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CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

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Committee Members Present:

Sid Gilman, M.D., Chairman
Claudia H. Kawas, M.D.
Richard D. Penn, M.D.
Gerald Van Belle, Ph.D.
James C. Grotta, M.D.
Ella P. Lacey, Ph.D., Consumer Representative
LaRoy P. Penix, M.D.

Sandra Titus, Ph.D., Executive Secretary

Oncology Consultants:

Sandra Swain, M.D.
Bill Dahut, M.D.

MS Consultants:

Jerry Wolinsky, M.D.
Howard Weiner, M.D.

Neurology Consultants:

Richard Lipton, M.D.
Michael Grundman, M.D., M.P.H.

FDA Staff:

Russell Katz, M.D.
Gerald Boehm, M.D., M.P.H.
Robert Temple, M.D.

C O N T E N T S

P R O C E E D I N G S

DR. GILMAN: Good morning. My name is Sid Gilman, and I am the chair of this committee.

I would like to go around the table and have people introduce themselves, and would the FDA also introduce any other members of the Department who are here that you would like to recognize.

Let's start with Dr. Katz.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products.

DR. BOEHM: Gerry Boehm, Medical Safety Reviewer, Division of Neuropharmacological Drug Products.

DR. GROTTA: Jim Grotta. I am a neurologist at the University of Texas in Houston.

DR. LIPTON: Richard Lipton. I am a neurologist/epidemiologist at Albert Einstein and Innovative Medical Research.

DR. PENIX: LaRoy Penix. I am a neurologist at Moorehouse School of Medicine.

DR. TITUS: Sandy Titus. I am the Executive Secretary for this committee.

DR. GILMAN: And I am a neurologist at the University of Michigan Medical Center.

DR. KAWAS: Claudia Kawas. I am a neurologist at Johns Hopkins School of Medicine.

DR. WOLINSKY: Jerry Wolinsky. I am a neurologist at University of Texas-Houston.

DR. VAN BELLE: Gerald Van Belle. I am biostatistician at the University of Washington in Seattle.

DR. PENN: Richard Penn. I am a neurosurgeon at Mount Sinai Hospital in New York.

DR. LACEY: I am Ella Lacey, Professor Emeritus, Souther Illinois University at Carbondale. I am a consumer representative.

DR. SWAIN: Sandra Swain, medical oncologist from the National Cancer Institute

DR. GRUNDMAN: Michael Grundman, neurologist, University of California, San Diego.

DR. DAHUT: Bill Dahut, a medical oncologist from the Medicine Branch of the National Cancer Institute.

DR. GILMAN: Would the sponsor like to introduce any of your team?

DR. HAYES: I am going to do that in my introductory talk.

DR. GILMAN: That's just fine. You are perfectly free to do that.

Let me just make a few opening remarks. It is a pleasure to see you all here and to welcome the new members of the panel and the consultants to the panel.

We will be discussing NDA 21-120, Novantrone,

Immunex proposal for the treatment of multiple sclerosis.

In the course of your presentations, I ask both the FDA and the sponsor to present your material in any way you would like, but please, let us ask you questions along the way. As you have seen in Dr. Katz' narrative, a number of issues have been raised, and we will want to have you address some of those issues, so please answer immediately if you possibly can--respond to the question' don't put it off. It is much more helpful if you will do that.

And for the panel, please signal to me that you wish to ask a question or make a comment so that we can have an orderly meeting.

With that, I will introduce Sandra Titus, who will read the Conflict of Interest Statement.

DR. TITUS: The following announcement address the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

We would, however, like to note that one of our consultants has had an interest related to Novantrone that

we believe should be disclosed. FDA believes that it is important to acknowledge the participant's involvement so that her participation can be objectively evaluated.

Dr. Sandra Swain previously participated as a principal investigator on a study of Novantrone for use in the treatment of breast cancer.

With respect to FDA's invited guests, Dr. Howard Weiner and Dr. Jerry Wolinsky have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Weiner would like to disclose that he is a consultant to Teva/Marion on Copaxone. Further, Dr. Weiner's employer, Brigham and Women's Hospital's Center for Neurological Diseases, will be participating in a trial of Copaxone.

Dr. Wolinsky would like to disclose that he served as a consultant to Immunex for two years. In addition, he is the principal investigator on a trial sponsored by Teva/Marion.

In the event 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.

That ends the formal announcement. Dr. Gilman is going to informally respond to a statement that has been made to him.

DR. GILMAN: I'd like to inform the sponsor that I consulted with Biogen Company when they were preparing their presentation for the Food and Drug Administration approximately 8 years ago. My consultation was after the trials had been completed, and they wanted some help in determining how they would present their material to the Food and Drug Administration. I have had no contact with them since that time.

All right. Are there any other comments about this?

[No response.]

DR. GILMAN: If not, we'll ask Dr. Katz to make his presentation.

DR. KATZ: Thank you, Dr. Gilman.

I'd like to welcome the committee back again. Thank you very much for braving the cold and coming here. I would particularly like to thank a few of our invited guests for coming--Dr. Lipton, Dr. Wolinsky and Dr. Grundman, and

particularly, Dr. Swain and Dr. Dahut, who are oncologists, as you have heard, and have experience with the product under discussion today.

[Slide.]

What I thought I would do in my presentation is really to just give you an overview of the issues that we would like you to think about before you vote on the formal questions that I'll pose at the end of my talk.

These are issues that have occurred to us in the course of our review of the NDA, and of course, if there are any other issues that you feel need discussion, obviously, we would love to hear those as well.

As you know, we are here to discuss NDA 21-120, which was submitted by Immunex Corporation last June for Mitoxantrone, known as Novantrone and anthracene dion [ph.].

The proposed indication from the sponsor is: "to slow progression of neurologic disability and reduce the relapse rate in patients with progressive multiple sclerosis." It is important to keep that in mind throughout your deliberations.

[Slide.]

The drug was approved in the United States in 1987 first for the treatment of acute non-lymphocytic leukemia, and then again in 1996 had additional indication for treatment of pain related to hormone-refractory prostate

cancer. And it is approved, I believe, worldwide in over 50 or so countries for various other types of cancers.

[Slide.]

The application contains the results of two randomized controlled trials which I will very briefly go over, and you will hear much more about it in detail from the sponsor, and safety data in about 600 patients. There were 145 patients in the two controlled trials, and there are about 450 patients in a retrospective German cohort. We'll talk a little bit about what methodological problems there were with that cohort, but nonetheless, that was the database submitted, as well as reference to the fact that the drug has been marketed for quite some time.

[Slide.]

Study 01 was a randomized controlled trial comparing 5 mg per meter squared, 12 mg per meter squared, and placebo, given every 3 months for 2 years.

The primary outcome was a complicated multivariate measure which combined results on several scales, including functional measures, the EDSS, a commonly used scale in drug trials of MS, the Ambulation Index, a scale called the SNS, which as far as I know was not used prior to this study, and two measures related to relapse--I think it was time to first relapse necessitating steroid treatment and the number of relapses necessitating steroid treatment.

[Slide.]

Study 02--this slide is just wrong in its description of the trial, so I will correct it--was a randomized controlled trial which compared 25 mg of drug plus methylprednisolone versus methylprednisolone alone, and these patients were treated monthly for 6 months, a very different dosing regimen and duration of trial than the first one.

Here, the primary measure was an MRI measure which is the proportion of patients with no new gadolinium-enhancing lesions. So the primary outcome here was an MRI measure, not a clinical measure.

[Slide.]

In Study 01, the patients enrolled had either secondary progressive MS or relapsing progressive MS, and they were about split evenly between those two diagnoses. There were about 190 patients or so in this trial.

The functional measures were assessed by a blinded neurologist, but the relapse diagnoses were not. Now, in my memo in the booklet that you have, I say in there that at the time I wrote that, I believed that the relapse-related diagnoses and treatments were made by a blinded assessor; that we have learned from the sponsor that that is not true, that the diagnosis of relapse and decision to treat the relapse with steroids were made by an unblinded treating

physician.

There were presumably criteria laid out prospectively against which the relapse diagnosis was to be made, but the diagnosis itself was made by an unblinded rater.

[Slide.]

Study 02, patients were enrolled who had what the protocol called "severe" MS, which was ill-defined, and "active" MS, which was defined as at least two relapses in the year prior to enrollment, or an increase in the Kurtzke score of two points after a relapse, I believe. This is also slightly incorrect.

Actually, though, this was the inclusion criteria. Actually, 75 percent of patients were diagnosed with relapsing remitting MS. And here, the MRI was reviewed blind.

I should also say that in Study 01, MRI was done in a subset of patients, and those MRIs were read by a blinded panel. Here, the MRI was reviewed by a blinded reviewer, but again, the clinical events which were measured, EDSS and relapses as well in this study, were made by an unblinded clinician who knew treatment assignment.

[Slide.]

Before I go into the issues that we would like you to discuss and that I have outlined in the briefing package,

I want to briefly go over the standard in law for a finding of effectiveness. It will hopefully be a review for some of you, but for some of you, it may be new, and I think it is important to understand what the rules are while you are deliberating and trying to address some of the issues I have raised.

The sine qua non for approval is a finding of substantial evidence of effectiveness, as described in the law. This ordinarily comes from at least two adequate and well-controlled clinical trials. The law says "adequate and well-controlled investigations, including clinical investigations, and that has routinely been interpreted as meaning more than one investigation. So this really just incorporates the bedrock scientific standard of independent replication of a finding or corroboration or what-have-you. So that's the traditional definition of substantial evidence.

[Slide.]

But in November 1997, the law was amended to permit the Agency to make a finding of substantial evidence on the basis of a single adequate and well-controlled trial with what was called "confirmatory evidence."

[Slide.]

Neither the law itself nor the legislative history gave any guidance as to when the agency should rely on a

single trial or what "confirmatory evidence" is.

[Slide.]

Nonetheless, the Agency has written a document which provides guidance to some extent on the matter of when would one study be adequate and what might "confirmatory evidence" be. And ordinarily, a single adequate and well-controlled trial with confirmatory evidence would be relied upon in a setting where there was an effect on mortality or irreversible morbidity or some serious outcome and in which the finding could not be replicated for ethical reasons more often than not--in other words, the trial really could not be repeated, and we would be left with just one trial.

And it talks a little bit about the sorts of things that might constitute what you would call confirmatory evidence. In a multi-center trial, for example, all the centers going in the same direction, with some of the centers yielding statistically significant results by themselves, very low p values, constant findings across various subgroups enrolled in the trial--in other words, people with advanced disease, people with mild disease, and the same sorts of findings--findings on disparate outcomes--a clinical outcome plus perhaps some radiographic outcome, which are somewhat independent, might be the sorts of things that could serve as confirmatory evidence in this setting of only one trial having been

performed.

I think it is important for you to know and remember these definitions of substantial evidence, because I think the issues I have raised relate to the nature of substantial evidence in this application.

[Slide.]

Let me outline briefly what the issues are that we would like you to think about. First, again, is the question of replication and has the sponsor provided the replication of the findings in the proposed population. Now, remember, the population for which the drug is being proposed is patients with progressive MS.

In Study 01, as we talked about, all the patients had progressive MS--half had secondary progressive, half had relapsing progress, but they all seemed to have progressive by diagnosis. But in Study 02, the vast majority of patients had relapsing remitting disease.

[Slide.]

So we have to ask whether or not there is sufficient information or substantial evidence of the finding in the population for which the drug is being proposed to be used. Now, there certainly are precedents for a lack of replication for a particular population which have been approved, and I will call these potentially relevant, because they are slightly different from the

situation that we have here, but they give an idea of the ways we have thought about similar problems in the past.

For example, most anti-convulsants are initially approved as a treatment for partial seizures, and they are usually approved on the basis of at least two adequate and well-controlled trials showing an effect on partial seizures. But then sponsors may want to get a claim for primary generalized seizures. In that case, they would ordinarily only need to do a single trial in that setting.

Similarly, some Parkinson's drugs have been approved on the basis of two trials, one done as adjunctive therapy in late Parkinson's disease and one done in early Parkinson's where the investigational drug is used as monotherapy. But if they do one trial in each setting, they can get a claim--a global claim--as an anti-Parkinson's treatment.

These approvals are based on our view that the diseases being treated are very similar to each other, and the conditions or symptoms being treated are similar enough to each other so we can gain strength from what we know about one indication and let it support the second indication, even though in the second indication, there may be only be one trial.

[Slide.]

So we have to ask the question here, are the two

types of MS that patients had in these individual trials sufficiently close to each other so that we can say that there is a replicated finding in patients with progressive MS. There are experts in MS who feel that these may just be on a continuum of disease, and there are other experts who feel that these may be disparate, pathologically different entities. So we would like very much to hear what the committee thinks about that.

[Slide.]

That's the population that the drug is being proposed for, but there is a specific claim being proposed as well, and that is to slow progression of disability and prevent relapses. So we have to see if there are replicated findings for each of these claims.

Ordinarily, the use of the word "progression" in a proposed indication implies to us an effect on the underlying pathophysiology or pathology of the disease as opposed to a symptomatic treatment. The studies that were done were not directly designed to examine the question of whether or not the drug has an effect on progression. Such a design would usually involve some variant of withdrawing the drug or a randomized withdrawal and seeing if the patients who had been on drug but now are on placebo in a withdrawal phase, whether or not their condition approaches that of patients who were on placebo from the beginning.

And if they do tend to approach each other, we would generally tend to think that the drug has not had an effect on the underlying structure of the disease, but just simply a symptomatic effect, and when the drug is removed, the patients get back to where they would have been had they never been on the drug in the first place.

These trials, of course, were not designed to look at things in that way. It should be noted that one of the approved treatments for MS, Avanex [ph.], I believe, has a claim for progression of disability--I believe that's the claim, or something very close to it--and I believe that was granted on the basis of a finding on the EDSS, I believe--which again, there is here in at least one of these studies.

So we have to think about whether or not it is appropriate nonetheless, even given that precedent, to use language like "progression" in the face of the particular trials that we have done here.

[Slide.]

Now we come to the question of relapse. As I have mentioned, in both trials, relapses were counted, and they were assessed, but in both trials, we now know that the diagnosis of relapse, the decision to treat with steroids and all relapse-related phenomena, were made by unblinded clinicians, the physician who knew the treatment assignment. So we have to ask the question whether or not we think there

is a bona fide finding on relapse in either of these studies and certainly whether or not there is a replicated finding on the relapse rate.

[Slide.]

Then we come to the issue of the reliance on MRI as a primary measure of effectiveness. It was the protocol stated primary outcome in the second study, as you know, and in its strictest reading, one can at least make the case that it is the only reliable evidence in that second study because the clinical was unblinded in that study; and one could make the case that all clinical data coming out of that second trial may be unreliable because of the unblinding. Again, as I say, there were criteria specified, presumably prospectively, about what would constitute a relapse, so the physician would theoretically make the diagnosis consistent with those criteria. But nonetheless they were made in an unblinded way. So in the second study, you could say that MRI is really all we have that is reliable.

The Division has never, as far as I know, relied on a nonclinical measure to approve a drug, but certainly the agency has in many cases--in a number of cases, anyway. Certainly cancer drugs are approved, as I understand it, on the basis of effects of tumor burden which are assessed by radiographic techniques and the like, and that is done

routinely.

And in betaseron, while the approval wasn't based on an effect primarily on MRI, I believe it is fair to say that the committee--this committee, actually--took the MRI findings very much into account when they were deciding about whether or not they would recommend the drug be approved. There were clinical findings as well in the one trial in which that approval was based, but nonetheless MRI was the basis. Technically, that approval was granted by the Center for Biologics--we are the Center for Drugs--and we in the Neuro Division in Drugs have never done so.

[Slide.]

Certainly the reliance on surrogate markers, which are nonclinical measures that are not directly measures of clinical effect--certainly, the Agency permits it, as I said. There is certainly precedent. It has been in the regulations under what is called the "accelerated approval" provisions or a number of years, and recently the statute was amended to include the provision that the Agency could determine that substantial evidence has been shown when there are effects shown on surrogate markers. A surrogate marker, though, in that case if it is not completely validated would have to be shown to be reasonably likely to predict a future clinical benefits. Of course, "reasonably likely" isn't well-defined, but it talks about reasonably

likely based on epidemiologic or pathophysiologic data or some sort of evidence that would to an expert suggest that it would be reasonably likely to predict a clinical outcome of interest.

[Slide.]

There are issues, though, that one has to think about when deciding whether or not it is reasonably likely that a finding on a surrogate marker like the MRI would predict clinical benefit. One would be, for example--this is not an exhaustive list--but one would be, for example, whether or not the treatment applied has any interaction with the measurement itself so that it is really not affecting anything that you would care about pathophysiologically, but it just interacts with the measurement system and shows an effect--which would, of course, not really be particularly useful.

Certainly there are many examples where effects on surrogates have been misleading. A treatment may have an effect on a surrogate but have no effect on the underlying condition of interest, or in fact could have a deleterious effect and still have an apparently beneficial effect on the surrogate itself. So there can be a disconnect there, and it is very difficult to know if that's going to be the case in any given case, and then you have to think about, for example, whether or not an effect that you see on a

surrogate in a relatively short study will actually persist in time and therefore predict the clinical benefit out in time.

So there are certainly problems and pitfalls in the use of surrogates in general.

[Slide.]

The use of the MRI in this case, however, can be seen as a different type of surrogate as well. As opposed to one that predicts clinical benefit in the future, it could be seen as one that reflects the underlying pathology at the time the scan is done. I would say that there is probably general agreement in the MS community as far as I know that MRI is probably an accurate reflection of the underlying pathology. I would be interested to hear today what those data are for the particular MRI measure that we are talking about here, which is for the most part gadolinium-enhanced lesions. But nonetheless I think there is a general view that it is a reflection of the underlying pathology and therefore that any effect on the MRI will accurately reflect on the underlying brain disease and therefore must be good, because less pathology is presumed to always be better than more pathology.

Of course, it would be interesting to know what the specific pathology of the particular MRI parameter that we're looking at reflects, if it does, and here, as I say,

we are talking mainly about gadolinium-enhanced lesions, and we would be interested to hear the discussion of what people think that that represents in terms of the underlying brain event.

And then, of course, we have to think about what the relationship of any effect on that surrogate, on gadolinium enhancement, means for clinical purposes. Again, any effect on a surrogate in order for it to be useful presupposes that it, either at the time contemporaneously or in the future, will have a clinical benefit. If a drug doesn't have any clinical benefit, there is really no point in approving it.

So when we talk about this sort of use of the MRI as a contemporaneous surrogate, we also have to think a little bit about the size of the treatment effect. Ordinarily, in a typical trial where we have a clinical outcome that we use, seizure counts or whatever it is, we take a face-valid clinical outcome, and any change from placebo, if it is statistically significant, we make the assumption that that is clinically meaningful, and that would be the basis for a typical approval.

But when we are talking about a sensitive radiographic technique, we have to ask whether any change we see on it in facta reflects something that could possibly be useful to the patient either now or later. For example--and

I think I mentioned in the briefing book--if the test were so sensitive that it picked up damage to 10 neurons, it is hard to believe that that could ever be clinically meaningful to a patient, so we have to ask questions about treat effects, size--the questions we ordinarily don't ask in a typical clinical setting.

[Slide.]

Another issue has to do with the appropriate dosing regimen. The sponsor is proposing a particular dosing regimen that comes from one of the trials, but the two trials use widely disparate dosing regimens, and we have to ask under the heading of replication or corroboration is there sufficient information, given the findings in the study with the dosing regimen that they are not proposing, whether there is substantial evidence that this particular dosing regimen will have the effect claimed by the sponsor.

There is one other issue which I don't have a slide for, before I get to safety, and that has to do with the fact that the two studies were entirely foreign. The first study was done in Germany, Belgium, Hungary and Poland, and the second study was done in five centers in France. There is no requirement that a sponsor submit studies performed in the United States in order to gain approval--certainly, approval could be granted on the basis of entirely foreign data.

We are entitled, though, to ask for a trial in the United States if we think it is important to do so, and the committee should think about this, I believe, in its deliberations. Were the patients diagnosed in these places the way patients are diagnosed in this country? Did those patients receive the sorts of typical care that patients would receive in this country? And are the results from those particular foreign sites relevant for the United States population?

[Slide.]

There are the safety considerations which you will need to think about, of course. As we mention in the documents, we didn't see anything in the population studied that would in our view preclude approval if you found that effectiveness had been established. But we know that there are risks associated with increasing cumulative dose of Novantrone. I believe that somewhere, the literature suggests that there is a risk of about 2 percent of hear failure up to a cumulative dose of about 120 mg per meter squared, and that risk rises when the dose goes to about 160 mg per meter squared or thereabouts, although there aren't many patients described well in the literature at those higher doses.

This drug if approved would be to treat a chronic disease that goes on for years and years and years, and one

has to ask the question as to whether or not these sorts of cumulative risks for these sorts of events are acceptable for a disease to be treated chronically. We have few, if any, precedents for this sort of thing in the neurological world. So I'd like the committee to think about that in its deliberations as well.

[Slide.]

Those are the issues that occur to us. The Agency is not going to present the specific safety and effectiveness data--the company will do that--because there is largely agreement between the Division review team and the company about the results of the trial. We believe that they have met the particular specified primary endpoints, and again, you will hear the details. But it is the interpretation of those results that we bring to you today.

[Slide.]

So the first question we have is: Has the sponsor submitted substantial evidence of effectiveness to support their proposed indication? Here again, I would ask you to think about whether there is substantial evidence of effectiveness for the particular dosing regimen that is being proposed as well. That's the first question; it's the usual first question.

[Slide.]

But if you find that they haven't submitted

substantial evidence of effectiveness for the particular indication that they are proposing, we would ask you if you think there is any reasonable indication in any well-defined MS population that the data do support effectiveness for. And if the answer to this question is yes, we would very much appreciate your letting us know what specific indication you think that is.

[Slide.]

And the third question: Do you believe that the safety data presented and available from its previous approvals support the safety of the drug and appropriate labeling?

There is another safety-related question that I'd like to ask which is not up here, which you don't necessarily have to vote on, but we would like you to discuss, and that has to do with whether you think any restrictions need to be imposed on this use. It is a toxic drug; it is more toxic, I would say, than the drugs that we are used to dealing with in neurology. And right now, the drug does have a boxed warning which says that only physicians who are experienced in the use of these sorts of agents should use it. We would like to know whether you think the use should be restricted to oncologists or neurologists in conjunction with oncologists or particular centers, or those sorts of things, or what sorts of

monitoring you think might be appropriate either in the short-term or in the long-term if the drug were approved.

Those, as I say, are probably just a subset of the issues that will be discussed today, but those are the ones that occur to us, and I think I'll turn it over to the company, or back to Dr. Gilman, if there are no questions.

DR. GILMAN: Thank you very much.

That was a very nice overview of the material that I know the sponsor has had access to and the committee has had access to.

There are a couple of other issues, a couple of which Dr. Katz did have in his narrative, that you didn't mention here. One is that the software that was used for the analysis was not a software well-known to the FDA--in fact, it was unknown to the FDA; it was produced in Germany, and apparently, not a lot is known about that software. I gather that is not a particular issue for you, though, Dr. Katz. Is that right?

DR. KATZ: Yes. The company will talk a little more about the details of that, but yes, it was unknown to us, and we had no experience with it. But again, as I alluded to, the initial assessment was done in this complicated--I'll call it complicated; it was to me--multivariate sort of an outcome measure consisting of these five other individual measures. But when you look at the

five individual measures by themselves, they are quite statistically significant on their own, so that certainly provided us with a great deal of comfort about what that meant and about the findings.

DR. GILMAN: The other issue that you touched on here, but let me just make it explicit, is the question of what total dose in the life of a patient should be permitted. Should there be some sort of limit set on that total dose? And also, I am wondering what is the total duration of a single infusion of this agent. In other words, can the patient look forward to an effect that will last 3 months, 6 months, a year, a lifetime? Is there evidence bearing on that question? That has to do with the total dose that you might want to restrict a patient to over the patient's lifetime, incidentally.

The other question that occurred to me is has the SNS been validated in some time? That is not a scale that I had previously been familiar with, and I hope you can address that question along the way--reliability, validity between individual examiners.

I am curious to know also why you used five measures as your primary endpoint. That's rather an unusual approach, and it is interesting, but I am wondering how you arrived at that decision to do that.

After we had our introductions around the table,

Dr. Temple came in, so I'd ask you, Bob, to introduce yourself.

DR. TEMPLE: I am Bob Temple. I direct the Office of Drug Evaluation I.

DR. GILMAN: Thank you.

Are there any issues that committee members would like to let us know about before the sponsor begins?

[No response.]

DR. GILMAN: All right. The sponsor has read Dr. Katz' narrative and is familiar with the questions, and of course, we are all familiar with the questions, so I hope that in your presentations you will address those questions specifically.

Let me introduce Dr. Ann Hayes, Senior Vice President for Medical Development, who will introduce the sponsor's team.

DR. HAYES: Thank you, Dr. Gilman.

Good morning. This morning I will provide you with a brief overview of Mitoxantrone, and then we will introduce the principal investigators of the studies and the consultants we have with us today.

[Slide.]

As has been indicated, Mitoxantrone has been marketed in the United States and in Europe since 1987, and we are pleased to be here today to present data in support

of an additional indication which we believe demonstrates that Mitoxantrone can produce significant clinical benefit for a population of patients within the area of multiple sclerosis.

[Slide.]

Mitoxantrone is currently approved for two indications. It was approved in 1987 for the induction of remission for acute myelogenous leukemia and was approved for the treatment of hormone refractory prostate cancer in 1996 based on its ability to provide palliation of pain with a manageable and acceptable side effect profile.

[Slide.]

Since its initial approval, well over 180,000 patients in the United States have been treated with Mitoxantrone, with more than 400,000 patients treated worldwide.

Mitoxantrone is administered in different doses and schedules depending on what the clinical indication is. For acute myelogenous leukemia, the dose is 12 mg per meter squared, but it is delivered daily times 3 every 4 to 6 weeks for the induction of remission. In solid tumors, the dose of 12 mg per meter squared, or between 8 and 14, depending on the studies, is delivered every 3 to 4 weeks either for induction of remission or actually for a fairly long period of time to maintain remission.

Mitoxantrone is also delivered in high-dose chemotherapy for both AML and in proliferative regimens for bone marrow transplant at doses up to 80 mg per meter squared as a single dose.

In oncology, obviously, the drug is most frequently delivered in combination, and in actual fact, its other approvals in AML are in combination with cytosine arabinoside and in prostate cancer in combination with steroids.

Twelve years of postmarketing experience with this product have shown that the acute side effects of the drug are quite manageable and of short duration. The long-term cumulative effects such as the potential for cardiotoxicity, although dose-limiting over time--and we will discuss this in fair detail today--can also be managed quite safely with proper precautions and monitoring.

[Slide.]

Mitoxantrone is a synthetic anthracene dion [ph.] for intravenous use only. It affects both dividing and nondividing cells by inhibiting DNA synthesis and the repair mechanisms for DNA. The two major mechanisms are intercalation within DNA and the inhibition of DNA topoisomerase II [ph.].

[Slide.]

The proposed mechanism of action for Mitoxantrone

in MS involves forth its antiproliferative effects and its immunomodulatory effects. This agent is antiproliferative, and it does lead to decreases in B-cells, to a less extent T-cells and also macrophages.

Its immunomodulatory acclivities, other than its effect on the cells involved, can also act indirectly by decreasing antigen presentation and by decreasing the production of the cytokines such as TNF-alpha, IL-2, and Interferon-Gamma.

Mitoxantrone has been shown to be active in the in vivo EAE model, a model, as you know, frequently used to screen drugs for multiple sclerosis. And conclusions from those studies and also the proposed mechanism of action in studies done both in vivo and in vitro led to the human clinical trials in multiple sclerosis that Dr. Ghalie will discuss with you today.

[Slide.]

As you are all aware, multiple sclerosis certainly can be a debilitating disease and afflicts about 350,000 Americans, of which about 140,000 have a progressive form of the disease for which there is no currently approved treatment.

[Slide.]

Just a brief history of our interactions with the FDA in terms of this product for MS. The data from the

registration trials was first presented to the FDA at the end of a Phase III meeting in November. The application was further discussed with the Division in April of 1999, and based on these discussions, the NDA was filed in June of 1999. The application was then reviewed and received priority review status due to the lack of approved other therapies in progressive forms of MS, and orphan drug designation was granted in August of 1999 for both secondary progressive and progressive relapsing forms of the disease.

[Slide.]

The data that Dr. Ghalie will present to you today and which you have in your briefing documents, we feel supports the expanded indication for Mitoxantrone. We are requesting approval for the use of Mitoxantrone to slow the progression of neurologic disability and to reduce the relapse rate for patients with progressive forms of MS excluding primary progressive disease.

[Slide.]

We will have two further presentations this morning. Dr. Richard Ghalie will present the efficacy and safety data supporting the indication and also will specifically address each of the concerns that Dr. Katz has brought up with data that we feel supports our filing.

Dr. Fred Lublin from Hahnemann University will then conclude with a summary of the patient populations

which he feels may benefit from Mitoxantrone and also a summary of current treatment opportunities for these patients.

[Slide.]

We also have with us today the principal investigators from Europe of these studies who are here to answer questions that you may have concerning the studies.

Professor Hartung was the principal investigator of the Phase III trial. Professor Edan was the principal investigator of the MRI supporting trial, and Professor Erich Mauch is the medical director of the clinic in Germany which has provided us with over 500 patients for safety from his clinic.

[Slide.]

Dr. Hill Panitch and Dr. Craig Smith are also with us as physicians here in the United States who have used this product in their patients, and also for their expertise in MS, and Dr. David Alberts from the University of Arizona Cancer Center, who is a recognized expert in the use of Mitoxantrone in oncology is also present with us today to help address your questions concerning this drug.

I would like now to introduce Dr. Richard Ghalie, who will do the presentation on efficacy and safety of Mitoxantrone.

DR. GILMAN: Dr. Hayes, before you leave, I wonder

if you could answer one question. In cancer patients, has there been any total dose limitation over time with this drug?

DR. HAYES: Yes. The recommendation for the delivery of Novantrone in cancer patients is that patients have a baseline cardiac evaluation, and then, either based on any clinical evidence there may be cardiac problems or when they get to a total dose of approximately 140 mg per meter squared, that the patients be evaluated prior to each course for left ventricular ejection fraction function.

It is really a physician decision of whether they go to a higher dose because as Dr. Katz indicated, once you get beyond about 140 or 160, you do get an increase in rate of cardiac involvement.

The thing is that in oncology, this drug is delivered on a much more frequent basis, and if we have questions later about this, Dr. Alberts can address it, but there certainly is a dose intensity both in dose and frequency of delivery that does bear upon the incidence of cardiac problems with this drug.

DR. GILMAN: I didn't see this in your proposal for the package insert, but would you have some sort of guideline for the physician about the total dose that you would recommend?

DR. HAYES: Yes. I can address it right now. Our

recommendations would be that the patient do have a baseline left ventricular evaluation before they start; that when they get to around 100 mg per meter squared that they then start having it prior to each course. And our recommendation will be in multiple sclerosis--because we don't know if you give it every 3 months what the long-term effects will be, and with time, we will be evaluating that--that MS patients not receive more than 140 mg per meter squared.

DR. GILMAN: Thank you.

Dr. Penix?

DR. PENIX: In regard to the oncologic indication, are there specific recommendations about the monitoring frequency, the frequency of monitoring the hematology parameters and also the echo?

DR. HAYES: Yes. For hematology, in oncology, the normal practice would be that CBCs with white blood count differentials are done prior to each course. Now, it is being given every 3 weeks, so they want to make sure the counts are high enough to give the next course.

Our recommendations for the delivery of this drug at any time would be that a blood count be done prior to the delivery of the course to make sure that their counts are within normal range, and between courses, the most likely time that you are going to have a hematologic dip in your

counts with Mitoxantrone is between 7 and 14 days, maybe up to 21. So if in that period of time a patient has fever or feels ill or develops an infection or a cold, they should have their blood counts checked to make sure they don't have a low count.

DR. PENIX: Are there guidelines in the package insert that indicate when--

DR. HAYES: We are proposing that there will be guidelines, yes. Right now, I believe the package insert just reads that frequent blood counts should be obtained prior to dosing. But we would propose definite guidelines before each course, and if a patient develops a fever between courses, especially in the window of time where one would suspect the blood counts--yes.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Is there any information about the possible impact of dexrazoxene [ph.] on cardiac toxicity with this drug?

DR. HAYES: I believe there is. Dr. Alberts--may I defer to Dr. Alberts to answer that question, please?

DR. GILMAN: Yes. Dr. Alberts?

DR. ALBERTS: Yes. There actually have been some in vivo and in vitro studies. Our group at Arizona showed actually showed that Xenocar [ph.] really did not affect Novantrone cardiotoxicity, but the same experiments

published in the European Journal of Cancer clearly showed that--of all things--a thiol [ph.] prevents cardiotoxicity from Novantrone. I think that what that points out is that the mechanism of cardiotoxicity is quite different between those two drugs. We all know that doxorubicin's toxicity is considerably greater and has a much more destructive cumulative long-term effect.

DR. HAYES: Does that answer your question?

DR. SWAIN: I have another question for Dr. Alberts.

What is the proposed mechanism of cardiotoxicity of Mitoxantrone? I know it looks like there is no free radical formation with the drug. Do you have any idea?

DR. ALBERTS: Well, it seems to affect the sarcoplasmic reticular endothelial [ph.] system and affects energy metabolism in the mitochondria. There is evidence that this drug is actually an antioxidant as opposed to doxorubicin, which is a known pro-oxidant. So it is very, very different from what has been shown. It has also been shown that it affects calcium transport.

So it still is in somewhat of a black box exactly how it does this.

DR. GILMAN: There was some mention of leukemia as a consequence in a small percentage of patients. Is that dose-related at all?

DR. HAYES: The probability of a second malignancy following treatment with Novantrone is clouded by the fact that it is rarely given as a single agent. It is usually always given in conjunction with other agents which are known to also have an incidence of second malignancy.

So that's a very hard question to answer. And as far as we know, this is not dose-related, but it is a very low incidence with Novantrone, and as I say, it is clouded by the fact that it is always given with cyclophosphamide [ph.] or cytosine erabinocide [ph.] or VP-16, which is notorious for causing second malignancies.

DR. GILMAN: Are there any other questions?

[No response.]

DR. GILMAN: Thank you very much, Dr. Hayes. We'll move on, then.

DR. GHALIE: Good morning. My presentation today will be divided into two parts. First, I will present efficacy data from two randomized trials in multiple sclerosis and then safety data from these two trials and a single-center retrospective study. I will also provide information on Mitoxantrone safety from the 12 years' worth of experience with this agent in cancer patients.

The second part of my presentation will consist of a benefit-and-risk assessment of the use of Mitoxantrone in patients with multiple sclerosis. I will conclude by

providing answers, or at least Immunex' perspective, to the issue that Dr. Katz raised in his introduction.

I trust that this presentation will demonstrate that Mitoxantrone fulfills an unmet medical need in patients with progressive forms of multiple sclerosis. We exclude in our minds here primary progressive MS, for which we have no data in the clinical trials. These are disease forms that currently have limited therapeutic options.

[Slide.]

The efficacy of Mitoxantrone in animal EAE models which Dr. Ann Hayes alluded to earlier led to the conduct of a number of open-label studies and randomized studies that are shown on this slide.

[Slide.]

Data from five dose-finding studies and one randomized placebo-controlled trial have been published in English language journals. These studies involved a total of 100 patients who received Mitoxantrone at doses ranging from 8 to 14 mg per meter squared with intervals between courses that went from every 3 weeks to every 3 months.

The aggregate of these studies led to the conclusion that Mitoxantrone when used at the same dose that is used in cancer patients--that is, 12 mg per meter squared--was also well-tolerated by patients with multiple sclerosis and therefore that further controlled trials in

patients with multiple sclerosis were indicated.

[Slide.]

As a result, two randomized studies were conducted--study designated 901, which was a Phase III randomized placebo-controlled study, and Study 902, a Phase II randomized corticosteroid controlled trial. These two studies serve as the basis for the Immunex filing.

In addition, in our filing, we have added Study 903, which is a single-center respective analysis of the experience of a single center experience with Mitoxantrone and multiple sclerosis.

Taken together, these represent data on 689 patients, of whom 603 had received Mitoxantrone. Collectively, in our opinion, these data provide evidence of Mitoxantrone's effectiveness and safety in patients with multiple sclerosis.

So I will first present the design and efficacy results from the two randomized trials, and I will begin with Study 901.

[Slide.]

Study 901 was a Phase III randomized placebo-controlled trial. It was conducted in 17 centers in four European countries. It enrolled 194 patients. IT was co-chaired by Professor Hartung, who is here, and Professor Gonsette from Belgium. The German regulatory agency, BfArM,

approved the design and the conduct of that study. The first patients were enrolled in June 1993, and the study concluded in July 1997. These data were presented at some meetings with Dr. Hartung in the last 2 years.

[Slide.]

The main inclusion for that study are listed here, and they include patients age 18 to 55; diagnosis of multiple sclerosis according to Poser's criteria; and a diagnosis of secondary progressive or remitting progressive multiple sclerosis. Again, this study was designed before the 1996 classification, so I would like to explain what is meant by "remitting progressive" multiple sclerosis. Those are patients who have relapsing remitting disease with a residual deficit after an attack. When Dr. Lublin comes up at the end, he will also have some slides to describe how this fits in the continuum of patients with multiple sclerosis.

Additional inclusion criteria consisted of active disease as defined by an EDSS progression by at least one point in the 18 months that preceded enrollment in the study; and finally, EDSS ranging from 3 to 6.

[Slide.]

To illustrate to you what is an EDSS between 3 and 6, this is a graphic description. The EDSS scale is a 10-point scale that describes disability in patients with

multiple sclerosis. An EDSS of 3 represents moderate disability in one functional system or a mild disability in three or four functional systems. An EDSS of 5 or greater indicates an ambulation of impairment. An EDSS of 6--the upper limit for enrollment in this study--indicates a patient who requires intermittent or constant unilateral assistance to walk--cane, crutch, and so on. An EDSS of 7 represents a patient who requires a wheelchair.

[Slide.]

The main exclusion criteria are listed here, and I would like to point to the fact that patients with benign MS or primary progressive MS were excluded from this study.

[Slide.]

Patients were randomized in this trial to one of three groups--placebo group; Mitoxantrone 5 mg per meter squared; and Mitoxantrone 12 mg per meter squared. Treatments were given intravenously by 5-minute short infusions, and they were repeated every 3 months for a total of 8 courses or 24 months. In addition, patients were examined at month 36, which is one year after receiving the last dose of study drug, to evaluate disease activity and any delayed toxicity. I will present the data also on month 36.

The interval of 3 months between courses was decided based on the promising data that were published in

pilot studies by Professor Mauch in the early nineties. The dose of 5 mg per meter squared that was tested in this trial was added as an exploratory dose to see whether a lower dose may also have an effect on patients with multiple sclerosis.

[Slide.]

A number of precautions were taken to reduce the risk of bias in the interpretation of the disability assessment in the study as well as the MRI results, and these are listed here.

Methylene blue was used to mimic the color of Mitoxantrone which, as you imagine, is blue, and it served as a placebo to mask patients. The evaluators of neurologic disability--and these are the scales that I will describe to you in a moment--were masked to study drug, and they were not involved in patient management.

The physicians who evaluated the MRI scans--and I will explain that a little bit later--were also masked to study drug and also to clinical outcomes. They did not know the patients' response to treatments.

The treating physicians who were responsible for study drug administration were not masked to study drug; they knew what they were giving their patients. They were also responsible for patient management, for assessment of adverse events and the safety profile and also for assessment of relapses and deciding when to treat relapses.

[Slide.]

The protocol defined one primary efficacy criterion and multiple secondary efficacy criteria. So I will guide you now through this primary efficacy criterion that Dr. Katz had difficulty understanding.

It was a single multivariate test in one hypothesis of five variables. Three variables assessed treatment effect on disability using three complementary scales--the EDSS scale, the Ambulation Index scale, and the standard neurologic disability status score. Two other variables assessed treatment effect on relapses, which is time to treated relapse and the number of treated relapses.

The primary analysis in this protocol was defined as a comparison between placebo and the test dose of 12 mg per meter squared with an alpha equal to 0.05.

Now, if this multivariate test was significant with p less than 0.05, then each of these variables were to be tested sequentially in a predetermined order that was defined in the protocol and that is listed here, that is, beginning with EDSS and going down to the SNS score.

There were very strict rules on when to stop doing these comparisons. For example, just to give you an example. If, for example, Variable 3 was not significant with p greater than 0.05, then Variable 4 and Variable 5 were automatically declared not significant, and that is how

they were sequentially tested.

The number of patients needed for that study was estimated to be 60 patients per group. That provided a 90 percent power with alpha equal to 0.05, as I mentioned.

So as you had requested before, I will review for you now the three disability scales that were used in this study--and copies of these scales were attached to the back of the briefing document that we submitted to you.

[Slide.]

This is the Kurtzke Expanded Disability Status Scale, the EDSS scale. It is a 10-point scale with 0.5 point increments--so 0.5, 1.0, et cetera, until 10. It is based on the evaluation of seven functional systems listed here and something called "Other." EDSS scores of 4.5 and lower are based on these functional scores with specific criteria how to determine scoring. EDSS scores of 5.0 or higher are really based on ambulation impairment.

[Slide.]

The second disability scale used in this study was the Ambulation Index scale, which is again a commonly evaluated scale that is used in the U.S. and other countries, and it is a 10-point scale with one-point increments. It is really focused on ambulation impairment. An Ambulation Index greater than 3 indicates ambulation impairment.

The third and last scale used in this study is the Standardized Neurologic Status score scale, or SNS. To make it easier, I will say "SNS" from now on. It was developed in Germany by Professor Mauch, in fact, who is here, and it has been used there for over 10 years to assess neurologic disability. It is a 99-point scale with one-point increments, so it is more refined in its increment points than the other two scales.

It evaluates five functional systems which are listed here, but 50 of these 100 points are weighted by supraspinal evaluations. I must say that this scale has not been used in the U.S. but is commonly used in Germany, where it was defined, and it was included in the study design.

[Slide.]

I will now present to you patient disposition and demographics. One hundred ninety-four patients were enrolled in the three groups. Three patients were found to be ineligible after randomization and before they had received any study drug. These three patients were withdrawn from the study and never received study drug, and they are not included in any of the safety or efficacy analyses I will present today.

Three other patients received a single dose of study drug and then decided to leave the study before undergoing the Month 3 evaluation. Therefore, we have no

efficacy data on these patients, and we did not include these patients in the efficacy analysis; we did include them in the safety analysis.

As a result, there were 188 patients total who were evaluable for efficacy--64 in placebo, 64 in Mitoxantrone 5 mg per meter squared, and 60 in Mitoxantrone 12 mg per meter squared. Thirty-nine patients shown here discontinued study drug before completing the 2 years of treatment and all associated procedures that were required for that study. Overall, if you follow the patient disposition, 73 percent of the patients randomized to placebo, 84 percent of patients randomized to Mitoxantrone 5 mg per meter squared, and 80 percent of patients randomized to Mitoxantrone 12 mg per meter squared compared the 2 years of treatment and all the tests that were required for these 2 years of treatment.

[Slide.]

This slide and the next one present patient demographics and show that really, there were no differences between the three groups in patient demographics--female, age, and type of MS.

A typical patient was a 40-year-old patient with a disease history of 10 years. This population had an average of 1.3 relapses in the year preceding enrollment, and EDSS increased by 1.6 points in the 18 months preceding

enrollment.

Mean baseline EDSS at enrollment was roughly 4.7 in the three groups, and an EDSS of 4.7 represents a patient who had imposed full limitation to full activity or where minimal assistance to walk was required.

[Slide.]

I will now turn to the efficacy results of the study. Again, as the protocol defined, the primary comparison between placebo and Mitoxantrone 12 mg per meter squared, for all the efficacy results I will present now, the p values on these slides correspond to this comparison--12 mg per meter squared versus placebo. We did put on the slides the data from 5 mg per meter squared to really demonstrate a dose response effect in the study.

[Slide.]

Let me begin first with the primary efficacy criteria. And again, this was mentioned earlier in the study. As you see here, it was met with p less than 0.0001. As a result, each of the five primary efficacy variables was tested sequentially as described in the protocol, and as can be seen here, each of these variables was significant with p less than 0.05.

I will now show you each of these variables on a different slide so you can look at them individually.

[Slide.]

This slide shows the mean EDSS change between month 24, the end of study, and baseline in the three groups. To help you read the slides, since the EDSS scale as it increases means worsening in the EDSS scale, a positive number indicates worsening in the EDSS scale whereas a negative number indicates improvement.

There was a significant difference in favor of Mitoxantrone 12 mg per meter squared with p listed here at 0.0194.

[Slide.]

Let's look now at the second disability scale, the Ambulation Index. It follows the same rule--a positive number means worsening. Again, we are comparing month 24 to baseline. Here again, there was a significant difference in favor of Mitoxantrone 12 mg per meter squared, with the p listed here of 0.0306.

[Slide.]

I will now turn to the third disability scale, the SNS score. Again, this follows the same rule--a positive number indicates worsening, a negative number indicates improvement, comparing month 24 to baseline.

Here again, there was a significant difference in favor of Mitoxantrone 12 mg per meter squared, p equals 0.0269.

[Slide.]

I will now present the two primary efficacy variables that assessed treatment effect on corticosteroid-treated relapses.

There was a 69 percent reduction in the total number of treated relapses with Mitoxantrone 12 mg per meter squared compared to placebo; 24.1 total number of treated relapses versus 76.8, with p listed here at 0.0002.

[Slide.]

And if we look now to the time to first treated relapse on the study, here again, there was a significant difference in favor of Mitoxantrone 12 mg per meter squared, shown in yellow, compared to placebo in gray, with p shown here at 0.0004.

[Slide.]

This busy slide, which is also reproduced in the briefing document, presents the results of secondary efficacy variables defined in the protocol. As can be seen, Mitoxantrone 12 mg per meter squared was consistently better than placebo for all of these variables.

There are two places where you see "Not significant," but again, when you look at the results, they were better than placebo, albeit not significant.

Of all these results, I will present to you first EDSS data, and then I will present data on relapses.

[Slide.]

This graph shows the mean EDSS change from baseline at each evaluation from month 3 through month 24. Mean EDSS improved in the Mitoxantrone groups in yellow and blue; mean EDSS increased in the placebo group.

[Slide.]

Now I present to you another way to look at EDSS, and this is the number of patients who have a one-point EDSS increase that was sustained for 6 months. Neurologists consider a one-point EDSS that was confirmed 6 months later as a clear indication of progression of disability.

Here again, there was a 64 percent reduction with Mitoxantrone 12 mg per meter squared in the proportion of patients who had EDSS progression by one point confirmed at 6 months compared to placebo, with p equal 0.045.

[Slide.]

Another measure of EDSS that is also commonly looked at by neurologists is categorized EDSS change by one point--that is, patients whose EDSS increased by one point or greater, who remained stable within the more or less one point, or improved by one point.

Here again, one can see the benefit achieved with Mitoxantrone 12 mg per meter squared. There was a significant difference in the proportion of patients who had deteriorated by one point--8 percent in Mitoxantrone versus 25 percent with placebo, p equals 0.013.

[Slide.]

I will now move from disability scales to talk about treatment effect on relapses. Fifty-seven percent of the patients who are randomized to Mitoxantrone 12 mg per meter squared did not have any relapse--they were free of relapse during the 2 years of treatment--compared to 36 percent of patients who were randomized to placebo, and the p value here is 0.021.

If one looks at the calculated annual relapse rate for Year 1, for Year 2, and for both years combined, and if we look at them compared to the baseline, again, there was a significant effect in favor of Mitoxantrone 12 mg per meter squared, and I will not go through the point values here because they are shown on the slide.

[Slide.]

As I mentioned earlier, patients were evaluated one year after completing study treatment, at Month 36. I will present to you now the data of the third-year evaluation. I must say right now that the protocol permitted unmasking patients on a per-site basis when they had completed the 24 months of treatment and all associated procedures.

[Slide.]

Let's look first at the disability scales, the EDSS, Ambulation Index, and SNS scores.

All three scales used to measure disability showed that patients who had been randomized to Mitoxantrone 12 mg per meter squared had less disability progression than patients who were randomized to placebo. I will take a moment with this slide because it is a little bit complex.

For EDSS--this is Mitoxantrone 12 versus placebo--that's a 36-month period of follow-up--this is the Ambulation Index, and this is the SNS score. Again, keep in mind the Ambulation Index and the EDSS are 10-point scales; the SNS a 100-point scale. That may also explain some of the differences in the bar graphs.

[Slide.]

Now let's look at relapse at month 36. The rate of relapse and the rate of the treated relapse during the third year of follow-up--so this is Month 24 to Month 36--was also lower in Mitoxantrone groups compared to placebo.

[Slide.]

Then, the last slide I will show about efficacy shows the time to first treated relapse, and looking at time to first relapse from baseline, because it is a Kaplan-Meyer [ph.] curve. Here again, it showed that patients randomized to Mitoxantrone had a longer time to first treated relapse than patients randomized to placebo.

The median time to first treated relapse was still not reached at Month 36 in the Mitoxantrone 12 mg per meter

squared, as you can see. This is 50 percent; it still wasn't reached there. So one can tell that there is at least 21 months longer time to first relapse in the Mitoxantrone 12 mg per meter squared group compared to placebo--that's a minimum of 21 months.

[Slide.]

So in conclusion, for Study 901, we showed that Mitoxantrone significantly slows the progression of neurologic disability; it decreases the relapse rate, and this is in patients with progressive forms of multiple sclerosis.

We can also tell from the data at Month 36 that there is no disease rebound one year after discontinuing treatment.

Mitoxantrone 12 mg per meter squared was significantly better than placebo for all five primary variables. Mitoxantrone 5 mg per meter squared--I do not show this data--was significant in placebo for two of these primary endpoints.

Therefore, in our opinion, this shows a dose response effect which supports the biologic activity of Mitoxantrone in this disease.

[Slide.]

The next series of slides I will present to you today are the MRI results of the study. Let me describe to

you the MRI protocol.

T1-weighted scan with gadolinium enhancement--or, for brevity, I will say "Gd enhancement," since most of you are familiar with the phrase "Gd enhancement"--and T2-weighted scans were performed following the guidelines published by Miller in the early nineties. Scans were obtained at baseline, the end of Year 1 and the end of Year 2, and they were obtained in a predetermined subset of 110 patients who were enrolled in the study. These patients were enrolled in sites that had expertise in doing MRI scans.

The review of the MRI scan was done at the end of the study concurrently for all the scans, by two investigators who were experienced in reviewing MRI scans and who were blinded, as I mentioned, to the treatment the patients were randomized to as well as the clinical outcomes. And to make it consistent with the clinical results, I will now present to you the results of Mitoxantrone 12 mg per meter squared and placebo.

[Slide.]

This is a slide that shows patients who have Gd-enhancing lesions on their scans, comparing baseline, end of Year 1 and end of Year 2. At the end of Year 2, there were fewer patients with Gd-enhancing lesions with Mitoxantrone 12 mg per meter squared compared to placebo--3 percent

versus 16 percent.

Also at the end of Year 2, no patients had new Gd-enhancing lesions in the Mitoxantrone 12 mg per meter squared compared to 16 percent of patients who were randomized placebo.

[Slide.]

The trend observed in the two sets of data I presented to you today suggest that Mitoxantrone reduces inflammatory lesions of multiple sclerosis in the central nervous system.

This graph shows the mean change in total lesion load for T2-weighted scans, so now we are moving to T2-weighted scans. T2-weighted lesions were scored from 1 to 5 using a scale that we had in the briefing document. As one can see on the slide, lesion load was relatively unchanged in Mitoxantrone 12 mg per meter squared for the 2-year period. T2-weighted lesion load increased in the placebo group.

[Slide.]

In conclusion, the MRI results in this study confirmed Mitoxantrone's ability to inhibit the inflammatory process associated with multiple sclerosis, and it can possibly be said that it inhibits the degenerative process associated with multiple sclerosis.

These MRI results in our opinion support the

clinical findings of the study.

[Slide.]

Let me turn now to the Phase II Study 902.

DR. GILMAN: Can I interrupt here for a question?

In the narrative that Dr. Katz provided concerning MR scanning, on page 4 of his narrative, he gave a base number of gadolinium-enhancing lesions of 0.44 in the placebo group, and in the 5 mg per meter squared group, 3.23, and in the 12 mg per meter squared group, 1.88. So baseline mean number of gadolinium-enhancing lesions was very much smaller in the placebo group than in the others.

I just wondered about that finding. It struck me in looking at these data. I wonder if you could address that issue or one of the other members, if not now, maybe later--I know I'm asking a very detailed question here.

DR. GHALIE: I would like to have Slide B-89, which will allow everybody to see what Dr. Gilman is alluding to. It is the number of lesions at baseline. It is shown here for the placebo at 12 mg per meter squared, where it was somewhat consistent between the two groups for the number of lesions. It is true that the 5 mg per meter squared group, just by randomization, has had much more lesions at baseline. Therefore, we felt that they were different from the other two groups we put in the comparison, and that's why we did not include them in the

comparison.

DR. GILMAN: Well, it's that the placebo group had 0.44. I don't know if that's significantly different from the 1.88 in the 12 mg per meter group, but you are quite right, the 5 mg per meter group did have a much higher number at base.

DR. GHALIE: Right. These patients, as you remember, were randomized not taking into account the MRI scans. There were no stratifications based on MRI. And as you may know, taking this into consideration, it is not surprising that there were some differences among the three groups with baseline value. This is why you may have noticed that we are talking about subset analysis, and we did not put p values on this slide, because we recognized this as being a subset analysis.

DR. GILMAN: Yes, Dr. Grundman?

DR. GRUNDMAN: Just a quick comment and then a quick question. As an oncologist, one thing that is interesting is that you could have patients on for 2 years, where 73 percent of the placebo group remains on study, while with an indication of prostate cancer, the median survival rate is only 10 months. So it shows you a dramatic difference between the two diseases.

Secondly, I was wondering what the criteria were for treating relapse. Was there a standardization or strict

criteria as to what happened in oncology based on progression?

DR. GHALIE: In this study--and the same will be true for Study 902, so I will address these two at the same time--the protocol specifically defines what is a severe relapse, what are the criteria for severe relapse, and also when a patient can be treated. This is when a patient has a severe MS relapse. Those are using standard definition of severe relapses. And the treatment for severe relapse is, again, a very standardized regimen which is high-dose methylprednisolone--corticosteroid--500 mg to 1 g daily for 3 to 5 days. So the protocol had a very strict and specific definition of what is a severe relapse and when it can be treated, and that was true for both studies.

DR. GRUNDMAN: Just a clarification. Which of the outcome measures were performed by a blinded rater and which were performed by the clinician who know the treatment and was treating the patients?

DR. GHALIE: The three disability scales which assessed neurologic impairment--that is, the EDSS, the Ambulation Index and the SNS scores--were done by the masked neurologic evaluators. These physicians were trained at the onset of the study about how to do the EDSS assessment, the AI assessment and the SNS assessment, and those physicians had no contact with the patients as far as management; they

had no access to the patients' records, and they were not to talk to the treating physician about the patient's condition. They just came and did the visibility assessment, and that was it.

The physicians who were treating the patients, deciding when to treat relapse were unblinded to study drug.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: In that regard, there is a lot of unblinding in this study as well as Study 902, and in many cases, some of the measures, including time to treating first relapse, obviously were being determined by people who knew whether or not the patients were on drug. The patients in some of these studies apparently knew. And all of your 36-month measures were also unblinded for the most part with regard to patients as well as physicians.

Why was that decision made, and what were the advantages of having so much unblinding done in these studies?

DR. GHALIE: Let's summarize briefly what is blind and what is unblinded. What was masked for study drug was the neurologic disability for Months 0 to 24. What was unmasked or unblinded was assessment and treatment of relapses. Treatment of relapses and assessment, although unblinded, were very well-defined and gone through in the protocol. The primary measure was Month 24, so let's focus

now first on the first 24 months.

The decision to have the treating physician treating relapses was made from the outset for practical reasons. As you may know, relapse in multiple sclerosis can occur at any time; it doesn't come at specifically predetermined periods. So it was logical to have the treating physician who knew the patients, who had access to the patients, to be the one who made the decision about treating relapse. This is very commonly used int rials in multiple sclerosis.

The question now is why the treating physician was unblinded to begin with, and that again is a decision that was made early on based on the fact that this is a chemotherapy, and it was felt--and I would like to have Dr. Hartung address this issue in a moment when I am finished--that it was for the patients' safety to have the treating physician, who was delivering the new investigational chemotherapy, be aware of what treatment the patient was on.

The patients were masked--they were receiving a placebo that was blue--so technically, they didn't know whether they were receiving Mitoxantrone or placebo; it is a 5-minute infusion, it is a blue infusion, the urine turns blue in both cases, so it was hard for them to tell what they were on. If they were to know what they were on--that was strictly said in the protocol--they were asked not to

tell the physician during the neurologic assessment what arm they thought they were on--they never knew what they were on, but if they were to know or thought they knew what they were on, they were to keep this information to themselves and not tell it to the blinded neurologic disability assessor.

For Month 36, it is slightly different, but before we get to that, I would like to have Professor Hartung comment on the fact of why they decided to unmask the treating physician in this study.

DR. HARTUNG: I can just reiterate that our foremost motivation to do so was to put the safety of the patient first, considering that we were dealing with a drug which had previously been used in a cancer population with potentially serious side effects and that the treating physician obviously had to have knowledge of lab count, et cetera.

Nevertheless, as mentioned, there were clearly laid down regulations, stipulations, as to what was considered a relapse, standard definition, a severe relapse, and a relapse necessitating steroid treatment. And adherence to these guidelines was verified by the audit procedure.

I think that looking at the magnitude of the effects on relapse, the consistent effects seen in looking

at all relapses, those that were considered to require treatment, make us confident that we were in actual fact looking at true effects of the drug.

DR. GHALIE: Thank you, Dr. Hartung.

DR. GILMAN: Dr. Penix?

DR. PENIX: I am still not exactly clear what the specific assessment criteria for the treating physicians were, but were you able to take that data and correlate it with the assessments of the blinded examiners?

DR. GHALIE: The blinded examiners looked only at disability; they did not look at relapse. So comparing disability and relapse are really two different outcomes, and therefore, trying to correlate the two was not necessarily something we could do.

What I would like to show you now is a slide that shows all the evaluations we did on relapse and how they are all consistent throughout the evaluations that were done. That will be Slide B-77, please.

[Slide.]

DR. GHALIE: If one looks at any type of relapses that were treated, relapses that were determined as being severe, relapses that were seen by the treating physician or relapses seen by physicians at home, and the treated relapse that was the primary endpoint, if one looks at all of them, there were really consistency of results with Mitoxantrone

that were highly significant compared to placebo.

So this magnitude of effect gives us some level of confidence of the robustness of the relapse assessment--again, comparing relapse to EDSS may become extremely difficult, because these are really two different endpoints in MS progression.

DR. PENIX: Since there were two different relapse assessments that were made by the blinded--the time to relapse and the number of relapses--and also the treating physicians determined whether there was relapse or not--was there any correlation between those two groups or those two situations?

Dr. GHALIE: It is the same individual who determined the type of relapse and therefore when the first relapse had occurred, which gave us the time to first relapse. That was the treating physician who was unmasked to study drug.

Again, the treating physician was the one who was in charge of patient management and who decided when relapse occurred. And when we talk about time to first relapse, that was when did this first occur in each patient.

DR. GILMAN: Dr. Lipton, then Dr. Temple, then Dr. Wolinsky.

Dr. Lipton?

DR. LIPTON: Given that you have several endpoints

that were assessed by a blinded rater than two endpoints that were assessed unblinded, why did you choose to combine ratings that would be relatively easy to have a lot of confidence in and ratings where knowledge and treatment effects might influence the assessment of the endpoint?

DR. GHALIE: This study, as you recall, was started in the early nineties, and at that time, it was unclear whether Mitoxantrone affected disability progression, relapse, or both. And as you know, when patients with multiple sclerosis have medical problems, they can have either disability progression or relapse. So it was unclear whether one needed to focus on one, the other, or both. Therefore, this is why it was decided to look at all these variables early on as the primary endpoint.

Now, it is true that there was a combination of endpoints that were masked and some that were unmasked, and this is where the primary multivariate test took into account the combination of the five variables. But if you look at them sequentially, the first two variables were the ones that were done by the masked neurologic disability assessor. So the two first ones are the primary ones. If those were not significant, the comparison could not have continued. The comparison would have stopped at one or two.

So the two primary variables of efficacy were the ones that were done by the masked evaluators, and they were

significant.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: A comment and a question. You obviously could have protected the patients by having someone like the local oncologist or someone take care of the drug administration and the monitoring of white counts and things like that, and have the neurologist be actually blind. I am sure in retrospect you might wish to have done that.

I have another question about the relapses. Did this involve just taking the neurologist's word for it, or did you actually review the description and make your own judgment about whether it looked obvious, borderline, or whatever? Have you rated the relapses in any way other than just yes, there was one, and we treated it?

DR. GHALIE: It seems like this is a question that a number of panel members are interested in, so I would like to have the slide that shows the definition of relapse--I believe that is Slide A-12--in which it spells out in the protocol for that study what is a severe relapse and therefore, the one that needs to be treated.

So it spells out it is a patient who--I can read it, or you may want to read it--they have to have new symptoms lasting more than 48 hours, two or more functional scores, or--I am not going to read it. So these patients

really had to have something that was clearly obvious as being a relapse.

There have been audits of that study since it was conducted, first by the auditors in Germany who did the study, then by Immunex, who had sent auditors to review the study, and then, finally, by the Agency's auditors, who were sent there also, at least, to some sites to audit the data. And there was no evidence from this audit that the definition of relapse was not followed, and whether the patients were treated erratically or not.

So we are confident that the definition of relapse was followed and that treatment for this relapse was done accordingly based on these three series of audits that we have mentioned.

DR. GILMAN: Could we have the slide back again, please?

So there had been a deterioration of functional status score, I presume, from what you have said there. Does that indicate that the patient had a new neurological abnormality on examination or just a change in functional status?

DR. GHALIE: I would like to ask Dr. Hartung, who was one of the investigators on that study and who had to make this determination, to answer this question.

DR. HARTUNG: Could I just ask you to repeat the

question, please?

DR. GILMAN: Yes. The change in functional status score of two points, did that require that the patient have a new neurological abnormality--in other words, an up-growing toe where there previously was not one; a change in spasticity that was obvious--what did you need to see?

DR. HARTUNG: A new abnormality, with an increment by two.

DR. GILMAN: You used just the scale; you did not require a new neurological abnormality.

DR. HARTUNG: Yes.

DR. GILMAN: That was my question. And could you tell us, then, what you mean by "severe"? It's not clear from that slide what "severe" means.

DR. HARTUNG: "Severe" was defined as an increase in the score of at least or greater than two points, or a deterioration of previously existing symptoms of more than one point.

DR. GILMAN: Then, would you define "relapse"--not severe, just relapse--please.

DR. HARTUNG: Yes. The occurrence of a new episode of neurologic symptoms or deficits last at least 24 hours in the absence of fever or other precipitants of a pseudo attack.

DR. GILMAN: Then, it was just the history that

gave the definition of a relapse?

DR. HARTUNG: History in the case when a patient who was not close to the MS clinic that participated in the trial was seen by a local neurologist, examination in these centers where we did see the patient.

DR. GILMAN: Dr. Wolinsky?

DR. WOLINSKY: The question I had intended before, I'll try to come back around to, but this turns out to be an interesting area to further explore.

So one of the first questions I have is that when we speak about EDSS, it turns out that there are various flavors. There is the one that Kurtzke described, where patients might or might not have been required to walk; there is the one that Ludwig Kapos [ph.] has a variation of; there are ones which were used in the Lindamide [ph.] trial, and they all have slightly different variations. One of the most important variations in terms of the total EDSS score is whether the patients are observed to walk a certain distance, and that becomes very critical as the patients get into this lower-mid portion of the EDSS score.

What EDSS definitions did you use?

DR. GHALIE: Dr. Hartung, please.

DR. HARTUNG: We did use Kurtzke's definitions as laid down in the neurology paper. And we did require the evaluating physicians to observe the patient walking and to

also time the walking.

DR. WOLINSKY: The next question--and this comes back to the issue of relapses--is was the evaluating neurologist required to examine the patient when a relapse was felt to possibly be occurring, and did the treating neurologist then look at the evaluating neurologist's scores to determine the relapse, or did the treating neurologist have his own scoring set and use those to determine whether the relapse was confirmed?

DR. HARTUNG: The latter is true.

DR. WOLINSKY: And if the relapse occurred distant from one of the sites and possibly was treated distant from one of the sites, how did you know whether or not the relapse was actually consistent with this definition using the EDSS and the functional scores to help you define it?

DR. HARTUNG: In those few instances where the patients were unable to visit the center, we did contact the local neurologist who thought that the relapse was severe [inaudible] and we checked whether these criteria were fulfilled.

DR. WOLINSKY: So did the neurologists distant from the sites undergo some kind of a training session to allow you to be sure that they were actually assessing patients in the same way that you would have at the study sites?

DR. HARTUNG: They had not undergone training sessions, but they were experienced in the treatment and assessment of multiple sclerosis patients.

DR. WOLINSKY: And when you say that this was a low number of attacks that were actually not confirmed at the study sites, could we actually see those numbers?

DR. GHALIE: Certainly. I would like to go back to the slide which shows all the relapses, B-77.

[Slide.]

DR. GHALIE: So these are the relapses that were treated by the treating physician.

DR. WOLINSKY: But these means that almost an equal number of relapses were not actually observed by the treating physician?

DR. GHALIE: No, not here. These are the total treated relapses, and these are the relapses seen by the treating physicians--treated relapses, in fact.

DR. WOLINSKY: But the number of relapses, which is the first level--

DR. GHALIE: Yes.

DR. WOLINSKY: --is higher than any of the other levels.

DR. GHALIE: Yes, for the total relapses. So there were some relapses that were seen by the physician near home, let's call it.

DR. WOLINSKY: So for example, for the placebo patients--that was almost 50 relapses--were not seen and confirmed in the centers?

DR. GHALIE: For general relapses. But for those who were treated--and unfortunately, I don't have it on that slide--most of the relapses that were treated were treated on the participating site. And I agree, it is not on that slide. This is all relapses.

DR. GILMAN: So we don't have the number of patients with relapses seen by their local physicians; you don't have that information for us, I gather. Is that the case?

DR. GHALIE: Well, actually, this slide shows the number of patients who had a relapse diagnosis at the instigation site, and total number of relapses. So the balance, indeed the difference, is what is seen by the local doctor. What I don't have here indeed is the number of treated relapses by the local doctor. I don't have it on this slide. But again, Dr. Hartung says--I don't have the data here, but our statistician may comment on that as well--that these number was a minority of those treated relapses.

DR. GILMAN: Please keep the slide on.

So--Jerry, you can figure it out--it is, what, 50 placebo cases, for example?

DR. WOLINSKY: It looks like--and my math was

never very good--

DR. GILMAN: It looks like about half.

DR. WOLINSKY: --about 50 of the placebo attacks and about 30 of the 5 mg per meter squared and roughly 18 of the Mitoxantrone attacks that contribute to the database were never confirmed at the site, as best I can deduce from this data.

DR. GHALIE: This is relapse in general. What we have looked at primarily was the treated relapses, and those are not seen here, that were seen by the doctor near home, and this is what Dr. Hartung is going to comment on right now.

DR. HARTUNG: May I just add that I think the crucial and critical point is those relapses considered to be severe and those that, according to the protocol, necessitated treatment, and you can see in Columns 2, 3, and 4 that there were marginal differences between those that were treated and seen by the treating physician at the center and the total number--66 versus 63.

Relapses, as you know, in many protocols, or the occurrence of relapse, can be by historical information alone.

DR. WOLINSKY: I'm not going to disagree with that at all; I am just trying to understand the data. So that when we talk about the time to the first treated relapse, we

are talking about the time to all of those relapses which are below the first line; is that correct?

DR. GHALIE: Yes, correct.

DR. WOLINSKY: So the Kaplan-Meyer curve, for what it's worth, is not contaminated by these locally reported relapses--in general.

DR. GHALIE: Correct.

DR. GILMAN: Dr. Hartung?

DR. HARTUNG: Well, you know, the treating physician--and that may be the complication or misunderstanding generated by this slide--the treating physician saw most of the relapses but decided not to treat them because they were not considered severe. So that is the larger difference that you see here in the slide.

DR. WOLINSKY: If I could change the questions a little bit because I'd like to understand what kind of patients we are treating and what the treatment effect looks like for different kinds of patients. So do you have a subgroup analysis that would let me see what happened to the change in the disability scores, the EDSS, et cetera, in those patients who never had attacks in trial by treatment?

DR. GHALIE: Certainly. We have, as you would imagine, looked at all of these subset analyses, and they are subset analyses based on whether they were defined as secondary progressive or remitting progressive, whether they

were defined as having had or not relapsed prior to enrollment and other variables. We have looked at that for the five primary endpoints in the three groups as well as for the two primary groups, and I have a number of slides that can look at that.

I would like to have Slide B-28.

[Slide.]

DR. GHALIE: This slide shows the five primary endpoints taking into account patients who had a relapse in the year prior to enrollment and patients how did not have a relapse in the year prior to enrollment in the three groups. That is the primary variable that I show here. We didn't put p values here, obviously, since those are subset analyses, but one can see that for each of these primary variables, it was always in the right direction. Again, negative values mean it is getting better, positive values mean it is getting worse. Mitoxantrone 12 and Mitoxantrone 5--that is placebo--is for EDSS in patients who had prior relapse. And if we look at no prior relapse in the preceding year, 0.13 as the mean change, 0.67 for EDSS. And if we go down the list for the other three disability scales, we have the same direction.

DR. TEMPLE: I don't think that's what the question was. The question was if you look at people who had no relapses during treatment, what was their disability

outcome. That is even a worse subset analysis. That is not even based on baseline characteristics. So--

DR. GHALIE: Therefore, we did not look at subset analysis.

DR. TEMPLE: Well, that's very prudent, but it still would be interesting.

DR. GHALIE: I am sure that we can do that, and Dr. Hartung would probably be interested in looking at that in his manuscript. We'll check it on our things to do.

DR. WOLINSKY: I think I can pass the microphone for a while.

DR. GILMAN: Dr. Swain?

DR. SWAIN: Well, Dr. Wolinsky asked a couple of my questions, but I had another question. In the FDA safety review, it was mentioned that I think 52 percent of the placebo patients were on other drugs for symptomatic relief, whereas only in the 30 percent range, the patients on Mitoxantrone were on other medications, suggesting to me that the placebo group was much more symptomatic at baseline and that it was very biased and that the randomization did not work.

Can you comment on that?

DR. GHALIE: Well, these patients were randomized, so if there was any different at baseline, again, these were not stratified based on symptomatic treatment.

What we have looked at in our analysis is what are the concomitant medications given while on treatment, and there was really no major difference among the three groups. Most of these symptomatic treatments that were used in patients with MS are antispasmodic or treatment for bladder or vitamins, minerals, herbs, things like that. So really, they did not think this would in any way affect the assessment of disability and relapse as we have seen in the study.

Maybe Dr. Hartung would also like to comment on what kinds of concomitant medication patients tended to use in this study and if he has an opinion as to whether this would in any affect assessment of treatment.

DR. HARTUNG: Well, again, I can only reiterate what you have already listed--the usual antispasmodics, the drugs to treat bladder problems, and alternative medicine/vitamins or whatever.

I am not aware that there was a significant difference in the usage of these symptomatic therapies in the various treatment arms.

DR. SWAIN: Well, that's not what the FDA review has. I think it has 51.6 percent placebo and 36.7 in the 12 mg, so there was quite a bit of difference in that.

DR. GHALIE: Slide C-42 in fact gives data per patient, so we can make the percentage and give the same

information. It is already here. So really, the patient on placebo had more myorelaxant and vitamins and antispasmodic--but again, you can see the difference is minor.

I would like to see if any of our consultants can make a comment that myorelaxants are likely to affect when we talk about treatment effect on EDSS and relapse.

Dr. Hartung, Dr. Panitch, would you like to comment based on your experience in patients with MS?

DR. PANITCH: Well, concurrent/concomitant medications to symptomatically treat MS are universally allowed in clinical trials, and I think that the number of patients that we have here is small enough that I don't know if these differences are significant, but I certainly would not expect the commonly used antispasmodic drugs--for example, xanoflex [ph.], to have an effect on the underlying progression of the disease. They might affect the EDSS, and one usually attempts to maintain a patient--if the patient is taking the drug at the beginning--to maintain the drug and the dose throughout the trial so that you don't change the results during the trial.

But these kinds of things are so generally accepted in treating MS that I certainly would not expect them to make a major difference.

DR. GILMAN: Dr. Swain, do you have anything further?

DR. SWAIN: No. I mean, I agree that they are used, and that's really not the point. The point is that there are more patients on the placebo receiving them, indicating that they have more severe symptoms, and also, since the time to relapse is not blinded, it is a very biased endpoint, and I have a real problem with using that endpoint and really trusting it.

DR. GILMAN: Dr. Katz first, then Dr. Temple, then Dr. Grotta.

DR. KATZ: A couple of things. One question. I note that the criteria for defining a severe relapse were either a new disability and a greater than 2-point increase in the Kurtzke, I gather, or a worsening of pre-existing symptom, and the worsening had to be of at least one point on one of four, or however many it was, functional scales.

I am wondering if we have a breakdown of how many of these severe relapses by drug group were defined by the first criterion versus by the second criterion?

DR. GHALIE: The data was not collected. The data was collected such that did the patient suffer from severe relapse or not, and whether treatment was given and what type of treatment. They did not collect data about what defined a relapse. It may be available in the patient's record, but it was not collected in the case record form, and it is not available to us.

DR. KATZ: So, then, we don't know the nature of the disability, or let's say you don't know the nature of the disability that someone called a severe relapse; you just have a box that was checked that said "severe relapse"?

DR. GHALIE: Right.

DR. KATZ: Okay, so we don't know what the patients looked like clinically.

I had one other sort of statistical question. The protocol, as you said, first required that the multivariate analysis be done, or multivariate measure be assessed, and if that was significant, then you went sequentially down, and you only went down as long as the one before was significant, nominally significant.

I am wondering if blind-breaking was at work here. Let's just for argument's sake say that there was a problem there. When you looked at the multivariate analysis that too would have incorporated that bias, because part of that was a result of blind-breaking. So I am wondering from a statistical point of view what is the appropriateness of relying on a measure to determine whether you can do subsequent tests of the individual measures when that initial measure might be subject to the bias introduced by potential blind-breaking.

DR. GHALIE: The data analysis was conducted by a CRO who was hired specifically for that task, and when they

did the analysis, they were still blinded to treatment arm. And it was only when all the analyses were completed that the unblinding was performed.

DR. KATZ: I don't follow. You said the analysis was done at the end of the study.

DR. GHALIE: Yes.

DR. KATZ: That doesn't get at the problem, I don't think, that I am raising, which is that the data are biased--allegedly, just for argument's sake, assume--so that when those data go into the multivariate analysis, the first screening analysis, if you will, those results might be unreliable. And it is only the basis of a particular result on that analysis that permits you to go down the list.

So I am just raising it as a possible concern. I don't know--Dr. Van Belle, does that strike you as being relevant?

DR. VAN BELLE: I think what you are saying is that the overall analysis, the global analysis, could have had a p value that was larger than you would expect because of the unblinding of the third, fourth and fifth outcomes where there was unblinding. Given that the first two blinded outcomes are also significant, I would not judge that to be a very important point.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Nothing further.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: I am just a stroke neurologist, but to my knowledge there have only been a few drugs that have been shown by evidence to affect the number of relapses, so I just need to be sure that none of the patients in this trial received any drugs that were either experimentally evaluated at that time or that have subsequently been approved to affect the number of relapses.

DR. GHALIE: This study and Study 902, which I'll present to you later, were both conducted before the Interferon and Latrimeris [ph.] data were approved in Europe, and therefore, none of these patients had received prior and definitely not while on the study any of these agents. So they were Interferon and Latrimeris [ph.]--and remained throughout the study.

DR. GROTTA: And that was true of both studies? We might as well get that out of the way for the next one.

DR. GHALIE: Yes, correct; for both studies.

DR. GILMAN: Dr. Penix?

DR. PENIX: Going back to the issue of concomitant medications, my understanding is that the patients who were on study drug were treated with the anti-nausea drug ondansetron, whereas the placebo patients were not given this--they were given a placebo agent. So what was the decision not to treat the nausea for the placebo group with

the same drug, and particularly since 76 percent of the patients on the 12 mg dose of the study drug had nausea and only 20 percent--a significant number of the patients actually got the treatment for nausea whereas the placebo patients did not. What was the choice for that?

DR. GHALIE: As you know, at the time when the study was conducted, mitoxantrone had been used in oncology experience for many years; it is known that one of the effects of chemotherapy is to produce nausea that can last a day or two. So to protect those patients who were going to receive the chemotherapy, the decision was made to give them an anti-emetics. The decision was also made at this time that patients who were going to receive placebo did not need an additional drug that they were going to have side effects from, and they decided to go for the matched placebo.

DR. PENIX: Even if they did have nausea--I mean, you were treating the nausea for that, so 20 percent of those patients did have nausea--that was not treated?

DR. GHALIE: I would like to ask Dr. Hartung to comment on that, whether patients who were randomized on placebo and did have nausea were still treated with an anti-emetic beyond the first day. But the bottom line I would like to come back to before I pass it to Dr. Hartung is that these patients received the anti-emetic for the day of the treatment, and it is extremely unlikely that ondansitron

given on day one would have any effect on effect on days 7, 10, 15, 21, et cetera.

But I'd like to have Dr. Hartung comment on whether patients who were on placebo and still had nausea eventually got some anti-emetic versus just the placebo.

DR. HARTUNG: They certainly did, but it was the idea, of course, that we didn't want to expose patients who were on placebo to a drug with possible side effects. That so many placebo patients in actual fact did have nausea was a little bit astonishing to us, but we know this from other placebo-controlled trials.

But yes, if they did become nauseated, they did receive symptomatic therapy.

DR. GILMAN: So this was not given prospectively, before the infusion.

DR. HARTUNG: No.

DR. GILMAN: It was given only with the symptom.

DR. HARTUNG: No. Initially, it was given prospectively for those who were randomized to receive mitoxantrone, and ondansitron placebo for the placebo patients. Only if those placebo patients did become nauseated did they receive symptomatic therapy.

DR. GILMAN: So that's a potential clue that patients that the patients being treated with real drug--I think that's your question as well--

DR. PENIX: It appears that the placebo patients were given a placebo drug for that. My concern is that I doubt if there was a treatment effect of taking this drug, but the 76 percent of your patients who were on the 12 mg dose did receive a drug that the placebo patients did not. Therefore, I just wonder if these was any concern about that--and is that typical for MS trials?

DR. GHALIE: I would like to clarify; I think I see where there is confusion here. All patients who were in this study got a pill before getting mitoxantrone or placebo. Before getting study drug, they all get something. The patients who were randomized to mitoxantrone 12 mg per meter squared or 5 mg per meter squared got ondansetron. Patients who were randomized on placebo got a pill that was a placebo, that looked identical to the Odansitron.

The protocol also allowed to repeat a dose of anti-emetic 8 hours after the dose of mitoxantrone administration or placebo administration, and that second dose was also either Odansitron for the mitoxantrone group or a matched placebo for the placebo group.

Beyond that, if a patient continued to have nausea, or particularly if the placebo patient had nausea, then they were to receive anti-emetics, no longer placebo.

So everyone got a pill before getting the study drug, and again, that's to continue the masking. Now,

again, as Dr. Hartung said, the rationale to give patients randomized to placebo a placebo pill as opposed to an active agent was based on why give active agents when we can give a placebo to the placebo patients. So it was a decision early on for the patients' safety not to give them Odansitron.

Now, we all know--and the oncologists around this table can mention it--that Odansitron is used extremely commonly in cancer patients. It is a very potent and active anti-emetic.

DR. PENIX: But in a cancer trial, would they also give the same drug to the placebo group?

DR. GHALIE: I am an oncologist by background, and I don't think I have ever seen a placebo-randomized trial in cancer patients.

DR. SWAIN: We have many placebo-randomized studies, but I think that normally, you would not give the active ant-emetic.

Do you agree, Bob? I have never really seen that done. I understand your point, though, because it could have some activity.

I have one quick question. How as the randomization done?

DR. GHALIE: The randomization lists were generated by computer program, and the randomization was done on a per-site basis to ensure balance within each site

and the number of patients assigned to these three groups.

The study was done in 17 centers in four countries, and for the mechanics of it, there were really two randomization centers--they all had the same lists--one in Germany and one in Belgium. For the Belgium centers, the randomization center was in Belgium; for the German, Hungarian and Polish centers, it was done in Germany. They would call there, they would get the patient's number assignment, and they would assign the patients.

DR. SWAIN: So the pharmacists were blinded at all the centers except the two randomization centers?

DR. GHALIE: I'll let Dr. Hartung speak to that. I presume the pharmacists knew what they were administering, because they knew it was placebo versus mitoxantrone. Again, the person who was blinded was the person who assessed disability--and the MRI, obviously.

DR. GILMAN: Dr. Grundman first, then Dr. Wolinsky, then Dr. Dahut.

DR. GRUNDMAN: With respect to the blinding of the person who assessed the disability, 60 percent of the patients were reported to have alopecia and 70 percent were reported to have nausea. Were there any measures taken to prevent the so-called blinded rater from noticing that the patient's hair was--

DR. GHALIE: There were no measures taken

especially to put a cap or a hat or something like that. However, I must say right now--and we'll get back to this when we talk about safety--alopecia in this trial was really not a complete hair loss as one would imagine with chemotherapy. It is really hair thinning. So that although one could tell maybe that a patient was on one arm or the other one, really, the alopecia may not have been by itself a clue.

As far as the nausea, as I mentioned earlier, if patients knew that they had a lot of nausea, they were asked not to tell the blinded neurologic disability assessor that they thought they were on chemotherapy.

And lastly, just to conclude my point, chemotherapy is given one day; neurologic disability assessment was done 3 months later for that cycle. So by that time, anything having to do with nausea, et cetera, would probably have completely resolved by that time.

DR. GRUNDMAN: Given that most of the patients who were receiving the active drug knew what they were on, or a good portion of them had that suspicion, is it possible that that might have tainted their effort in performing these ambulation studies?

DR. GHALIE: I don't know how we can tell that patients thought they were on chemotherapy or not. I'm not sure that this was always obvious to them. As you will see

in the safety profile, the drug was [inaudible] acutely, so it may have been that they were really masked to treatment. They were getting methylene blue, so they had the same kind of blue environment that I can describe about what happens when someone receives mitoxantrone.

Now, as far as can a patient have a different EDSS assessment based on the fact that they may or may not have inactive treatment, I would like to have our neurologic expert comment on that. Maybe Dr. Panitch would like to comment on that and then maybe Dr. Lublin or any of the study chairs also could comment on that.

DR. PANITCH: I think it is possible for patients to make very variable efforts in cooperating with neurological examination, but don't forget, these were all trained examiners who had been instructed in how to perform the EDSS, who were experienced in it, and should rely on the objective areas of the EDSS in scoring the patients.

A certain amount of variable effort is possible, but when this and the Ambulation Index are performed and performed correctly, I think that that is minimized.

DR. KATZ: Could I just ask a clarifying question? Which measures of the EDSS are objective in the sense that they don't require patient motivation or participation?

DR. PANITCH: Well, they almost require motivation and participation. Even performance of tendon reflexes can

vary depending on how a patient is feeling and how much coffee he has had that morning. But the ones that are generally considered the most objective are peramital, cerebellar, the brainstem, and one other--visual, I guess, although that requires a patient to read an eye chart--as opposed to sensory and bowel and bladder, which are more by patient report. So generally, more weight is placed on those.

DR. KATZ: Thank you.

DR. GILMAN: Dr. Wolinsky had some questions, then Dr. Dahut.

DR. WOLINSKY: A small point. Odansitron, apparently by some, is believed to be useful in symptomatic treatment for tremor. I assume all of the EDSS scores were done before the administration of the drug, so you will easily assure me of that?

DR. GHALIE: Yes. The answer is yes.

DR. WOLINSKY: The second is a little bit more bothersome, and I just think there is no way to get around this, and I'm not sure I'm very uncomfortable with it. But I assume that all the patients signed a consent form to participate in this study, and I'm sure that the consent form must have stated side effects which were well-known for mitoxantrone at the time. And I'm sure that many of the women in this study would have been able to figure out

whether they had thinning of their hair, even if the men couldn't, that they would have known if they were developing amenorrhea--although the men might have had a hard time--and that some of these side effects are undoubtedly unblinding of the patients. I think we just have to accept that.

DR. GHALIE: That's correct. This is why the protocol and the investigators agreed and explained to the patients that if they knew what arm they were on--and I agree with you they may have known--at least that was to be kept to themselves and not inform the investigators who evaluated neurologic disability.

DR. GILMAN: Dr. Dahut?

DR. DAHUT: I have a quick question about the EDSS. The main change in EDSS was a worsening in placebo group of 0.23 and an improvement in the mitoxantrone group by 0.13, so a total change of about 0.36, I guess. Is that a clinically important difference between neurologists, and would variability among the tests explain some of that?

DR. GHALIE: It is a difference and a significant difference--

DR. DAHUT: Statistically, but is it a clinical difference or just a statistical difference?

DR. GHALIE: It is a mean, so it includes patients who got better, who did not get better, who got worse. This is always why the mean gets to be so hard to separate. But

that was what was decided early on in the study design to do as primary endpoint. That was the early nineties study design.

But if you look at all the other EDSS measurements that I presented to you, the one-point change, the mean change over time every month, every 3 months until the end, they were also significant in favor of mitoxantrone and that gives us more confidence that really, there was an effect on disability which at least for some patients was real. Again, some people may like to talk about the EDSS one-point change that was confirmed at 3 months and 6 months. I presented at 6 months, but 3 months presented the same data. The proportion of patients who had a worsening of one point was significantly different in mitoxantrone, much lower than in placebo.

So although the mean change of 0.5 may not be clinically large, by all the other measures that looked at larger EDSS changes were also in the same direction, significantly in favor of mitoxantrone.

I don't know if other physicians would like to comment. Dr. Panitch would like to add to that.

DR. PANITCH: Your point is well-taken, and as a neurologist--I'm not going to speak for other neurologists here--a change of half a point on EDSS for an individual patient is not significant and is not replicable either by

the same examiner or by some other examiner. But if we're talking about group data and we're talking about statistics, then it becomes more relevant and, in my view, more compelling.

Nevertheless, even for group data like this, half a point is not a lot; it is when it is put in the context of all the other trends and significant outcomes that it becomes convincing.

DR. GILMAN: Dr. Ghalie, it is now 10:15. With your permission, can we take a 15-minute break and then come back to Study 02?

DR. GHALIE: Certainly grant this permission; I would love that.

DR. GILMAN: We'll reconvene in 15 minutes for the open public hearing.

[Short break.]

DR. GILMAN: Since the time of the break, we have been joined by Dr. Howard Weiner, who will introduce himself.

DR. WEINER: My name is Howard Weiner. I am at the Multiple Sclerosis Center at the Brigham and Women's Hospital, Massachusetts General Hospital in Boston, at the Harvard Medical School.

DR. GILMAN: Thank you, Dr. Weiner.

Let's resume, then. Dr. Ghalie, would you

continue on, please?

DR. GHALIE: I will continue my presentation where we left off by presenting now the data for Study 902, beginning first with the design and efficacy results.

[Slide.]

Study 902 is a prospective randomized corticosteroid-controlled trial. It was conducted in five centers in France. It enrolled 44 patients. Professor Edan, who is with us here today, designed and chaired the study.

The first patients were enrolled in April of 1992, and the study closed in March of 1995.

[Slide.]

The main inclusion criteria are listed on this slide and consist of patients age 18 to 45; a disease history of less than 10 years; and what is defined in the protocol as a "highly active disease" as defined by an EDSS progression of at least 2 points or at least two relapses in the 12 months preceding enrollment. So that's a highly active or rapidly deteriorating MS. Also, the baseline EDSS had to be 6 or less.

[Slide.]

The exclusion criteria as listed in the protocol are shown on this slide as well.

[Slide.]

Let me now describe the study design. Patients eligible for the study based on clinical criteria--meaning the 2 EDSS point progress or the two relapses or a combination thereof--underwent a 2-month triage lead-in period which is shown here. During this period, they received methylprednisolone one gram intravenously every month for two courses, and they underwent MRI evaluation before each of these two courses of methylprednisolone. Only patients who had active gadolinium-enhancing lesions detected on these two MRI scants were then allowed to be randomized into the trial. So to be enrolled in the randomized part of the study, patients had to have active disease based on both clinical criteria and active MRI gadolinium-enhancing lesions.

Patients were randomized either to continue on methylprednisolone alone, continuing on the same schedule, one gram intravenously every month, or to receive methylprednisolone at the same does plus mitoxantrone. Mitoxantrone was given at a fixed dose of 20 mg per course.

For those of you who are not familiar with the shift from meter squared to fixed dose, a dose of 20 mg in an average adult is very similar to 12 mg per meter squared.

Randomized treatments were given monthly for a total of six courses.

[Slide.]

Patients underwent monthly evaluations, both clinical and MRI evaluations. Dr. Miller in London reviewed all the MRIs of this study, and as you know, his center is the reference center for European MRI evaluation, and in 1991, he published "Guidelines for Conducting MRI Scans for Patients with Multiple Sclerosis."

During his review, Dr. Miller was masked both to study drug and to patients' clinical outcome. He just had a list of patient numbers and the MRIs that he reviewed.

In this study, the physicians were responsible for patient management, study drug administration, assessment of safety evaluations, as well as assessment of neurologic disability and relapse. These patients were unmasked to study drug.

[Slide.]

The goal of this study was to assess treatment effect on inflammatory lesions in the CNS using MRI scan as the marker. These scans were done monthly in this study, as I have mentioned.

The primary MRI efficacy endpoint as defined in the protocol was a comparison between the two groups and the number of patients who had new gadolinium-enhancing lesions on monthly MRI scans from Month 1 to Month 6. So that was the primary endpoint--patients with new Gd-enhancing lesions.

A secondary MRI endpoint was defined as a comparison between the two groups and the number of new Gd-enhancing lesions. So the first primary endpoint was patient, and we're now talking about new Gd-enhancing lesions, again on monthly MRI scans from Month 1 to Month 6. And there were also secondary clinical efficacy endpoints as measured by the EDSS scale that we described earlier and relapses.

The number of patients required for the study was 21 per group, and that was again based on published data from Miller et al. for an MRI-based study design such as this one. With these 21 patients per group, it was estimated to be possible to see a 50 percent difference in the number of patients with new Gd-enhancing lesions during this treatment period.

DR. GILMAN: May I ask a question at this point? When you talk about the number of new Gd-enhancing lesions monthly, do you mean relative to the previous month or relative to any of the previous months? What do you mean by "new"?

DR. GHALIE: "New" in this protocol and in the analysis I will present to you today is relative to the preceding month. Clearly, we have done evaluation now for any Gd-enhancing lesions, so it really doesn't take account compared to the previous month or to baseline. And I have

all this information available.

DR. GILMAN: So it is relative to the previous month only?

DR. GHALIE: Right. It is new compared to the previous month because one can conceive of patients have MRI lesions at one month, disappearing and coming back. In this case, it is considered something not good, so it is a new Gd-enhancing lesion.

DR. GILMAN: Please, Dr. Grotta.

DR. GROTTA: Just one quick methodological question. So the patients would come in, they assumed they would get their MRI scan before they were dosed with the study drug and steroids?

DR. GHALIE: Correct. And it was specified in the protocol to be done before the corticosteroid to be sure that it does not affect the MRI scan that would be performed at that time.

DR. GILMAN: Dr. Grundman?

DR. GRUNDMAN: Again, just a methodological question. The person who was looking at the MRIs did not look at the MRIs independently; is that correct--he had access to the previous month, so a whole series of those MRIs were collected and given to the rater.

DR. GHALIE: Yes. These scans were all done in these five centers in France, and they were all sent to