHREN: These were patients who had already made it to the end of the study and were being tapered and discontinued, who needed adjunctive medication.

DR. DENAHAN: Dr. Laughren, to answer your question, the patients were included in the analysis at the point of contamination. Thereafter, the data are excluded.

DR. FRANK: So over a four-week taper -- and that is what it was, right?

DR. DENAHAN: Correct.

DR. FRANK: The patients are counted as having a

DES if at any point in that four weeks the symptom is ten percent over baseline.

DR. DENAHAN: Let me clarify that. The discontinuation emergent symptoms defined prospectively in the protocol as any symptom during discontinuation that did not occur at baseline or during treatment, or if it occurred during treatment, was worse during discontinuation.

DR. FRANK: The ten percent was ten percent of patients having it.

DR. DENAHAN: No, it is the actual absolute difference between Deracyn and placebo. It is an arbitrary percentage that we adopted in order to show actual differences, meaningful differences.

DR. FRANK: What I am trying to get back to is Dr. Laughren's question, that is, the extent to which the data have been presented under estimate the actual portion of discontinuation emergent symptoms. If the patients who needed adjunctive medication in order to be withdrawn from the compound are excluded from this analysis, then this represents a serious under estimation of the extent of discontinuation emergent symptoms. I still haven't got a clear answer about that.

DR. DENAHAN: We do have a list of the discontinuation emergent symptoms without ten percent.

DR. FRANK: That is not my question. My question

is, are the data we just saw cleaned of any patient who required adjunctive medication in order to be withdrawn from the compound?

DR. DENAHAN: It is cleaned to the point where the patients discontinued because they had to have a contaminant medication.

DR. CHARNEY: Maybe I could ask it another way. Is it possible that you had a patient that got put on a benzodiazepine before they met the criteria that you're talking about, which would have resulted in an under estimation?

DR. DENAHAN: I cannot answer the question at this time.

DR. CHARNEY: Do you have the data on how many patients required adjunctive benzodiazepines?

DR. DENAHAN: We do have that information and we'll get that to you.

DR. LAUGHREN: Also, we plan on presenting that in FDA's presentation of safety data.

DR. FLEISHAKER: One way to address it is to look at patients who took benzodiazepines during the period of the trial. We did some monitoring which was not included in your packet, in terms of benzodiazepine use concomitantly during the trial. If you look at the taper weeks, the active treatments, we measured concomitant benzodiazepine

used by a specific method, the placebo group we used a non-specific screen. These are percentages of patients who were positive for benzodiazepines other than adinazolam during the taper period. There are no significant differences between those groups. You can see however that benzodiazepine use tended to increase during the taper period as compared to the treatment period.

DR. FRANK: So that would represent anyone whose urine screen was positive for benzodiazepines, irrespective of whether those drugs were prescribed by the treating clinician or the patient took them on his or her own, right?

DR. FLEISHAKER: That's right.

DR. FRANK: So what we're still not getting a picture of is the clinical judgment that the patient required help in coming off the drug.

DR. LAUGHREN: What you are showing in that slide is the background noise, the surreptitious use of benzodiazepines by patients in both groups. You're not seeing the clinically important cases, where a clinician recognizes that a patient is in so much distress that the patient needs to go back on a benzodiazepine during taper.

DR. FLEISHAKER: You're seeing both.

DR. LAUGHREN: Fine, you're seeing both. But after a decision was made to treat a patient with benzodiazepines, you are no longer screening their urine.

Or are those patients included in that sample?

DR. FLEISHAKER: If they were coming in for clinical evaluations, they were having their bloods drawn.

DR. DENAHAN: Dr. Frank, let me clarify my answer. If you are asking if the patients that required adjunctive therapy included in the analysis of the DES, the answer is yes, to the point of taking contaminated medication.

DR. FRANK: Maybe it would be helpful if we could go back and look at just a sample -- before you leave the microphone, if we could go back a couple of slides, let's take the sleep disorders. Now, what we have here are the percent of patients who at any time during the four-week taper were positive for a sleep disorder in the adinazolam and placebo groups, is that correct? So if the patient reported a sleep disorder at the end of week one of the taper, they would be counted among those 28.6 percent, and then moved out of the N of 266 at the point at which another benzodiazepine was prescribed. Am I understanding this?

DR. DENAHAN: That is correct.

DR. LAUGHREN: As I understand this analysis, the only way that an event gets counted, for example, insomnia, would get counted for a particular patient is if that patient didn't have insomnia prior to entering the taper period, or if the insomnia present during taper was at a greater level than it was at the start of taper. These are

new symptoms or worse symptoms occurring during taper or post taper.

DR. DAVIDSON: That is correct.

DR. HAMER: If I am interpreting this correctly, that means, for example, that if you had a patient who say during week one of taper had an emergent sleep disorder sufficient that the physician felt it was necessary to put that patient on a benzodiazepine and the physician did that, and at week two, that patient then had irritability, sensory disturbance or anything else, all those other things won't show up in this table.

DR. FYER: I have a question about some of the company's numbers in the discontinuation. Maybe we should wait.

DR. TAMMINGA: If they would be appropriate for Dr. Davidson now, go ahead and ask them.

DR. FYER: This is page 21 in this booklet. What I was trying to find out is, in 7400 and 7450, the numbers of subjects who proceeded through various stages. So it starts as people enter treatment, and then people who enter taper after the short term and then people who enter taper. What I wondered was, at the bottom, the people who enter the extension, there were 67, and 52 of those people entered the post taper. What happened to the people who left? The same thing for the acute phase. Twenty-three entered taper and

15 entered the post taper. What happened to the eight people in between?

DR. DAVIDSON: I don't have those numbers, but I think one of the earlier slides, there were a group of people for whom no further data was available.

DR. FYER: I wonder what the events were that led to those people --

DR. DAVIDSON: That is not a question I am able to answer at the moment. Dr. Denahan?

DR. DENAHAN: This data tells you, up to 23 patients who entered the short term taper, we only have 15 patients with data for two weeks post taper.

DR. FYER: The question is, what happened to all the rest?

DR. DENAHAN: All the rest of the patients did not enter post taper.

DR. FYER: Yes, but why?

DR. DENAHAN: Lost to follow-up and other reasons.

DR. FYER: You probably don't have information on that, is that correct?

DR. DENAHAN: We have information on those patients, but we have to look at the technical report to find out.

DR. LAUGHREN: But if for example a patient needed benzodiazepines, would that be a reason for them not being

included in that sample?

DR. DENAHAN: If they discontinued prior to the first day of post taper, week one, yes, they would have been included in that sample.

DR. LAUGHREN: But those are the patients that I think clinicians would be most interested in, those patients whose symptoms are so severe that they have to be treated with adjunctive medication. I am trying to focus this on the clinically relevant cases that most clinicians would be interested in looking at.

DR. CASPER: Returning to your urine screen, when you say you estimate the people who got additional benzodiazepines to be between 10 to 15 percent on your urine screen, does this mean that these might also be different populations during week one, during taper week one and two and so on? You told us that this includes the surreptitious use and the clinical use of benzodiazepine. So this could be in fact a much higher proportion of your sample than if you just look at the percentage of people who had other benzodiazepines in urine. Am I correct to assume that?

DR. FLEISHAKER: The way that we calculated the percentage is, they are calculated as a percentage of the samples that we received, not as a percentage of the total patient population.

DR. CASPER: So this does not give us any

information about the percentage of patients who might have been placed on benzodiazepine. We still do not know that number.

DR. FLEISHAKER: Right, you may not know that.

DR. FRANK: I have the impression that Dr. Jonas had something that he wanted to add.

DR. JONAS: As a point of clarification, the data for DES after contamination were included either before or within the next few days after the data were collected. But there is a separate analysis for patients -- to answer both your questions -- which we don't have with us, but which we will have faxed to us, that look at the individuals who were not included, to answer the clinical question that has been raised, as to what happens to those patients. So we do have some analyses on those. We will have those brought in.

DR. CHARNEY: Is it possible just to get data that would be fairly simple for us to understand, which is, how many patients required benzodiazepines?

DR. JONAS: We can give you the data also on subjects who required other psychoactives. We'll put that together for you now.

DR. LEBER: I think we're running into a fundamental problem of how you display data of this sort. It occurs to me, you're dealing very much with a declining cohort, and you want to look at something like a hazard.

You're reaching a given point in the taper. For those at risk, what fraction of them suffer various events? Because of the sensory, perhaps more sensitive people dropping out, you won't necessarily get the kind of information that you wanted, that Dr. Laughren was talking about, because the most sensitive patients may get salvaged. So the analysis has some kind of sensory going on that you can't beat. But it would still be useful, because you are presenting crude proportions, to have an idea of how much of this sample is being lost. Conditioned upon getting into ten days of taper, what is your risk over the next three days of suffering any one of these?

I think you will see it is changing. I don't know how big the dropout rate is across time. That might be the first thing to start at. What fraction remains at risk for suffering an event without having co-treatment or rescue treatment. That would be one thing to get, if you could get it for that. Then from that, maybe you can get at the hazard of at various times doing taper, recognizing that you may have lost the very sensitive people up front. I don't know how you deal with that, either.

DR. LAUGHREN: Dr. Knudsen will be presenting his data later, but I think he has a transparency that answers the question of how many patients needed adjunctive medication during taper and post taper.

DR. KNUDSEN: It is a simple little transparency, but it might resolve some of the questions that are now being posed. This pertains to protocols 7400 and 7450. Quite simply, to look at the adjunctive psychoactive drug therapy during taper, post taper in protocols 7400 and 7450. You know about the mean doses in both protocols, and obviously, you see the difference here. In protocol 7400, 11 of 67 patients required some benzodiazepine or adjunctive medication or contaminant, if you want to call it that, whereas one of 43 necessitated a placebo.

By the way, the so-called adjunctive therapy, for the most part, nine out of the 11 was alprazolam. In 7450, also, 30, 60, 90 treated patients required some adjunctive therapy, as did the placebo. In the 7450, there were a lot of so-called non-evaluatable patients after patients qualified for the rebound-relapse criteria, and these non-evaluatable patients the company may want to comment upon later.

DR. LAUGHREN: I have a question for the company on these data. My understanding of these data is that these are the patients who made it to the end of the respective trials, and entered formally the discontinuation period. There may have been patients who were lost before reaching week four in 7450, or I guess week 26 in 7400, who may have needed medication, that would not be included in this slide,

is that correct? So if you had information on those patients, it might be useful as well.

DR. FRANK: The data for 7450, are those the four week data plus the extension data, or are those only the taper occurring at four weeks?

DR. KNUDSEN: Four week data.

DR. SCHOOLER: One thing that this transparency highlights for me is that looking at protocol 7450, maintaining the distinction among the three doses of adinazolam seems quite important, whereas the slides that you presented previously, Dr. Davidson, where you were looking at the discontinuation emergent events for 7450, merged those three treatment conditions. I wonder if any of those discontinuation emergent events, even given that kind of analysis -- and we have all talked about some of the limitations -- would show dosage differences among the three fixed doses. I wonder if any of those data might be available.

DR. DAVIDSON: The dosage difference in the short term study did influence the rebound percentages, which went up higher at the 90 milligram dose. Relapse remained about the same, and the withdrawal incidence was also about the same. I have an overhead which I might be able to show on that.

DR. TAMMINGA: Are there any more comments or

questions? I'll bet we'll get back to some of this in Dr. Knudsen's presentation.

DR. DAVIDSON: What you have here is, rebound rates do go up from five percent at the 30 milligram level, up to 17 percent in the 90 milligram. The relapse rates don't follow any consistent pattern on the basis of dose.

DR. SCHOOLER: What about for any of the particular discontinuation emergent symptoms?

DR. DAVIDSON: I would have to turn to Dr. Denahan to answer that question.

DR. JONAS: These are the DES for -- we have broken them out by dose versus placebo. This is for 30 milligrams first. You will have to bear with us, because you will have to keep the number in your mind.

Let me give you a ten percent difference format. That is a little easier to look at. I'll just let you look at this. Let me begin showing the 60; we've got the summary slide for this. Just to remind you, for 30, sleep disorders were 33 percent, lightheadedness was 27.8 percent, sensory disturbances in the 30 milligrams were 27.8 percent. I guess drowsiness was the other one, 8.3 percent versus 8.1 percent here.

I'll show you the 90. This is again the ten percent difference in the fixed dose study, at 90. If it helps, I can go through the numbers again versus the 60.

Sleep disorder is 41.9, lightheadedness doesn't appear on this. Irritability, again not on the ten percent difference, and nasal congestion doesn't appear. The 60 has fewer DES overall. There were only seven that achieved a ten percent difference. So there are more at 90.

DR. TAMMINGA: I think we'll move ahead with the quality of life presentation.

DR. DAVIDSON: We have already seen some of the efficacy data using the more traditional measures of panic and phobic avoidance and anticipatory anxiety. There are other aspects to the way in which a person with panic disorder responds to treatment, and these impact upon quality of life measures and measures of disability.

We used in both studies one well and widely used scale, the Sheehan disability scale, which is a self report for the disability caused by the illness on family, life, work and social life and leisure activity. We also created for these clinical trials a self rated eight item patient status scale, which taps into the influence of the illness on their life, the degree to which their activities are restricted, the hardship that they feel the illness imposes on themselves and on their family, and a number of other questions.

In the fixed dose study, at the 90 milligram dose, we did find a significant effect of adinazolam at a P less

than .03 for family life on the Sheehan scale, and then a non-significant trend, P less than .15, on work and social life. On the patient status scale, there was a significant drug effect, and then looking at the change in score relative to baseline, comparing the drug against the placebo, there was a significant effect in favor of 90 milligrams of adinazolam.

In the flexible dose study, we used the same two scales and found that on social life -- this was at week four, after short term treatment -- there was a drug effect, and also a change in patient status on the patient status scale.

DR. HAMER: So in the previous slide, you only looked at the 90 milligram, or did you also look at 60 milligrams and found no significant differences?

DR. DAVIDSON: I have an overhead which I can probably retrieve in a few minutes. We did look at all the doses. There was nothing at 30 milligrams, and as I remember 60 milligrams, there was no significant effect. But I can certainly confirm that, if you like.

DR. LEBER: How many pairwise contrasts did you make?

DR. DAVIDSON: That would be a question for the statisticians.

DR. LEBER: You have a lot of different outcome

measures that you compared, so you're comparing between treatments on multiple outcomes.

DR. TAMMINGA: What is the total number of sub-scales on the Sheehan disability scale?

DR. DAVIDSON: Three sub-scales. Well, there are actually five, but we just looked here at three. The other two are not particularly pertinent to disability. There was an overall P that was determined before the pairwise contrasts were examined. I don't know if we could get that information from Dr. Denahan or Dr. Jonas, maybe.

DR. HAMER: So even if these were the only five comparisons you did, you also did these five for the 30 milligram group and these five for the 60 milligram group, so that is 15 comparisons, and three of them come out to be statistically significant.

DR. PEACE: It is my understanding that the analysis aimed to preserve the overall experiment wise error in terms of an LSD protected difference, meaning that they looked at the overall comparison first. If that was significant, only then was there an effort to explain the significance in terms of parallel differences.

DR. HAMER: In terms of overall comparison, you mean an overall Sheehan disability scale score?

DR. PEACE: No, overall test of significance comparing the four treatment groups.

DR. FRANK: On each of these individual sub-scales of the Sheehan disability scale?

DR. PEACE: That is correct.

DR. CASPER: Could you tell us what these numbers mean? Is the higher score a better score or a worse score?

DR. DAVIDSON: A lower score is the better score on the Sheehan scale, in which each of these three measures are rated on a visual analog scale of zero to ten, where ten is the worst. On the patient status scale, as the score goes down, it represents an improvement. The maximum score possible on that scale would be 40.

DR. CASPER: Did you look at these data individually, where you would compare the quality of life scale for individual patients, rather than means of the entire patient group? Individual patient comparisons for a particular patient's quality of life improvement.

DR. DAVIDSON: Are you asking about distribution scores? I'm not sure if I understand the question.

DR. CASPER: No. I'm asking whether you looked at -- I'm asking whether you adjusted the scores. For instance, if someone had fairly good adjustment, I'm asking basically whether you ran individual comparisons rather than mean comparisons for the group.

DR. CHARNEY: You mean, change from baseline?

DR. JONAS: That analysis was not done. Let me

just clarify one other point. This is basically what the scale looks like. There are only three measures on this. This is a separate patient status scale. It has a visual analog scale, zero to ten, that looks at work, social life, leisure activities and family life and home life, home responsibility. It has an index statement, two anchors, and then relative notations in between.

DR. FRANK: Could we go back to the overhead? What I am having trouble understanding is, if the highest possible score on the patient's status scale is 40, and a difference of roughly .7 between placebo and 90 milligrams produces a P of 0005, there must be no variability in the scale, is that right?

DR. JONAS: The Sheehan is a one to ten scale.

DR. FRANK: No, I meant the very bottom. I'm on the patient status change since the start of the study. You are telling us that range event scale is 40, right?

DR. DAVIDSON: It-is an eight item scale with five points for each item.

DR. FRANK: So the maximum score is 40?

DR. JONAS: Patient status question is one grade, and this is a separate question, which is an individual question. The patient status change at the start of the study --

DR. FRANK: Is an individual item on this scale.

It is not changed in the total. Now it makes a lot more sense.

DR. ESCOBAR: May I see the quality of life transparency again? When I look at quality of life, I think about practical aspects of things. In this one, placebo patients are doing very well. If you have a score of less than four, it means that you are doing reasonably well in terms of work and social life. So even though the difference may be statistically significant, from a practical perspective, I don't know if the impact on the quality of life is that significant.

DR. DAVIDSON: I think the difference of one point between the drug and the placebo is not uncommon with other clinical trials. Without having access to the baseline score, it is difficult to know how much movement there was across those two things.

DR. FYER: This is a four-week trial, and we're talking about things like work performance, social life. Maybe somebody from the company could comment on what the expectations were for change in these kinds of variables in this short a time frame.

DR. DAVIDSON: If anybody from the group would want to comment, feel free. I would say that certainly within four weeks, one would not expect as much change on some of these measures, particularly work, that you might

see later on, after 12 weeks or something.

DR. FYER: I would also raise some questions about the consistency of a one-week evaluation change on these measures within the context of a four-week study, in which we know some patients were only at an effective dose for even a shorter period of time. So I would be interested in what we think these mean.

DR. DAVIDSON: I think the best we can say at this point is with short term treatment, there are already suggestions that in some cases at a statistically significant level, there is greater change in the active drug group than there is with placebo. But we might expect further change, hopefully, with longer treatment.

DR. FYER: These are mean change scores, mean figures. What might be more interesting in this context, given the time limits, is how many patients went from being impaired to be minimally functionally impaired. That might be a more interesting way to look at the data in this context.

DR. CASPER: Could we go back to the scale? I think we are talking about shades of mildly impaired here. I think three is around mildly impaired, and 2.8 is a little less mildly impaired.

DR. FYER: I think it's the same. Dr. Caspar is asking the same question in a more elegant way.

DR. JONAS: We don't have individual breakout data in that fashion, or in a responder analysis for these criteria. I think four is moderate, and one to three is mild.

DR. CASPER: So what we are talking about are small changes in the mildly impaired range, and we do not have baseline data. We do not know where these patients come from, correct?

DR. JONAS: We can get you baseline question.

DR. TAMMINGA: I thought your question, Dr. Fyer, was a frequency distribution curve, like how many patients made what amount of change.

DR. JONAS: That data we don't have.

DR. FYER: There have been some studies done of panic disorder where people have looked at sustained response. Because of the variability of symptoms in this illness over time, sustained response over the course of a trial can be very helpful. That was another aspect of my question.

DR. DAVIDSON: I think the issue here is that the significance only appeared at the last visit, so we can't say in the short term study that it was a sustained response.

DR. TAMMINGA: Is your presentation finished?

DR. DAVIDSON: I was going to make a few comments

on risk/benefit. I think in general, we need to consider what the various choices are if we're going to administer medication for treating panic disorder. There are three or four groups of drugs that seem to both be effective and are used. Historically, we have the SSRIs, and certainly at the present time the benzodiazepines. Then fourthly, as a fallback for the people who don't respond, there are the MAO inhibitors.

If we just consider that in all of those, there are certain prices involved when we use the treatment, and it is possible for patients to get better, but sometimes at an unacceptable price. Obviously, in the case of MAO inhibitors, there is an eight percent incidence of hypertensive reactions which people would probably find very hard to live with.

In the case of the dX, there is data in panic disorder itself that the long term use of those drugs may be associated with as high as a 30 to 35 percent discontinuation rate, because of side effects. In the case of SSRIs, they are not as well studied as of this date, but we're certainly familiar with the fact that they can have some side effects, particularly commonly on sexual dysfunction, which present problems to patients.

In the case of benzodiazepines, we know fairly well what their side effects are. During the course of

treatment, many patients are well able to tolerate this group of drugs. When it comes time to reduce the dose, we are equally familiar with what can happen, and how best to minimize the risk.

There is one piece of data that I thought might help in terms of -- this is adding to what we have already heard and what we will hear later about the safety of the drug -- is the question of how many people who are on adinazolam with a diagnosis of panic disorder had to discontinue treatment because of an unacceptable medical event. With the two studies, we're looking at results which are not very much different from placebo. In the short term database, there was a dropout rate of 6.4 percent versus 4.5 on placebo, and in the long term, we had 3.9 versus 3.8.

So I think looking at this from the point of view of the overall risk/benefit picture, the data that we have seen so far are very supportive of this as a treatment which is both effective and has a favorable risk/benefit picture.

Just to summarize what we have heard both from Dr. Jonas and in the discontinuation data that has been available, we have a drug which is effective in the major domains of panic disorder, and also does impact positively on some quality of life measurements. We have an idea that the dose range is between 60 and 90 milligrams a day. So far from what we can see with the discontinuation profile,

it is relatively mild in terms of the severity and the discomfort. Then in terms of the risk/benefit I just mentioned, I think we see now evidence that the risk/benefit profile is fully supportive of its use in panic disorder.

Thank you very much.

DR. TAMMINGA: Questions that we haven't already asked Dr. Davidson? Thank you very much.

What we will do now, after we have heard the company's presentation on efficacy, is return to the FDA's presentation and hear from Dr. Knudsen on his safety review.

DR. KNUDSEN: You recall early this morning that Dr. Laughren talked about the historical aspects of Deracyn. I'm not only going to talk about SR, but also CT. You recall the adinazolam CT preparation, formulation, the compressed tablet immediate release was primarily used in depression studies, and the SR or sustained release formulation was used primarily in the GAD and panic studies.

I need to first acquaint you with some of the database. I did look at the phase one studies from the point of view of safety, but I will emphasize here the phase two and three studies. Here, you see the numbers of individuals participating in the adinazolam SR, 926, the CT, 2495, and the placebo and active control, 1409 and 2430.

We discussed this morning some aspects about the demographic profile, but let me present this information to

you as well. When we looked at the demographic profile in the phase two and three studies, as you see here, and from this information you can clearly see, I think, that as Dr. Lee also emphasized this morning, the patients were primarily white, middle-aged, and three out of five were females. Very few are greater than 65 years of age in this database.

The next slide provides an enumeration of patients who participated in the phase two and three studies according to daily dose and duration, the dose across the top and the duration in the left-hand column. As you can see, 80 percent were exposed to adinazolam, with regard to the maintenance dose, 30 to 90 milligrams, and 97 percent of the patients were treated for 36 weeks or less, a relatively short term experience.

You are familiar now with this other measure we use for expressing duration of exposure. That is, the patient exposure to drug expressed in patient exposure year. Adinazolam SR was equivalent to 142 patient years, and adinazolam CT exposure was equivalent to 457 patient years, or an exposure rate of three to one over placebo and two to one over active control. The relative exposure rates are also there for you to look at.

Now, with respect to background, let us focus on the goal of the safety review, which are to assess the

safety data with respect to looking at the treatment emerging events, namely, the ADR tables, laboratory data, vital signs and ECGs, as well as to look at the more serious and uncommon events for possible attribution, using such sources of information as mortality figures, dropouts due to adverse events, as well as some special searches, and lastly, overdose experience.

The next slide presents the common adverse events, which you are already aware of, but which we'll go over briefly. These are the common adverse events in the four pooled placebo control studies, 7400, 7450, 7300 and 7350. Using the Fishers exact test, we found that two treatment emerging events were reported at statistically significantly greater rates by the adinazolam SR treated patients than the placebo, namely, drowsiness and uncoordination.

Subsequent to the completion of this slide, sedation was subsumed to drowsiness. Hence, these numbers have increased somewhat to 60 percent of 661 and 42 percent of 384 when you subsume sedation to drowsiness.

What can be concluded from this table unexpectedly is that the common adverse event profile for adinazolam is similar to the marketed benzodiazepine hypnotics.

Next, clinical laboratory data were evaluated, chemistries and hematology, using the standard automated panels, routine urinalysis including the microscopic, vital

signs included weight, vital signs and pulse, ECGs were the standard ECG tracings, 12 lead tracings.

Here you have the strategies used to identify the important events associated with the laboratory chemistries. They are threefold, basically: changes from baseline, the incidence of potentially clinically significant values, and the incidence of dropouts for serum chemistry abnormalities.

Let me focus on number one first, the mean change from baseline compared to placebo, which did reveal a significant decrease in blood uric acid levels in adinazolam treated patients. That is both the SR and CT formulations, compared to placebo.

This is graphically displayed in this next slide. Incidentally, it is important to point out from the onset that mean post-treatment values remained within the normal range for uric acid. Although the (word lost) effect occurred in virtually all of the patients, data for the fixed dose study 7450 is presented here to show you more clearly the dose response with respect to baseline to the blood uric acid levels following treatment with adinazolam SR. The values did return to screened levels at the end of taper visits. Gratifyingly, there were no symptoms or medical events reported in association with this (word lost) effect, which reflected kidney dysfunction.

In addition to change from baseline, we looked at

the incidence of potentially clinically significant values. We looked at these with respect to the various pooled data, and we defined potentially clinically significant by preset criteria for each laboratory parameter. For example, for serum transaminases, it would be three times the upper limit of normal. As you can see here, there are no differences between adinazolam and placebo.

Lastly, we looked at the incidence of dropouts for serum chemistries. There were four. These occurred in the adinazolam CT treated patients. All were a result of elevated serum transaminases and none were drug related.

Hematology analites were assessed in the same way as chemistry analites. None of the differences between adinazolam and placebo were statistically significant; no dropouts. With respect to urinalysis analites, the same procedure was used to assess the data. There were no differences and no dropouts.

Next in our safety analysis, vital signs were examined, using the same approach as I mentioned previously, namely, changes in baseline, incidence of potentially clinically significant values and incidents of dropouts with vital sign abnormalities.

The next slide shows that in the fixed dose study, 7450, at the 90 milligram per day dose of adinazolam SR, there was a statistically significant decrease in systolic

blood pressure and diastolic blood pressure from baseline compared with the placebo treated group, and about six millimeters diminution in the adinazolam SR systolic blood pressure and about four in the adinazolam SR diastolic blood pressure. There were no serious sequelae as a result of this finding.

In addition to the change from baseline, we also looked at the incidence of potentially clinically significant values, using the preset criteria we had established. There are no significant differences between SR and placebo. However, there were differences in the comparisons between the systolic blood pressure in the adinazolam CT treated patients with respect to comparisons to placebo.

Although these numbers are very small, the fact of the matter is that they were statistically significant, when you look at the systolic blood pressure of the adinazolam CT treated patients compared with the placebo, and also the diastolic blood pressure in the adinazolam CT compared with the placebo. There are no differences between the adinazolam CT and the active treatment group.

You recall that we also looked at dropouts. There were two dropouts, one in the adinazolam CT, one on the adinazolam SR treated patients. Both of these occurred as a result of reports of syncope secondary to drops in systemic

arterial pressure. So obviously, you have the question now arising in your mind, were there other episodes of syncope in these studies, and of course,as you can see from this slide, there were. There was a total of 19, actually, all but five occurring in the adinazolam CT treated patients. Of the 16 reports of syncope with adinazolam, ten occurred during the first seven days of treatment at doses of 30 milligrams or less. Importantly, 14 of the 16 patients did continue treatment.

Lastly, we looked at ECG data, using similar strategies for the clinical laboratory and vital sign data. In the adinazolam and CT treated patients, there were no meaningful cardiovascular findings and no dropouts due to ECG abnormalities. ECG data were not collected in patients treated with adinazolam SR.

The next approach we followed to assess the safety profile of adinazolam was to examine the serious and uncommon events in the entire adinazolam database. First, we looked at the crude and adjusted mortality rates. There were 16 deaths distributed as you see here, 13 in the CT, one in the placebo and two in the active control treated groups. Differences in the rates between adinazolam CT and the other treatment groups were significant, whether you looked at the crude rates or adjusted the rates for exposure time, exposure differences between the groups. So as you see

the total of 13 deaths occurring in patients were distributed as follows: ten suicides, one MI, one was due to an automobile accident and one due to a homicide. In the placebo treated group, the death was the result of bronco pneumonia and in the TCA treated group, the two deaths were -- one was a result of viral encephalitis and the second was a result of a pulmonary embolus.

As you call, suicide was the leading cause of death. The following table shows the number of suicides among the groups. There were no reports of deaths in any group other than the CT adinazolam treated group. However, this may not be a fair comparison, in light of the fact that the adinazolam CT studies were in depressed patients, in which there was an active control TCA, probably imipramine, and no placebo control. Hence, comparisons were made between the effective antidepressant TCA and the ineffective antidepressant adinazolam CT.

The next slide compares the suicide attempts in the completed phase two-three studies, and you can see the preponderance of attempts in the CT treated patients.

This particular slide compares the suicides among the treated groups and the completed phase two suicide ideation among the treatment groups in the completed phase two-three studies. There were more patients in the adinazolam CT treated group who had suicidal ideation,

compared to the other treatment groups.

Although the numbers are rather small here, you can see that there were three reports of suicidal ideation in three patients treated with SR. Although the numbers were not statistically significantly different between the SR and the placebo, the rate per one hundred patient exposure years was three times greater than the placebo. I don't know how to interpret that right now. Maybe we can talk about it a little later.

Next we looked at the dropout rates in the SR and CT studies. In the first slide, in the SR studies, the percent dropping out, you can see that 13 percent of the placebo dropped out because of lack of efficacy, compared with five percent of the SR, and seven percent of the adinazolam dropped out because of an adverse event, compared to four percent of placebo.

A similar pattern for adinazolam CT is displayed here. Interestingly, you see here fewer active control treated patients dropping out because of lack of efficacy compared with adinazolam CT, and conversely, more active control treated patients dropping out because of adverse events, compared with the adinazolam CT treated patients.

The common drug related events causing dropout --

DR. HAMER: Excuse me. Could you go back to the previous slide?

DR. KNUDSEN: Yes.

DR. HAMER: Across the bottom, those are pretty high dropout rates. Are they dropouts during the extensions or dropouts during the acute periods of whatever studies they were?

DR. DENAHAN: This is a depression study. These are adinazolam CT patients.

DR. HAMER: I know, but I assume some of those studies were short term and some were long term.

DR. DENAHAN: Yes, that is correct. I cannot exactly tell you how many of these patients were in the long term study.

DR. KNUDSEN: Here you see the common drug related events causing dropouts in the phase two-three completed studies. The incidence rates are rather low. Not unexpectedly, the majority of clinical events were associated with the CNS difficulties.

In addition to dropouts and looking for deaths, we also searched for serious events in the entire database. First we have to provide a regulatory criteria for serious events. This is displayed here. Any event which is fatal, life threatening, permanently disabling or requiring hospitalization, results in congenital anomaly, cancer or an overdose was defined as a serious adverse event.

A tabulation of the number of serious and

potentially serious adverse events is displayed here for the entire phase two-three database. A total of 258 adinazolam treated patients had reports of serious events, the highest being with the adinazolam CT treated patients, fewer in the placebo and about the same number in the active control, compared to the adinazolam CT treated patients.

In the next few slides, I want to discuss some of the serious and potentially serious medical events, the first one being the occurrence of seizures. The occurrence of seizures in the clinical trials is presented here. Nine seizures occurred in the adinazolam CT treated patients. Four of these seizures occurred after drug withdrawal. In three cases, the seizures occurred either at the beginning or during adinazolam taper, and in the other cases, there were extenuating circumstances, for example, alcohol use or a history of seizures.

The duration of the adinazolam use in the nine patients prior to the seizures ranged from ten to 130 days, and the doses were as high as 120 milligrams per day. In addition to looking at seizures, which may occur after withdrawal of adinazolam benzodiazepines in general, another approach used to address the issue of symptoms occurring at the tapering of a benzodiazepine is to look at the symptoms following discontinuation.

This is a definition which you have heard already.

This is the definition that was used by the sponsor for discontinuation emergent symptoms, fairly straightforward. To elicit the DES, a symptoms checklist, which included benzodiazepine withdrawal, abstinence, symptoms and symptoms related to panic disorder was read to the patient. You have seen this table. It is a little bit different because we used five percent rather than ten, so it makes it a little more difficult to read.

Here we have a DES with an incidence of five percent more in the SR treated patients, and reported approximately two times or greater than the placebo treated in the short term phase of the 7450 and 7400. Most frequent DES were neurologic and psychiatric. Sleep disorder was the most frequently reported DES.

The cluster of symptoms presented in this table are fairly typical of those reported events of benzodiazepine withdrawal. For the most part, the symptoms were reported as mild and transient. However, there were three patients who had serious or potentially serious events reported during the discontinuation phase of the studies. One patient had a report of a severe upper respiratory tract infection and the second patient had a report of a suicidal ideation, and a third was hospitalized for depression.

We also wanted to examine the effect of a longer exposure time on discontinuation emergent symptoms. As you

now know, protocol 7400 addressed this issue from the point of view of the extension phase thereof. The DES which elicited this are presented here. Those highlighted events also occurred among the taper-post taper phase of the short term study discussed in the previous slide. From this table, there are more events reported following an extension phase. The events listed in this slide are characteristic of symptom re-emergence and adinazolam withdrawal symptoms typical of benzodiazepines in general. There were no life threatening or serious symptoms observed either during taper discontinuation or the two post taper weeks.

In addition to these DES, other adverse events considered serious or potentially serious were the events mania and hypomania. There was a higher incidence of mania and hypomania during treatment with adinazolam CT than placebo. Approximately half of these cases in CT and the active control occurred during the first week of treatment as opposed to the placebo group, which had an occurrence during the first week of treatment. Thirteen of the adinazolam treated patients dropped out due to mania, and there were no patients who dropped out of the active control treatment group because of mania.

In summary, the adverse events considered potentially important and probably drug related are listed here: seizures, discontinuation emergent symptom, mania,

hypomania, hypourecsemia, drowsiness and incoordination. Incidentally, we also looked at reports of overdose in the entire adinazolam database. There were no cases reported in the adinazolam ST treated patients, and six reported in the adinazolam CT treated patients, with a dose reaching as high as 600 milligrams. The outcome was that they all fully recovered.

There were also three cases of overdose among the 1209 active drug treatment patients. Importantly, there were no reports of deaths, cardiac or respiratory symptoms or significant changes in laboratory analites in those adinazolam treated patients who overdosed.

Our conclusion then. Review of clinical trials database in adinazolam of over 3400 patients revealed no adverse finding that would preclude its use in the treatment of panic disorder. The issue about adjunctive therapy we briefly touched upon in the transparency earlier.

Unless there are further questions, that is all I want to comment on at this point on safety.

DR. TAMMINGA: I have one question. This is in reference to your slide, patient exposure in phase two to three trials and patient exposure years. This would assume no relationship between duration of treatment and the kinds of symptoms that emerged, but there are some symptoms that -- the risk period is after treatment for six months or after

treatment for eight months. What number of patients have been treated with this compound for long periods of times up to a year?

DR. KNUDSEN: Very few. I think slide number four -- the percentage is very small, actually. Here you have the dose range and the duration: 36 weeks and greater, three percent. I know there are more now, because 800 more patient have been added to the database. But as of November 30, three percent have been exposed to relative small amounts at 36 weeks or greater.

DR. TAMMINGA: So there are a hundred patients on which we have nine month exposure data?

DR. KNUDSEN: The long term exposure was briefly mentioned in your document provided by myself, which is rather laborious to get through, I grant you. But the company supplied a more succinct document where they mentioned long term exposure also.

DR. DENAHAN: Most of our patients exposed long term is only up to six months with SR. We have very minimal patients exposed longer than six months. We have a humanitarian extension protocol, 0057, that has about 15 patients in it, of which maybe four went longer than six months.

DR. TAMMINGA: How many patients have been exposed for at least six months and how many patients have been

exposed for at least 12 months?

DR. DENAHAN: Exposure at six months is probably less than a hundred. I don't have the total number, but it is less than a hundred.

DR. TAMMINGA: And exposure to 12 months?

DR. DENAHAN: Very minimal, probably five or six.

DR. LAUGHREN: Could we go back to the slides on suicidality, I think slide 21? I wanted to make sure that these data are fully appreciated. The explanation offered here for why there are ten suicides in the adinazolam CT patients compared to none in the other groups is that these cases came out of depression trials done in Europe that were active controlled, not placebo controlled. I gather the explanation offered is that adinazolam CT is not an effective antidepressant, and therefore it is not unexpected that you would have more severe manifestations of depression in that population compared to patients getting the active comparator.

That is one possible explanation. Another possible explanation is that it is more than just an absence of an active effect, that there is some facilitation. One can't tell, because those cases arose out of active control trials, it is not placebo.

If you flip ahead to the next slide, looking at suicide attempts, it is essentially the same picture, a

crude rate of 0.8 percent for the CT, no difference in the rates for SR and placebo. Of course, the SR and placebo are coming out of trials in patients primarily with anxiety disorder.

But now if you flip to the next slide, here you are looking at suicidal ideation. Here, you begin to see a slight difference in the rate of suicidal ideation for SR compared to placebo, arising out of trials in patients with generalized anxiety and panic disorder. It is not a difference that achieves statistically significance, and obviously it is a very small number of patients. It is a total of three patients on SR and one patient on placebo, but it is a difference. I just wanted to make sure that the committee was aware of that and had a chance to think about that.

DR. CHARNEY: Is this treatment emergent suicide ideation, which means that at baseline they didn't have any?

DR. LAUGHREN: Good question.

DR. CHARNEY: The numbers are too small. They are not realistic. But you have a much higher rate of suicide ideation in depressed patients than --

DR. LAUGHREN: These are not depressed patients. That is the point I'm making here.

DR. CHARNEY: In the active comparator. Two out of 1300 is not reality in terms of the frequency of suicide

ideation in a typical depressed group.

DR. LAUGHREN: Do we know what the counting strategy was here? Maybe the sponsor could respond to that.

DR. DENAHAN: The suicide ideation medical event came out of our regular reporting medical event form. They are usually reported when the event occurs. So these are medical events, actually.

DR. FRANK: So you count them at any point during active treatment?

DR. DENAHAN: That is correct.

DR. FRANK: Then I would argue that Dr. Charney's point is well taken, that to have 1338 depressed patients in whom you only have two that at any point during treatment report suicide ideation is an unusual depressed group.

DR. LAUGHREN: I am assuming, looking at these data, that the rule must have been that these are events that the investigator attributed to drug. That could be the only possible explanation here.

DR. ESCOBAR: Suicide as a treatment emergent symptom.

DR. TAMMINGA: Is this clear amongst the committee, or do we need to ask the company to clarify it more?

DR. DENAHAN: I just want to make a clarification. The medical event is reported as a medical event. From our

perspective, it is independent of causality.

DR. LEBER: If you recall, when we were very concerned about suicidality induced by Prozac, we looked at one particular item that was a change from those with 01 on the HAM-D suicidality at entry, and whether they had an increase, specifically looking for phenomena that changed over the course of the trial. This particular system may not have done it the same way, might have been extremely insensitive.

The problem is, we don't know. Until we can clarify what it means, it probably shouldn't be on the table. I don't think we know what it means.

DR. LAUGHREN: Has the company done an analysis looking at changes in the suicide item on HAM-D?

DR. TAMMINGA: While the company is getting that ready, maybe we could address whatever additional questions you have for Dr. Knudsen.

DR. FYER: Are we going to go back and discuss the discontinuation at all, or would this be the time to --

DR. TAMMINGA: We have just heard the FDA safety presentation, so this would certainly be the time to talk about everything that we have an interest in talking about, about drug safety.

DR. FYER: I have a question about some of the things that Dr. Davidson presented, about discontinuation,

which I had thought would be answered during Dr. Knudsen's presentation. I am having a little difficulty getting a clear idea of what happens when you take patients off of adinazolam with panic disorder, patients who have been responders, not panicking, what it looks like. In the adinazolam data and in some of the studies that have been done with imipramine, there is some sense in the field as to what proportion of the patients will start panicking when, and whether it goes away or not. I don't see any data that shows, like, week one, how many patients are panicking again, and week two, week three, week four, what is actually going on.

DR. HAMER: You mean week one, two, three, four of the taper.

DR. FYER: Of the taper, and then the two post taper weeks. I would like to get some sense of how this drug looks compared to alprazolam and imipramine.

DR. TAMMINGA: I think we ought to ask the company one question at a time. Dr. Knudsen, do you have data to address that?

DR. KNUDSEN: I do not. The article you published on alprazolam addresses many issues which I found not addressed by the present submission, and left me somewhat in an enigma as well. So it is conceivable that the company could answer better than I. I did read your article,

because I thought it was germane to the present situation that we're dealing with, the one by you and Liebowitz. Many of those questions I could not answer with respect to adinazolam, but the company could probably answer much more clearly than I.

DR. DAVIDSON: If this would answer your question, I've got frequency of relapse, rebound, and also frequency of withdrawal at each point along the way during the tapers.

DR. FYER: That is a part. The other part is to see how many people come through fine. At any cross section, there will be a certain percentage of people who are ill again, and there will also be a certain percentage of people who have a sustained okay and are okay at the end.

I think the issue here is that this is complicated stuff to look at. The question I have is, if you are treated with adinazolam, what is the chance that you'll be okay at a certain point post taper, and what is the chance that you will have some difficulty, and then be okay?

DR. DAVIDSON: Let me see if there is anything on that. This does give a sense of the percentage of people at each visit with relapse and rebound, which remains about the same throughout. And then the percentage of people with withdrawal cluster symptoms, which peaks around the end of taper and then diminishes.

DR. FYER: Who are these people?

DR. DAVIDSON: This is the pooled data from the flexible dose study, at the end of long term treatment.

DR. FYER: These are just responders?

DR. DAVIDSON: Yes, these are the responders after long term treatment.

DR. FYER: When you say long term treatment, are you talking about the 26 week data?

DR. DAVIDSON: Yes. Sometime along the way you have the -- it is all the way along.

DR. CHARNEY: What does it mean, the first taper? Your sample size is changing dramatically.

DR. DAVIDSON: I may need to turn to Dr. Denahan or Dr. Jonas to help me with the explanation of that. But first, taper is essentially at week one. Mid-taper would be about week two, and last taper should be at week four, and then first post taper would be one week post taper and then two weeks post taper.

DR. FYER: Are those the same people or different people?

DR. CHARNEY: Why is there more people at mid taper than at first taper?

DR. DENAHAN: First of all, let me answer the question on the Ns, who are those people. These are people who have taper data for that specific period. There were four weeks of taper and two weeks of post taper, so that is

where you get the first taper, mid taper, last taper. Mid taper is about the second or third week, we collapse them, and then the last week is the fourth week of taper. The N are the number of patients who have data for that period.

DR. FYER: So the mid taper group could include the same patient twice?

DR. DENAHAN: The mid taper, correct. It could be patients who had data in week two and week three.

DR. FYER: So the reasons for there not being data on people would be what? They didn't show up for their visit or they dropped out because they were too sick to stay in the taper, or what? Do we know?

DR. DENAHAN: It could be a combination. They just forgot to fill out the form for that specific week, or they just dropped out from the study.

DR. FYER: The reason that people dropped out could be that they got so sick between visits from relapse that they couldn't maintain the taper?

DR. DENAHAN: That is correct, that could be one. But that is not the overall reason.

DR. LAUGHREN: Another piece of information that is important in that overhead is definition of relapse and rebound and withdrawal. It was never clear to me in the earlier presentation what that meant, relapse and rebound in particular.

DR. TAMMINGA: We should have a clarification of that now, because it is basic to the understanding of data.

DR. DAVIDSON: Relapse and rebound was determined on the basis of -- you had the three efficacy measures, the number of panic attacks, which -- if the patient was still 50 percent improved relative to baseline, they were considered to be a responder. If they had a return of score which was less than a 50 percent improvement or a slight increase of up to 50 percent relative to baseline, that was counted as a relapse. Then anything worse than that, worse than a 50 percent increase over baseline was rebound.

I may have an overhead which I can look for on that.

DR. LAUGHREN: And withdrawal again was defined in terms of these indicator symptoms?

DR. DAVIDSON: Withdrawal was the presence of at least three of these indicator symptoms from that list that was derived by the method mentioned. In other words, if the symptoms tended to occur more frequently during the taper or post taper period than they do the baseline.

DR. LAUGHREN: So for the entire sample, you define symptoms that you consider to be possibly representative of withdrawal, and if any one patient had several of those symptoms, they would be judged to be in withdrawal?

DR. DAVIDSON: If they had at least three of those symptoms in any visit, then they were counted as meeting the criteria for having withdrawal cluster symptoms.

DR. LAUGHREN: A question I have about that is how it is related to a clinician's judgment about any particular patient and whether or not that patient is having what any reasonable clinician might consider an important withdrawal event. Maybe that is not something that is easy to do, but it just seems like there might be many patients who have three of those indicator symptoms that may not be experiencing withdrawal, they may be experiencing relapse. Also, I would think there would be a considerable range.

I would be interested in some method that captures the important patients, the patients who have what reasonable clinicians might think would represent important withdrawal, for example, looking at patients who need to be retreated with benzodiazepines. It is not clear to me how one translates these rules into clinical reality.

DR. CHARNEY: It could be done by what Abby was suggesting. At some key points, you would provide data that says how many patients had enough symptoms to merit treatment again, like you were just saying. How many of the patients had panic attack frequency that now were the same as when they started treatment. So I think there are ways that you could make it more clinically relevant.

The other point is, from a clinical point of view, you can tell what is withdrawal and what is relapse by the nature of the symptoms. There are certain benzodiazepine specific withdrawal, neurologic type symptoms that involved altered sensory perception that you just don't get with the illness, and that would clearly put you in the range of a true withdrawal rather than a relapse.

DR. DAVIDSON: We have the withdrawal indicator symptoms, which I can show.

On the left-hand side is the extension treatment, and on the right is the short term fixed dose. You are looking at features which are very similar to withdrawal symptoms as they have been described in other reports of benzodiazepine withdrawal: weight loss, abnormal smell, clouded sensory, constipation, uncoordination, muscular type symptoms, increased appetite, tinnitus, sensory changes, paresthesia. The ones that are asterisked also appeared in the alprazolam withdrawal as well.

DR. SCHOOLER: I wanted to raise an issue which may be naive and based on my lack of direct experience with panic disorder. To me, there seems to be a difference between relapse and rebound. I might be prepared to take relapse as an indictor of efficacy of the drug, in other words, when you stop it, the symptoms return. But I would be more concerned about a symptom state which has you more

severely impaired than you were at the beginning.

My question is, is there a difference between the two? Is that a meaningful distinction, and have you looked at it at all?

DR. DAVIDSON: Well, clinically it is meaningful, because it is a lot more distressing to the patient. I suppose there is perhaps more urgency that we need to do something to help them. It does seem to return back to recovery from the database.

DR. FRANK: I think Dr. Schooler's question raises a point that Dr. Fyre was trying to make earlier, that I think maybe we passed over too quickly. That has to do with the issue of a stable baseline and what is the meaning of any single point of data, any single week observation, how meaningful that is in a disorder that is defined by a certain frequency of panic attacks over a four-week period. There is a certain amount of natural variability in patients who continue to meet criteria for the disorder from week to week.

So when you ask the question of rebound, I think you can only answer that question if you are looking at, is the four-week period after taper is completed worse than the four-week period that was the period that got the patient into the trial in the first place.

DR. FYER: One thing that occurred to me that

maybe we could get about this drug would be, I think when you look at discontinuation data in terms of panic patients, there are some patients who are well for the treatment period and will stay well in terms of panic attacks, and maybe even their global condition, through discontinuation. Then there is a group of patients who will relapse in terms of having recurrent panic, and sometimes they will also have global disability as well. Maybe if we could get how many people went through fine, how many people had problems, and then of the people who had problems, how many people regained their clinical recovery and how many didn't, and what the levels of disability were in those two groups.

Now, one problem with recurrent studies is, there is not enough post taper follow-up, in terms of design issues.

DR. TAMMINGA: Does the company have data like that?

DR. DAVIDSON: We have two overheads here. One of them indicates those who went through withdrawal, or in fact the whole population who went through the taper, how many of them were free of withdrawal at the end of the study. So that gives you the rendering of the percentages.

DR. LEBER: What is evaluable patients in that context?

DR. DAVIDSON: It is patients who completed the

entire tapering and post tapering period.

DR. LEBER: I wanted to ask a question which goes back to the questions that Dr. Laughren posed to the committee as a whole in the very beginning. There is an attempt going on here to make the best we can of data which may not be by design capable of answering many of the questions. Dr. Fyre's suggestion, for example, to compare what is going on in taper to the way patients were four or 26 weeks earlier doesn't look at what happens over the course of time in the march of the individual's life. It seems to me that when we were discussing this in 1989 about Xanax, we talked about parallel discontinuation or re-randomization designs, where the same population of patients who had recovered are reassigned by random process to maybe one or two taper regimens, and somebody else just maintained on their drug. At least there, you have a contemporaneous measure of what would have happened had you not been withdrawn, rather than having the added problem with time. Those kinds of studies simply aren't available for this particular data set.

Even if we enumerate the actual values that are seen in this tapered withdrawal, compared to what? Is it fair to compare it to the way a different set of patients were in the past? I don't know if you can get there from here, and it might be that the committee has to think about

that.

DR. TAMMINGA: I would like to make sure that we have all -- that we are as far as the company thinks we ought to get in answering this question.

DR. DAVIDSON: Let me comment on this overhead, which addresses the question of how severely distressed people were as they experienced either relapse or rebound or withdrawal. The criterion that was taken was the CGI improvement score, the integrated overall measure of improvement or well-being.

What you see is that there were very few people, less than one percent in the fixed dose study and none in the flexible dose study, that had severe distress as reflected by what would be a CGI of I think seven. Moderate distress occurred in about ten percent of the flexible dose and four of the fixed dose, and the majority of the cases where there was any of those withdrawal phenomena were either mild or minimal.

DR. FYER: This addresses discontinuation emergent symptoms as a whole, including panic? Or without disorder related events? In other words, are you including what has been described as relapse here, or just withdrawal?

DR. DAVIDSON: It could be relapse, it could be rebound or it could be withdrawal. It is any of those things.

DR. LAUGHREN: An important question. Did this analysis include those patients who needed to be treated with another benzodiazepine or not?

DR. DAVIDSON: Angie? Did this include people who required treatment with another benzodiazepine?

DR. DENAHAN: Of those patients who required another benzodiazepine, we only included their clean data, non-contaminated data.

DR. TAMMINGA: The implication is that this would include them at their last symptom state before they took the benzodiazepine.

DR. SCHOOLER: So that one could argue that if you're taking any unfavorable discontinuation emergent symptom that one should add in the need to use benzodiazepines to control symptoms. The question is whether these numbers would change any if that were added as a fourth event. So you had relapse, rebound, withdrawal symptoms and use of benzodiazepine.

DR. FRANK: The other issue is that in a protocol where clinicians are allowed to add a compound to treat discontinuation emergent symptoms, it would be unlikely to see severe events, because they are being treated before they get there.

DR. TAMMINGA: My suggestion would be to listen to Dr. Fawcett's data on suicidality, and then continue the

discussion amongst the committee. We need to make sure that we get all the information that we can.

DR. FAWCETT: I am showing you data on emergence worsening and improvement of suicide ideation in three different conditions: placebo, in this case adinazolam CT and in comparators. You can see some differences here between the CT with emergence. This is with depressed patients. Most of the patients had melancholic depression in Europe. You can see a lower incidence of improvement in the same sample.

The next slide should show you SR. Here is both the CT and SR studies, and here are suicide -- that is the CT data you already saw, here is the adinazolam data, comparator data. Down below, you can look at these Fishers exact tests, CT versus placebo, CT versus active comparator, and the SR with no events.

DR. LAUGHREN: Could you go back to the first slide, please? What was your definition of suicidability here?

DR. FAWCETT: This is worsening, probably on item three of the Hamilton, during treatment.

DR. LAUGHREN: Any worsening from baseline? Not a worsening from zero, one, to three or four, but any worsening?

DR. FAWCETT: I think this is a worsening of one

of more. Angie, is that correct?

DR. DENAHAN: This is based on a Beaseley analysis, similar to what was done for alprazolam.

DR. FAWCETT: This was the same one done in the filoxitene analysis.

DR. LEE: What we did is, we followed Beaseley's article, which defines the emergence as -- the patients reported a score of zero one in question number three of the HAM-D total, and then move it to three or four any time during the treatment. Worsening is defined as any increase of a score of one or more, any time during the treatment. And improvement was defined as a decrease of score of one or more at the end of the treatment. Then we just calculated how many patients fall into those three categories for each of the treatment groups.

We have another slide for all the SR studies combined.

DR. TAMMINGA: This slide would show that the adinazolam is significantly worse than placebo at worsening suicidality?

DR. FRANK: I think the overhead projector is cutting off part of the key that might help us to interpret the -- there is a little shadow.

DR. TAMMINGA: So adinazolam is worsening suicidality more than placebo?

DR. LEE: These are depression patients under adinazolam CT.

DR. FAWCETT: Patients are worsening more. We don't know why.

DR. LEBER: I don't understand how that jibes in with the title, which appears to suggest that you combine the compressed tablet with the sustained release.

DR. LEE: That is a continuation slide. The second slide for SR --

DR. FAWCETT: I was looking for that, but it is not there. Oh, there it is.

DR. LEBER: One other point. By combining across studies with different strata of placebo versus comparator agents, you are getting a curve comparison with anything that is probably not interpretable this way. If anything, you should do the comparisons within the study, and then try to get a relative risk on each study, try to combine the relevant risk. I think this is an extremely difficult and unreliable analysis, because you don't know what the differences are. I think it is called Simpson's paradox, but you will be adding these things together in a way that may totally distort what the relative risks are.

DR. LEE: The reason we did it is, we tried to follow the article.

DR. LEBER: But I think there, they had a sense

that they were dealing with patients in a large development program that more or less were entered into trials in a similar fashion. They were assessed in a similar way and they were dealing with similar time points. Even then, that is hazardous, because it is like combining across centers and getting a crude overall risk, which may invert what you want to do.

It is not that I don't praise the attempt. It is just that this data may not be capable of doing some of the things we are trying to push it to do. I don't know if the company would disagree with me on that.

DR. LAUGHREN: What is the pool that is used to construct this slide here?

DR. FAWCETT: These are all the SR studies that have been done, both panic and GAD.

DR. LAUGHREN: So the two panic studies and the two GAD studies?

DR. FAWCETT: Yes, those are pooled studies.

DR. LAUGHREN: And the comparator here is what?

DR. FAWCETT: I imagine it was -- was the 0090 study in this?

DR. DENAHAN: The SR studies combined panic -- they include all the completed and ongoing studies that we have utilized adinazolam. The comparative here most likely included 0090.

DR. FAWCETT: So this would be imipramine.

DR. LEBER: Do you have any idea of what the size of the N these percentages refer to, the entire pool?

DR. DENAHAN: The entire pool for adinazolam is a total of 926 patients.

DR. LEBER: Under SR?

DR. DENAHAN: Under SR.

DR. HAMER: Would it be fair to say this slide is the patients who received adinazolam for panic disorder, and the previous slide -- excuse me, this slide is the panic disorder studies, and the previous slide is the depression studies?

DR. TAMMINGA: They are different drug formulations, too.

DR. HAMER: Right, but the two different drug formulations are coincident with the two different patient populations.

DR. LEBER: But this sample appears to be larger than the one we have been dealing with throughout most of the day, so it must include the generalized anxiety disorder trials.

DR. FAWCETT: Right. It says so right up here.

DR. LEBER: So it is even more admixing of different people admitted under different conditions in a crude pooling. I am just emphasizing, the pooling

undermines the contrast.

DR. HAMER: Although it is not uncommon, both in the FDA safety analysis and what sponsors have done before to look at suicidality lumped together across a bunch of studies, but they are all the same disorder.

DR. LEBER: Not only that, but we have tried to pool across studies of similar duration and similar entry criteria. It would be almost silly to take open studies that go for years or months and combine them with six-week and eight-week trials. We try not to do that, usually.

DR. HAMER: But Dr. Knudsen's analysis was -- in terms of the suicides, it was all suicides, all lumped.

DR. CASPER: In response to Dr. Hamer, I think there is a difference of whether someone has ever been suicidal in the history of her life before, or whether you are talking about -- depression with suicidality is not uncommon in the clinical picture. That is what I think Dr. Leber meant by analyzing homogeneous populations. Then you would really and truly have so-called treatment emergent symptoms.

DR. HAMER: But in this case, these two slides separated the depressed population from the panic population. They didn't combine those two together.

DR. LEBER: But you know as well as I do, if you had studies of an equal size, and some had GAD which had a

lot of comormid depression, and you mixed them together, you could end up having a very unfair comparison, because the weighting system wouldn't represent them proportionately to their numbers.

DR. HAMER: The issue of Simpson's paradox is a very real issue. You could wind up with a completely different indication out of a lumped set of data versus in each of the strata that might have gone into it, which is why you would want to do something like Cochran mental Henzel(?) statistics or present them separately.

DR. CHARNEY: In study 7400, how long in general did it take to get up to 90? This study, the findings are somewhat weaker than 7450, when you look at the group that got -- the fixed dose study.

Let me phrase it again. How long did it take you to get up to the 90 in 7450, and in general, how long did it take to get up to 90 in 7400?

DR. DENAHAN: It took the same time, 18 days.

DR. CHARNEY: So you don't think that would be a difference between the two studies in terms of the duration in general, on a 90 milligram dose? You don't see that as a variable that might account for some difference in efficacy?

DR. DENAHAN: One study is a flexible dose study, so it can go up to 120.

DR. CHARNEY: I understand, but your mean dose was

84. Most patients got up to 90, right?

DR. DENAHAN: Right.

DR. CHARNEY: So I just want to be clear that that wouldn't account -- the time on the top dose would not account for any differences in efficacy.

DR. JONAS: I don't think you could say that. In both of them, you only have 11 days at the top dose, and in the flex dose study you did have the ability to titrate beyond that. So that may be a factor in looking at the titration schemes. In the fixed dose study, if you look at the titration schedules, you began everybody who was on 30 in week one, and then by week two you have the beginning of a bifurcation. It is only by day 17 that you have the true separation in the three doses.

DR. CHARNEY: So you're not biasing against -- 7400 is not biasing against the dose.

DR. JONAS: Right, I wouldn't say that.

DR. CHARNEY: Do you have any data in either 7400 or 7450 that relates severity to outcome? In the study 90, you were trying to make the case that maybe there was a relationship to severity. Is there anything that you have that would be consistent with that assertion in the other two studies?

DR. JONAS: We have esome data for this, so give us a moment and we'll get it for you.

DR. HAMER: I don't know if this is the right place to ask this question. What other studies are going on that we don't know about?

DR. DENAHAN: I have been delegated to answer this question. For the adinazolam SR studies, we have a discontinuation study which is protocol 0101, that looks at the difference of discontinuation with and without placebo. It is a blinded study. That is ongoing right now. We only have a few patients, I think less than 20 patients in this study right now.

DR. HAMER: What do you mean, with and without placebo and that it is a blinded study?

DR. DENAHAN: Let me describe the study. We have a four-week open label study where we allow the patients to respond to 90 milligrams. And the responders after four weeks are then randomized to three arms. One arm has continuation of treatment for four more weeks. This is all blinded. One arm is discontinued with a placebo in it, and the other arm is discontinued without placebo in it. So we are looking at both the psychological and the physiological component of discontinuation.

DR. FRANK: So it is partially blinded.

DR. DENAHAN: It is partially blinded, because the responders would have to discontinue also if they are at the end of four weeks.

DR. ESCOBAR: Following the same line of questioning, I heard Dr. Liss' name quoted at the beginning as someone who is doing some studies in pharmacokinetics of adinazolam. Since one of the problems here is that you have such a small number of minority respondents, I was interested to see if you have any data on how Asians and some other groups do.

DR. FLEISHAKER: The study was designed to look at Asians, African-Americans and Caucasians, looking at differences in pharmacokinetics and pharmacodynamics between those groups. That study is complete in clinic, but we don't have the statistical analysis available on that quite yet.

DR. HAMER: I still want to clear up my question about the discontinuation study. In the case where the subjects are discontinued and they don't get a placebo, who is blind?

DR. DENAHAN: As I said earlier, it is partially blinded.

DR. HAMER: So are the physicians ever blinded? Is this a single blind in the case of two of the arms and no blind in the case of the other arm?

DR. DENAHAN: Two arms are blinded.

DR. HAMER: Single blind or double blind?

DR. DENAHAN: Two arms are double blind, one arm

is single.

DR. TAMMINGA: This is the only ongoing study?

DR. DENAHAN: We have another study that compares -- this is panic disorder, and we look at inter-dose anxiety as well as discontinuation, and the comparator is alprazolam. We have a whole bunch of studies for GAD, generalized anxiety disorder, that we reported to the IND and not reported today as part of this package.

DR. CORRIGAN: Just to respond, Mattock and Carter did an analysis looking at presence of past major depression in the flexible dose study and found for the group with a number of past major depressive episodes a statistically significantly worse outcome. So there was that variable that was looked at in terms of its effects on later treatment outcome.

DR. TAMMINGA: I think we're still waiting for the answer to Dr. Charney's question, aren't we?

DR. CHARNEY: I'm giving them the opportunity, whatever they have.

DR. JONAS: That was the analysis on the (word lost).

DR. TAMMINGA: Am I correct now in suggesting that we have concluded the presentation and the questions from both the FDA presentation and from the Upjohn presentation, and we're ready to begin our deliberations?

I would again read the questions that we are asked to deliberate. Has the sponsor provided evidence for more than one adequate and well-controlled clinical investigation that supports the conclusion that Deracyn is effective for the treatment of panic disorder? Also, has the sponsor provided evidence that Deracyn is safe when used in the treatment of panic disorder?

To some extent, we have been discussing those questions throughout the presentation. It might be correct to say there might be some disagreement, or people might be taking different positions about the answers to these questions.

DR. CHARNEY: Rather than render a position yet, to lay some of the issues out, at least for me, that is, 7450 to me is without a doubt a study that demonstrates efficacy. 0090 to me doesn't. I view it as a negative study rather than a failed study. So to me, it rests on 7400. If one of the criteria is that we have a replicated finding, 7400 to me is mixed, in that you don't get efficacy on panic attacks which I view as critically important in a study that does not have behavioral therapy associated with it. So most of us feel that the drugs initially attack panic attacks, they reduce panic attacks, and then secondarily you get effects on quality of life and phobic anxiety. So a drug that doesn't give you meaningful

significant efficacy on panic attacks, you worry about the true drug effect.

In this study you don't have it on mean change, but you do have it on percent responders. I think that is my dilemma.

DR. ESCOBAR: I agree with Dr. Charney. I view 7450 as a highly positive study, and 90 I interpret as negative.

The problem I have is with 7400. I am leaning towards viewing it as a negative study. It may be unfair, but in the case of panic we wish we had the HAM-D or white box or BPRS, the type of instruments we have for some of the other diagnoses.

The reason why I am leaning towards a negative vote is because of the inconsistency of the findings. Even when we use the six outcome instruments, 7400 only shows an advantage of adinazolam on the SCL phobia scale, which is a minor piece, and also on the avoidance, I believe, but not in the overall phobia scale. I have a hard time on the basis of those six outcome measures, trying to get the right assortment for me to feel comfortable about deciding that study number 7400 is a positive study.

DR. LEBER: This is part of asking the committee a series of questions perhaps to stimulate things. One of the questions Dr. Laughren brought up in the beginning is the

question of duration. Another question is also one speaking to the reprsentativeness of the patient sample, the type of extrapolation one can make to labelling, and not merely a vote on the internal validity of whether a study shows a difference between levels of drug and placebo.

So the broader question for this committee, by way of a charge, is not that you can find one, two or three studies negative or positive, but whether you believe on the evidence that there is a basis to fairly and reasonably conclude that this drug can be marketed for a particular claim in labeling, and safely so. When doing that you have to consider not just internal validity.

One of the questions Tom was getting at, and one we were criticized for by outside sources, is duration of study. You call 7450 positive. I want to emphasize it is a four-week study. It entered patients who were not that depressed. In fact, they made a great effort to exclude depressed patients, and yet we know comorbidity with depression is very common in the panic population. So that also speaks to the external validity of labelling and how this would be used.

I would like to produce discussion on those aspects of this.

DR. FRANK: I think Dr. Fyre and I are probably going to say the same things, although she is the expert on

this disorder. It seems to me that from what I know, what we are talking about is either a chronic or a chronically relapsing disorder. We're asked to answer the question of whether efficacy has been demonstrated in at least two adequate and well-controlled trials. I have a real question about whether a four-week trial is an adequate test of a drug for panic disorder, when what we're evaluating are data at the end of four weeks in a disorder that is defined by a month's duration of symptoms.

So I think there is a kind of -- by definition, the outcome variable is inadequate to the definition of this disorder.

DR. CHARNEY: It is a tricky question, because on one hand, it is chronic without treatment, but on the other hand it can respond very rapidly to treatment. So a drug can show efficacy in as short as a four-week trial, depending on what your key variables are. Panic attacks can respond very quickly to benzodiazepines, we know that. On the other hand, phobias reflect a maladaptive process to panic attacks in most patients, and may require more than four weeks. That is where I think some of the studies suffer, if you're looking at the reduction of phobias the key variable versus the reduction of panic attacks.

DR. FYER: I agree with you, Dr. Charney, about that. But I think there is an additional point about

evaluating panic attacks. These are patients who for a four-week period who supposedly had one attack a week. We treat them for four weeks and we take one cross-sectional period.

My experience with this patient population is that I would not feel comfortable treating a patient -- if a patient came in one isolated week and said they happened not to have a panic attack that week, that they were well from the disorder. I think to approve drugs on the basis of that kind of evaluation is probably not a necessary or appropriate thing at this stage of our knowledge of the disorder. I would feel much more comfortable if you knew that the patient was even partially better, if not panic free over a period of several weeks of time, that we had treated this patient.

In fact, in clinical reality, that is what clinicians do. They don't treat patients at cross sectional -- I would just say as a public health statement about this, the panic consensus conference that was run a few years ago, one of the more interesting outcomes of it was that much of the outcome data -- there is a tendency to under treat these patients and be satisfied with less than effective treatment.

This is a disorder that I feel most patients can become panic free, and yet many clinicians are not aiming

high enough. So I think we need to foster that expectation.

DR. HAMER: Can I ask Dr. Fyre to -- you used the word panic free or cured, I've forgotten which. Can I ask you to extend that further? One week reporting no episodes, that wouldnt' even be sufficient for you to say that there was a remission.

DR. FYER: That can happen for a variety of reasons. That doesn't prove that someone is well.

DR. HAMER: Not even well, let alone in remission.

DR. FYER: Right.

DR. HAMER: It doesn't prove a remission, let alone well.

DR. FYER: I think that if we were in a world that didn't require economics, what I would like is several weeks of people being panic free as well as some of the additional aspects of the disorder.

DR. FRANK: I realize that what we are asked to evaluate here are pharmacologic compounds relative to placebo or other pharmacologic compounds. But I think sometimes it is relevant to look at non-pharmacologic therapies as telling us what the possibilities for remission or recovery are with the disorder. As I understand the data on behavioral therapies of this condition, it is not unreasonable to expect patients to become panic free for sustained periods of time. So I think that speaks to your

question.

DR. HAMER: So in this case, we don't have the data to answer the question, can this medication do something similar. With the four-week study, all we really know is that patients reported being panic free for a week or so.

DR. TAMMINGA: To what extent can you exclude that these patients who come in once a week for ratings and contact and all are receiving no behavioral treatment?

DR. FRANK: I think the placebo response would suggest that they are receiving substantial psychological benefit from the clinical contact. Whether you would call that psychotherapy, it is certainly not like a well-designed exposure therapy, but they are certainly receiving substantial benefit from the clinical management that they are getting. There are marked changes in the placebo groups.

DR. LEBER: I was at a conference recently in which I heard reports that behavioral intervention can have very high and positive success rates. But that always begs the question of, are the patients the same, are the same kind of client going to the psychologist who does behavioral intervention as are rendered in these trials. If that is not the same patient population, it is not a fair comparison or a fair test. To raise that as the standard might be

unfair to those who want to develop pharmacological treatments. That is something that I would like to hear discussed.

DR. FYER: There is a whole area of controversy about which patients drop out or whether there is selective bias, and also about whether you have comparable samples.

DR. LEBER: That is why I wanted to bring this to the fore. We have to make a fair test that doesn't necessarily have to compare itself to other available treatments, except in the sense that you as experts want to be able to conclude from the evidence that this drug will do what its labelling claims it will do, and that the risks of treatment are outweighed by the benefits conferred.

You needed consider how well behavior therapy allegedly does in reaching that. But you have to be convinced on the evidence you have seen adduced from more than one controlled trial that the other things are true. So I'm trying to draw a very sharp distinction about how this is done.

DR. TAMMINGA: The evidence that the committee has seen and heard in detail the FDA's review of is the 7450 and 7400 data. From what I am hearing people say, people have a lot of questions about efficacy based only on those two studies, not even addressing the 0090 study.

DR. HAMER: My position would be that the 0090

study is either a failed study or a negative study. Whichever it is, it is not part of the two adequate and well-controlled studies that would demonstrate efficacy. So to me, I am left with considering either 7450 and 7400. I am left to considering them, wondering whether I as a member of this committee and the committee as a whole haven't gotten into some sort of feeding frenzy, in the sense that once 0090 hit, we all had so many questions that there is a tendency to view everything in a negative light.

Having considered that, I am left to consider 7400 not sufficient for me to say that it has demonstrated efficacy. In a situation where you have a bunch of potential dependent variables, in this case we had five or six of them, and no good way to choose among one of them and demonstrate that one of them is the primary efficacy variable, then you are stuck with doing either a multivariate analysis, which wasn't done, or a bunch of tests on each variable, and hope you get consistent results. If I get consistent results, then I am willing to say we've got five or six variables here and we have demonstrated efficacy most of the time on most of them. But in the case of 7400, I don't think we have sufficiently consistent results for me to say that.

So I would say that 7400 has failed to demonstrate to me in an adequate and well-controlled study that

adinazolam is efficacious in the treatment of this disorder, even leaving out the four weeks issue, of in order to be efficacious in treating this disorder, do we need to demonstrate that panic attacks are reduced in a sustained manner for more than four weeks and not just one week of zero panic attacks.

DR. TAMMINGA: And people would be tending to answer Dr. Laughren's initial question, how important is number of panic attacks, more or less as essential, that demonstration of change in the number of panic attacks is essential for --

DR. HAMER: No. I am a statistician here, I'm not a clinician. But what I hear the clinicians telling me is that that is an important variable. It may not be the only variable, but it is important. The definition of the illness involves multiple weeks -- according to DSM-III-R, multiple weeks with at least one panic attack.

DR. PEACE: I would like to make a comment about two points. One point concerning whether what you see just at a particular week gives you any clue, or whether that is sufficient to claim efficacy.

I don't think the data have been analyzed in the following way, but it would be possible for you to compare the placebo group and the Deracyn group in 7400 as well as in the other studies, in terms of the proportions of

patients who are panic free as an example at week one and at week two and at week four. That would give you some idea of the duration and onset of the effect. As a matter of fact, you could do analyses that typically are kind of done in analgesic studies, where you are looking at time to onset and duration of effect.

I would admit that you are limited in terms of the number of observation points there, but nevertheless, those analyses could be done to address that particular issue.

The other issue is whether one counts the percent of patients who become panic free. It would seem to me that that would be the gold standard, particularly when you view the data in terms of the actual numbers of panic attacks.

Earlier today, there had been some discussion about, maybe the median is more appropriate than the mean. Here is 7400, which shows you the distribution in terms of the number of panic attacks at baseline of the two groups. Quite frankly, as the statistician I would not be satisfied in analyzing the data only looking at means or mean changes, because of the means being so highly influenced by large observations which you see occurring here.

So it would seem to me that in view of this, and also in view of the skewed distributions to the left, that what you might be more interested in is how many patients are actually panic free. What you have noticed in this

study, reproducible in the 7450 study, is about 63 to 65 percent of the patients are panic free at week four, as compared to 38 to 40 percent in the placebo group. If I have a panic attack, I would want to get rid of it, rather than have it reduced by a certain amount.

So I would encourage you to rethink, if you would, the reasonableness of the proportion of patients panic free as being the primary end point for summarizing efficacy in terms of panic attacks rather than means or mean changes.

Now, having said that, earlier this afternoon, there was --

DR. CHARNEY: They were not mean changes. The mean changes were not significant in study 7400.

DR. PEACE: But the percent of patients who were panic free at week four was roughly 62 percent for Deracyn and roughly 38 to 40 percent for the placebo group, a highly significant result.

DR. CHARNEY: That is the percent of patients who had had one week free of panic.

DR. PEACE: We don't really know that.

DR. CHARNEY: But from what I hear -- but we don't know that it is more than one week from your data. From what I hear the clinicians telling me, one week free of panic does not necessarily indicate efficacy.

DR. PEACE: I acknowledged at the outset that

those analyses could be done looking at the proportions of patients in the treatment groups who were free of panic at week one, at week two and at week four to get at that kind of information.

If I could just conclude, at one point this afternoon, the discussion was drifting toward, could you accept this responder analysis for panic attacks, because maybe most of your patients didn't have far to travel. You see that in this case. However, when you analyzed the data in terms of responders, when you adjust for the number of panic attacks at baseline, the significance is maintained.

Thanks, Miss Chairman.

DR. CASPER: I think you fortunately addressed one of the problems we have been having, namely, to have a clear idea about the patient population you have studied, about the severity of the patient population. I think you are beginning to give us these transparencies which tell us that most patients had one or two panic attacks to begin with. So this was a fairly mild population.

DR. TAMMINGA: We have to make an assumption at some time that the company has presented all the data that they want us to consider for this NDA. I think I see enough heads shaking yes. So what we have to consider now is what we have to consider.

DR. CASPER: Exactly. What we have to consider

now is, however, we do not know for how long these patients had the panic attacks, if they only improved for one week. We do not have data on the cause of the illness to say with any certainty that the adinazolam is an effective treatment for the reduction of panic attacks. Even 7400 is not -- you have not persuasively shown that it does reduce panic attacks, except for the mean scores. But even the mean scores were not significant.

DR. LEBER: I wanted to ask Dr. Hamer something. The impression I get out of it is, if you had two four week studies that looked at the outcome variables that were looked at in these two studies, 7450 and 7400, and had they both been robustly positive, you would consider that sufficient to establish the effectiveness of a treatment for panic disorder. Does the committee feel that way, that two four week studies would be good enough?

DR. CHARNEY: I believe when you look at study 7450 you're getting efficacy in weeks other than week four. You can look at page 26 of the company's brochure. While four weeks is at best a bare minimum, I think if you were to design this again you would have at least an eight-week study. But 7450 is so positive, you are getting efficacy across many dimensions of the variable, that the field would agree covers most of the spectrum, that is, panic attacks, phobias, and you got a CGI improvement by week two in the 90

milligram dose.

So you're raising that four weeks, no matter what you find, would be not an adequate trial, I don't think I agree with that, even though I don't think it is an optimal trial by any stretch of the imagination. If we saw findings as we see in 7450 and 7400, I would think this was an approval drug. But we just don't see it in 7400 to the same degree.

So I wouldn't a priori say no way you can show efficacy for such a drug in four weeks. I think you can.

DR. TAMMINGA: I have a question about panic disorders. Are panic disorders characteristically treated for periods of time, or are they characteristically treated chronically? Psychosis and schizophrenia are characteristically treated over a lifetime. Perhaps other kinds of diseases are treated in clusters.

There is another time issue here, too. Not only is the efficacy data of rather short duration, but the whole safety profile -- I found the table that Dr. Knudsen put together, which is on page 20, Table 5.132. It shows the total number of patients treated for any period of time, and there are only 50 patients that have been treated for up to a year, and only ten patients that have been treated for more than a year. That means that the safety profile, let alone the efficacy profile, on these data is defined through

two months. Most all of the patients, out of a total database of about 3,000 patients, most of those patient days are treated for two months. So the amount of safety data that is available for patients treated from two months on is precious little, and wouldn't do anything to define the kind of side effects that could occur after a period of time.

DR. HAMER: Except that we were talking about efficacy. As a non-clinician, I would like to have you clinicians help me know how to feel about efficacy. From what I hear you all saying, is it correct or incorrect that this is an illness that is an episodic variable illness, at least from week to week, that a patient could well have three attacks in one week and zero attacks the next, and two attacks the week after that and five attacks the week after that and so on? Am I correct in that?

DR. FYER: I think one thing to remember is that, compared to certain other variables, like schizophrenia and depression, there is still a relatively small database about these kinds of things about panic disorder. So that is the first thing.

The available evidence, of which there is very little prospective data, suggests that that is the case, that there is an enormous amount of variability over time, both within one patient and among patients as to patterns. On the other hand, I think this company and most companies

have selected a subset of patients who have at least four weeks of a panic attack week, so presumably they have limited that variable to some extent.

I would probably agree with Dr. Charney to some extent, but I wouldn't arbitrarily say you could never demonstrate efficacy in a four week study. On the other hand, I think saying that you're satisfied with efficacy on one week out of four weeks, I wouldn't feel comfortable with. I would prefer at least an eight week study, and moreover, I would like to see the sustained response analysis, which is by the way in the literature, in the alprazolam literature. There was an article by Mike Liebowitz which said how many patients became panic free and sustained that response to the end. That is a very simple thing. It doesn't require a lot of fancy statistics, et cetera. So I would probably come down in the middle someplace.

DR. SCHOOLER: This has been very instructive for me. I've been sitting here, trying to think what I think. The sense that I have is greatly enhanced by Dr. Hamer and Dr. Fyer's exchange at the end here. It seems to me that in a situation where you're talking about a disorder that can wax and wane in this way, one of the questions that you have to consider is, when you have had a period where for at least four weeks there has been at least one panic attack

per week, there are two possibilities. One is that in terms of regression toward the mean, that person is eligible for some panic free weeks. The other is that this is a person who is on a course, which suggests that because they have had four weeks that have had panic experiences, that they are unlikely, unless something happens to intervene, to have a change in that.

So my question then becomes, where did the decision come from in this disorder that a four week trial was a legitimate trial to consider. My assumption would be that the assumption that says a four week trial is right is that when you're on a trajectory, that trajectory is not going to change without an intervention, rather than when you have had four weeks, that means you are eligible to go in the other direction.

I was looking at Dr. Laughren's list of questions, and it seems to me that seems to be the very basic question that isn't addressed in that. Given that the question isn't there, I have to assume that it was considered in the development of this drug in relation between the FDA and the company, that four weeks was a legitimate period of time.

DR. LEBER: Point of personal privilege on this matter. The planning of these studies is not jointly planned with the FDA and the firm. The firm did this on their own, according to their development plans. They take

full responsibility for them. Is that fair, Tom?

DR. LAUGHREN: That's fair. In fact, an added point. Five years ago, we brought Xanax to this committee. Many of the issues that are being discussed today about necessary duration of trials and need to look carefully at discontinuation and so forth, need to figure out what to do with patients once you get a responder, were addressed at that meeting.

DR. SCHOOLER: Were addressed or answered?

DR. LAUGHREN: Were discussed, and proposals were made by the committee about the need to address them in development programs.

DR. TAMMINGA: So it would be fair to say that the company has heard these kinds of discussions before.

DR. SCHOOLER: Then let me ask another question. That is, which of the two hypotheses is the more tenable one in terms of panic disorder? In other words, if you are somebody who has had four weeks during which you have had at least one panic attack per week, are you ripe to come to a situation where you are likely to see weeks in which there are none? Or are you on a trajectory that says, less I do something that is going to cut into this, there is not going to be a change.

It seems to me that that is a really critical question in evaluating whether one swallow makes a summer,

and the no panic experience in that week is a legitimate outcome measure.

DR. CHARNEY: I think we make the risk of making this issue a black and white issue, and it really isn't. I think in most patients that come in with four consecutive weeks of panic, that is going to continue to be a problem.

I understand the point you're making, but I think in general clinical experience, they come in, they are sick, they need treatment, they are phobic and so forth. I think you can assume that in general, the problem will continue. On the other hand, there is a pretty high placebo response rate, 30 to 40 percent. So it does go down, but these patients do respond to reassurance.

So while some patients do get better, that is why you need a placebo. We do have a placebo in this study, and there is a very big difference in 7450 between placebo and active drug.

The second point I would like to make is that we do now lots of experience now with benzodiazepines in this disorder. We generally know that once they work, they continue to work, that tolerance is not a problem for the vast majority of patients. So we know a lot about this class of compound in panic. There have been millions of patients treated with it. If this was a novel class, then I would see the four week issue as being a much greater issue

than it currently is.

On the other hand, I generally agree with everybody else's comments. If this was an eight week study, I would feel a lot more comfortable with assessing the efficacy.

DR. ESCOBAR: From the perspective of the clinician who treats many of his patients, if I look at the 7450 study, the number of responders that had zero panic attacks is about 45 percent of those on placebo and 59 percent of those on adinazolam. I don't think I would treat them with adinazolam. Given the list of problems that were delineated in terms of discontinuation and rebound and so on, and given the availability of some non-pharmacologic therapies. So even the 7450 data in many ways is not as practically significant as it looks.

DR. CASPER: I would like to support Dr. Escobar's comment. Aren't we perhaps seeing in these studies almost the cause of the illness? Because there is such a high placebo response in these patients who have one panic attack per week, let us assume this were to be a highly effective drug, could we even with the most effective drug which would reduce panic attacks by a hundred percent compared to a 46 percent placebo response, could we without looking at relapse and rebound studies which were to be followed later, which would show us the re-emergence of not just one panic

attack per week, but worsening, but without longer relapse and rebound studies, could we say this drug is effective in this kind of a population.

I am still worried that this population we are seeing here and the number of panic attacks might not be a sick enough population to show you if you have a mildly to moderately effective drug.

My second question is, would any other benzodiazepine aside from alprazolam, show pretty much the same effects as your benzodiazepine is showing? Are we seeing a general benzodiazepine effect? Are we seeing in any way a specific anti-panic effect?

DR. TAMMINGA: I would have a comment to make about the mean response data. I am assuming that -- at least, I would think that there are some patients that might be highly responsive to behavioral treatments and other patients that are not highly responsive. So that at some times there would be what one would need to use a drug. Looking at the mean response doesn't give you an idea of those patients that might in some special way need a drug and be unresponsive to behavioral treatment.

DR. CHARNEY: To respond to Dr. Casper's point, I think the available data is that all benzodiazepines are anti-panic, if you go into the right drug. This drug to me is behaving like a benzodiazepine. If you look at the

effects on anticipatory anxiety, they are very strong. That tends to happen before you get a full anti-panic effect.

So I think this looks like a benzodiazepine. Probably, if they kicked the dose up higher and looked at that higher dose for a longer period of time, this would look exactly like clonopin, lorezipam, xanax and so forth. There is nothing unique about this compound.

DR. LEBER: I have a question, again trying to push you more towards external validity, which relates to the first two trials, and fairly tough exclusion criteria, giving you a pure panic population. The problem always is robustness of a drug program's evaluation. How many, for how long?

To use Carl Peace's example of pain development studies, we don't just look at one pain model; we look at several before we approve a product, because we are usually interested to see how it performs in dental pain, thoracic surgery pain and the like.

Part of the question that is important for us to understand, particularly since we think comorbidity with depression is so common, is how do you weight study 90? The reason we brought it to you, the reason we were so concerned about it being a negative rather than a failed study was, it may speak to the issue of how well this product does in the presence of depression. One of the reasons the firm was

offering for study 90 failing was that the patient population was depressed. However, if that is how the drug is going to be marketed and used, that raises additional questions.

So I would like to hear how you evaluate the studies that don't come out. This isn't a simple, count, find two and quit. It is to look across the entire set of studies in drug development and factor them all together. How do you read study 90?

DR. TAMMINGA: Some of that would depend on what the relative prevalence is of panic only disorder patients and panic plus depression and comorbidity patients.

DR. FYER: I think in the ECA, and I think there is some recent unpublished examples from clinical samples as well, if you look for people who only have panic disorder with or without agoraphobia and have nothing else, it is about 20 percent of that population. So that is a rare thing, and it looks somewhat different. I think at least 50 to 74 percent of patients have major depression, and some people think even more, over the course of lifetime.

So I think Dr. Leber's point is well taken in that sense. I think my personal opinion about it would not be that a drug shouldn't be considered effective if it doesn't work with depression, but rather that that needs to be clearly delineated, in the same way that co-effectiveness

with social phobia and other kinds of things ought to be clearly delineated.

DR. TAMMINGA: There certainly doesn't seem to be any evidence from the data that we saw today that this is an effective anti-panic disorder in patients comorbid for depression.

DR. CHARNEY: I think the data is generally that patients with comorbid depression do not respond as well to drug treatment or cognitive behavioral treatment in general, so it tends to be a more treatment refractory group. But I do take study 90 to heart, in that it may suggest that the relative potency of adinazolam is weaker than a drug like imipramine or perhaps MAO inhibitors.

DR. SCHOOLER: It seems to me that one of the things that is giving us difficulty is that the clinical trial base that we are being asked to evaluate is so very limited. In other words, we have got two studies which are in pure panic and about one of them, there is some question. Then we've got one study that looked at a population that was comorbid for depression. The question is whether we're talking about either a failed trial or a negative study.

The fact is, there are very few additional data to fall back upon that can augment what we think. There ain't nothing else there. The sense from the question that Dr. Hamer asked about, so what else is going on, is that there

weren't a lot more studies that are down the line, that are going to augment these things. It is not that there are longer term trials that are going to be available in a year or so, or that there is a much richer database that is going to be coming along. I think that is reflected in your comment, Dr. Tamminga, that there is very little long term safety data.

One other question that I would like to raise is, my sense is that the responder extension is a study which apparently addresses longer term efficacy, but that is a study that we have chosen to dismiss. Am I correct about that? That is the general consensus of the group, that that doesn't enter into consideration of effectiveness.

DR. FRANK: I think all that that extension study can tell us is in what proportion of patients who responded to each of the two treatments, that is, active compound and placebo, maintain their response. It can't tell us anything about the relative efficacy of the active compound versus the placebo.

DR. FYER: I want to respond to Dr. Leber's statement about 0090. In thinking about it, I think I also consider it a negative study rather than a failed study, because of the fact that so few of the adinazolam treated patients became panic free. And imipramine, even at what is now considered a relatively low dose, 150, was quite

effective, even better than it is in many of the published studies that are a considered demonstration of efficacy.

I think that even more than the four week raises some questions in my mind.

DR. CASPER: I would like to respond to Dr. Schooler about the response study, and emphasize your point. In both groups, the response study tells us a lot about the fantastic placebo response, because the placebo group maintained their gains through four weeks of placebo, and it was about the same proportion as the adinazolam proportion.

So in that sense, I think the response study does tell us something, namely, it tells us something about what Dr. Fyer has described, that there is a strong response to behavioral intervention, support, interest and reassurance in a group which might not be having a severe intensity to panic attacks. So it does tell us something.

DR. LAUGHREN: There has been a lot of discussion surrounding deficiencies in this program. One of the things that I would like to see come out of this meeting -- obviously it is not a workshop on developing drugs for panic disorder, but it would be nice for some conclusions about what ought to be in a good panic disorder development program to offer to companies who are interested in developing drugs for this disorder, before you vote and we finish up.

I'm getting bits and pieces from various people about what you think might need to be in there. Carol, you mentioned a lot more long term data. There has been some discussion of the need to study the drug in populations other than pure panic disorder populations. There has been some discussion of the need to do longer term studies. How long, and what kinds of designs to look at relapse prevention, or to look at issues related to discontinuation emergent symptoms. Are there some obvious strategies that companies ought to be using, and that we ought to be advising companies to use in developing these drugs.

DR. TAMMINGA: I guess if you ask a group of experts, they don't have to pay the bill for designing studies, but maybe we could respond, keeping in mind that as citizens, we all eventually pay the bill, anyway.

DR. FRANK: I was going to begin my comments taking economic reality into consideration. I think at a minimum, what I would like to see is something on the order of a 12-week trial with a blinded discontinuation that is variable, so that some patients are taken off at one point and other patients are taken off at another point, and both patients and doctors are blind to when the discontinuation is actually occurring. It seems to me that there is in this population a lot of sensitivity to expectations. I don't know how else to put that.

So I think a longer trial, in the best of all possible worlds with no constraints on economics, I would say four months, six months. But let's say three months, and then with probably another two months added in, where patients are taken off the compound at different points in that time, and everyone is blind to when patients are coming off. And enough patients in each of the cells.

DR. TAMMINGA: Give us an idea of what enough patients is, in a population like panic disorder, where you have the kind of diagnostic makeup that we have already discussed.

DR. HAMER: That is a question for the sponsor's statisticians, who have access to the data that they need in order to do the power calculations that they need to do when they design the studies. You can't just in the abstract say 150 patients is enough. There is a bunch of data that needs to go into making that decision.

DR. FRANK: I think that is one other issue I would add to this ideal design. I'm not sure I know how to solve this problem, but I think there is a real problem with this disorder. There are three component parts to the disorder. There is the panic attack part, there is the anticipatory anxiety part, and I would need to think through carefully, and I couldn't do it off the top of my head, how I would want to see those things all taken into account

simultaneously in some kind of outcome variable that is both clinically relevant and combinatorial.

DR. HAMER: This is not the only psychiatric illness that has several component features. In many of those other illnesses, people have managed to construct scales that address the different pieces of it. Obsessive compulsive disorder is an obvious one.

But the other thing is that the sponsor does not have to come here and attempt to claim that it has a drug that addresses panic disorder. It could come here and claim that it has a drug that addresses phobic anxiety in the context of patients with panic disorder. It could come here attempting to get efficacy for -- no? Am I wrong?

DR. LEBER: Just to answer as a point of information, anyone can claim anything. But you realize there are constraints about what we would describe in the past as pseudospecificity. What happens if someone came here and made a claim for anxiety in New Jersey housewives, which is one of my favorite examples of the genre.

The idea is, you have to really believe that the effect is in some way linked beyond merely chance to the claim you are making. The trouble is that something like anxiety is so pervasive that you really do want to get people to deal with entities that are recognized sui generis as being a phenomenon in their own right. If you start

piecing it out and saying anxiety in cardiovascular patients, anxiety in brain surgery patients, et cetera, you end up with an elaboration of possible claims. We have tried to avoid that as a matter of policy. That doesn't mean that they couldn't succeed if they had a committee that agreed that it was unique. But I think the goal here was, they came forward with the aim of making a claim for the treatment of panic disorder. They might take less now, I don't know. I haven't heard the vote yet.

DR. CHARNEY: I generally would agree with the type of design articulated by Dr. Frank, although I probably wouldn't make it any longer. I think we should await the findings of the multi-center study sponsored by the NIMH, which is comparing cognitive behavioral therapy to medication and the combination, because it may be unethical to continue a drug-only treatment beyond several months, if it is found, for example, there is a strong benefit to combining therapies.

So I think that we want to have a duration that would allow us to definitively evaluate effects on panic attacks, which I view as key, because we don't have a drug that is anti-phobic but not anti-panic. So you have to have enough time to show anti-panic efficacy and enough time to show that that effect lasts. I think a 12-week design is adequate.

DR. TAMMINGA: Minimum, from your point of view?

DR. CHARNEY: I would say that's about right. I wouldn't go necessarily much further, because we are withholding therapy that has been shown to be effective, that is, cognitive behavioral therapy. So I would await the results of that trial before maybe advocating maybe a longer than 12-week trial. But the withdrawal issue is quite important.

With regard to your question on safety, given that the standard treatment is generally six to nine months of drug treatment with full reduction in phobias and having a normal lifestyle, you need that kind of duration of treatment in your safety armamentarium, with any new drug. So you have to combine that extension of treatment to the four months.

DR. SCHOOLER: It seems to me that the design that Dr. Frank proposed, which includes a randomized discontinuation at unknown points from the point of the patient and the treating clinician, is a design which turns out to be a relatively economical one. It would mean that I think you could go with a somewhat shorter minimal period of treatment exposure before you began the phased-in withdrawal.

In other words, if your general feeling is that 12 weeks is the length of trial that you would like to see in

order to see optimal efficacy, it would be desirable to start the discontinuation phase before that 12-week period, because what that would help you learn is whether indeed the 12 weeks is the right length. So you would have some people who were discontinued at a period that was earlier than the optimal length of time to show efficacy, in order to determine whether premature discontinuation leads you to a higher rate of relapse than does discontinuation that takes place after the point that you think is the optimal stage.

I don't know what that does to the statisticians or the data analysts, possibly give them fits. But the fact is, it seems as though that might be a more economical design.

One thing that leads me to think that periods of trial longer than four weeks would be very desirable is the fact that within the four week trials, you can't start to pick apart either dosage or placebo in terms of dropout rate. I would like to see a trial that went long enough so that that very important empirical variable was starting to tease apart the groups, so that you had a higher placebo dropout rate. You obviously don't want to get to the point where it is a disaster. But here, you cannot tell the groups apart by looking at that 88 to 87 percent. That is a remarkable similarity.

So I would think that you would want to go to a

trial where you were starting to see that difference, and before the point that you were getting too high in that. So to me, the 12-week would feel like an outside number, in that that might be the kind of length of time where you would start to see it. And I would like to see the discontinuation design as a very important part of the package.

Another question that I think is difficult to work at is the issue that was described in the study that is ongoing at the company now, which is both placebo controlled and open discontinuation. That is a very important kind of issue, but it is a very tricky one in terms of design. But the question is whether you need both placebo control discontinuation and discontinuation where patients know they are no longer receiving the treatment.

DR. FRANK: I think the data we saw today speak to the issue of what happens when patients know that they are being discontinued. If you look at the treatment discontinuation emergent symptoms in the placebo patient, they were quite substantial. I think they do reflect the extent to which this patient population is sensitive to expectations. That is part of the definition of the disorder. These are patients who are sensitive to expectations about things. They expect to have a panic attack, and they worry about it. They expect to be taken

off the drug, and they develop symptoms, even though it was a placebo.

DR. TAMMINGA: There is a big difference between what the committee is talking about as adequate requirements for demonstrating efficacy of a drug in panic in the data that we have seen today.

DR. FYER: In addition to agreeing with Dr. Charney and Dr. Frank and Dr. Schooler, I want to bring up two other issues. One is, I think the study Dennis alluded and many other studies now have manuals for a psychopharm approach to panic. I think many years ago Dr. Fawcett wrote a wonderful one.

In terms of controlling for sensitivity and susceptibility, I think it would be useful if trials that came through for indications did use some psychopharm management manual in order for us to be sure. I think the placebo response rate is probably quite sensitive to that, and that might tend to create some uniformity.

The other thing is, Dr. Frank alluded to the issue of non-panic outcome measures. I think there is a growing feeling among people who treat panic disorder that these things may have an importance in terms of long-term course. I think it would be very useful to have the FDA encourage inclusion of more sophisticated quality of life and what in the behavioral therapy field is called high in-state

functioning measures as part of a trial.

The final thing is, I have a lot of discomfort with these mean change scores in terms of panic attack frequency because of the variability in patients. I think that it will be more constructive to try to encourage people to have percent of patients panic free for a duration of time. I think we saw a good example of the confusion mean change scores generated also in the beginning of this meeting.

DR. CASPER: If we give ourselves a chance to learn from having sat and discussed the drug here today, I think Dr. Laughren presented us with a nice work sheet. For instance, one of the issues we have not discussed much but we have discussed is the dosage issue. I think one clear message from these data is that probably, the 90 milligram dose, most patients only got 90 milligrams for 11 days in the study, might be on the low end. If this were to be a specific drug for panic disorder, you might want to go to a higher range of 120 milligram for the next study, in order to explore the full range of the dose.

Another question which we have raised and which has not gotten the attention it should in panic disorder is Dr. Wiseman's data on suicidality and completed suicides in panic disorder. I think we learn more and more about the long-term cause of panic disorder and the high association

with suicides. I think that also needs to be taken into account in the rating forms, both retrospectively rating patients, but also rating patients during treatment and prospectively, in relation to whether this drug does induce suicide.

I don't want to bring up this issue, and I don't think we have any evidence for it. Indeed, we might see actually not the drug's effect, but we might see the high association between suicide and panic disorder in this population which the drug might potentiate. But I think this needs to be taken into account in a new study.

DR. ESCOBAR: Just to agree with the idea of the design that has been suggested here, to remind the committee that there needs to be a lot of work done. On the basis of our ECA data, for instance, we were unable to separate anxiety from the present syndromes in the thousands of cases in the ECA study. Even though there are discrepancies about this, there are serious questions about diagnosis, depending on the number of elements we include in the formulation.

Also, I think we need to look a little bit into some kind of instrumental development, something like the equivalent of the white box or the Hamilton depression scale, something that could merge some of the six key variables into something that we could use as a total score or something.

DR. TAMMINGA: I have a question for the committee. Is the committee saying that drug companies shouldn't bother developing drugs for panic, that there are good enough behavioral treatments already, and concentrate on something else?

DR. FRANK: This isn't my area, and I feel that that is appropriately addressed by Dr. Fyer. But I think the first study that might even begin to address that question is the multi-centered trial that is being conducted right now, and we won't know what the answers are --

DR. TAMMINGA: But are you as a clinician who treats panic disorder interested in drug companies working on drugs to treat panic disorder?

DR. FYER: At the risk of being mowed down, I think I am less convinced of the efficacy of cognitive behavioral treatment and its equivalency to pharmacologics than many other people. I think it is an open question. I have seen patients that get better on pharmacology; I have seen a lot more that get better with panic. My guess is that it is some combined form, particularly in long term. That is why I said I was interested in this idea of other than panic variables being added to assessments.

I think the real problem with these patients is, can we get them better for over the course of their life, and what can we do for that. I think it is probably going

to end up being some combined thing. I know this sounds a little trite, but as Dennis said, we have to wait for the multi-center study.

DR. TAMMINGA: So we are interested in encouraging Upjohn to move ahead with developing drugs for panic disorder, but this particular drug might be premature?

DR. CHARNEY: That may be true. I hope we don't come away with the impression that we're saying that new drugs aren't needed for panic, because I think they are. There are many open questions with cognitive behavioral treatment, some of which we'll probably never be able to solve. Many patients refuse to go into trials that only offer cognitive behavioral therapy or have that as an important arm. So there is a role for medications and there is a role for newer, more effective, safer ones.

DR. ESCOBAR: But also, we would hope to see something new. In the days when we had one morphinothiasine, we begin to wonder here, one more benzodiazepine. So I agree, we need more drugs. But I would like more creativity in that process.

DR. TAMMINGA: Maybe I could focus people by way of making a specific -- drawing this discussion to a conclusion. We do have a question in front of us. I think we have addressed rather broadly more issues that have been raised than just the simple question. But do we conclude

that Deracyn is effective for the treatment of panic disorder, or that we have not yet seen the data to support that? We could either take a vote, or we could go around and make a statement, because some people might be interested in saying more than just raising our hands. Does anybody want to start with giving their conclusion?

DR. HAMER: I'll start. I have not seen evidence for more than one adequate and well-controlled clinical investigation that supports the conclusion that Deracyn is effective for the treatment of panic disorder.

DR. TAMMINGA: Do people disagree with this position, or is this more or less the committee's conclusion?

DR. ESCOBAR: I don't think I would disagree with that assessment.

DR. FYER: I would agree with Dr. Hamer also, but I would just like to reiterate that there is a really strong need for more effective medications for panic. I think I probably disagree with the idea that -- I would encourage the company to try to develop benzodiazepines that are effective, because I think as we have seen with xanax, they do have a definite role in treating this patient population. So I would just add that.

DR. TAMMINGA: You would still vote in the negative and say that perhaps this is just a premature data

set?

DR. FYER: I concur that we haven't seen evidence for more than one effective trial, but I was a little concerned by your statement that maybe the committee was saying that medications were not worthwhile to develop for panic disorder, or even the idea that benzodiazepines are old hat or not of value, because I think that there are a group of patients in this patient population for whom the low side effect profile for benzodiazepines is very useful in rapid onset of action. I think it is important to encourage companies to develop such drugs, because they play a role. It is that in this case, we haven't seen demonstrated efficacy for more than one trial.

DR. FRANK: I think as the psychotherapy researcher in the group, I would underscore that strongly. I think there are two issues that Dr. Fyer alluded to. One is the rapid onset of action of benzodiazepines, which is very important with this patient population.

The other is that not every patient who has panic disorder is willing to do the work necessary to achieve a response. Even if the behavioral treatments were a hundred percent effective, we would still have the problems of those patients who are too ill to engage in the treatment to begin with, or too busy or too whatever, too lazy to do the hard work that is necessary to achieve a response in

psychotherapy.

So I think we need a broader spectrum of available treatments, and having a treatment that does not carry with it a big side effect burden and does have a rapid onset of action is something we would give our right arm for in depression treatment studies.

DR. TAMMINGA: Those of us who are smiling might only hope that we fit in the too busy group. I must admit by way of my own opinion that I was impressed with the robustness of response in the 7450 trial, and wondering what I thought about the 700 trial. But based on the opinion of the clinicians that the actual response of the panic episodes is very important, I would probably find myself suggesting that maybe these data are premature either by duration of treatment or perhaps dose.

On the other hand, calling attention to the relative robustness of the 7450 trial.

DR. SCHOOLER: I would agree that the data are not sufficient to support efficacy. But I would like to comment that what I think that reflects, if you linger particularly on number of panic attacks, what that reflects is the very strong placebo response in study 7400. If you look at 7450, that is not as strong. If you just look at the lines -- and I know we're always being cautioned that you can't combine lines across studies, the fact of the matter is that if the

placebo response in 7400 had been like it was in 7450, I think we would be looking at something quite different. Is that not so?

DR. FYER: I don't think so, because the mean panics in the 7400 at the end are still over two, while in the 90 group in 7450, it is under one.

DR. SCHOOLER: What I am looking at are the slides that Dr. Lee had presented, which are changes from baseline rather than mean numbers.

DR. FYER: I think changes from baseline are difficult.

DR. SCHOOLER: Right, but the fact of the matter is that that is what we end up with if you look at the 7450.

DR. FYER: In 7400, there are over 50 percent of patients panic free, and the mean number of panics per week at the end in the 90 milligram group is the low one. That looks like a reasonably effective panic drug. In 7400, it is still over two panic attacks a week. It is hard to feel that those people are well.

DR. SCHOOLER: But the fact of the matter is that it is very similar to the placebo response in 7400. It looks very much like the placebo response. I'm looking at Dr. Lee's slides, and the slides that I would be looking at are the ones on page nine, which was for 7450, and then the one on page 17, which was for 7400.

I guess what I'm saying is that the question is the sensitivity of the study in 7400, the degree to which that was adequately sensitive. So I would be certainly encouraging that 7450, it seems to me, suggests that it is possible to design a study perhaps by carrying it longer, perhaps with some other strategies, that is going to provide the kind of evidence that would suggest that this drug is effective.

DR. CHARNEY: I go along with the group. I would also add that I fully expect that if they had a longer study with the dose being kept at the higher level longer, that this drug would look just like alprazolam.

In terms of advice to the industry, I'm not anxious for another benzodiazepine. We have many on the market. I am only anxious to have a drug that interacts with that receptor if it has some side effect benefit. That is, it produces less sedation, less withdrawal and so forth. It is not clear that this drug does that, however.

DR. CASPER: I don't particularly like the comparison to the pain studies. I think panic disorder is a very distinct and intensely distressing experience, and is a psychophysiological response. So in this sense, I would like to add to Dr. Frank's list those who are perhaps not even capable, persisting and looking and working with psychological means, to reduce the intensity of the anxiety

or panic attacks.

So I think definitely, we would benefit from medication for panic attacks. But I think that the question we are asked is fairly easy: has the company shown in more than one trial convincingly that this is a drug which specifically reduces panic attacks. I think I would say no. I concur with the rest of the committee.

DR. TAMMINGA: Let's just have a simple show of hands then about a vote on the conclusion that Deracyn is effective for the treatment of panic disorder. Those of us who would say yes, raise your hand. Those of us who would say no, please raise your hand.

DR. BERNSTEIN: The record shows eight, no.

DR. TAMMINGA: Although that is probably a disappointing answer, has the sponsor provided evidence that Deracyn is safe when used in the treatment of panic disorder.

DR. LEBER: May I suggest you defer that? You can't really consider safety except in the presence of knowledge of effectiveness.

DR. TAMMINGA: What I would actually say about the safety profile that has been presented is that these data that would contribute to what Dr. Frank said about an ideal study is that certainly, drugs are going to be used in the treatment of any condition standardly for six to nine months

ought to have extended safety data.

DR. SCHOOLER: I certainly concur. I would also like to add that it is particularly important to look at diverse populations. There was an indication somewhere early on this morning that there were some differences for African-Americans. I forget what that was in, but the fact is that that was based on an extraordinarily small number of cases. I think that something that does need to be addressed in the future.

DR. TAMMINGA: Does anybody else have any additional comments? No.

DR. BERNSTEIN: I just want to remind everybody, we are back here tomorrow at 8:30 promptly, please.

(The meeting was adjourned at 4:57 p.m., to reconvene Tuesday, April 26, 1994 at 8:30 a.m.)