their opinion, there is no increased incidence of toxicity due to the fact that they had received Interferon previously.

Having said that, as a company, we have been approached already by investigators wanting to study Mitoxantrone in patients who had failed Interferon therapy. So there are two ongoing studies right now, pilot studies, safety studies, very carefully designed to look at safety. I do not have the data yet. These studies are currently ongoing.

DR. WEINER: The second part of my question is is there any theoretical or pharmacological reason to believe that patients on Interferon would have more likelihood of having toxicity from Mitoxantrone?

DR. GHALIE: I am not aware of any theoretical reason, but I would like to ask any of our consultant experts who have used Interferon.

Dr. Lublin, you have used Interferon--please.

DR. LUBLIN: No relationship to this.

DR. GILMAN: He has nothing to say.

DR. GHALIE: Dr. Alberts has something to say.

DR. ALBERTS: I can't comment on betaseron, but with alpha-Interferon, there are large databases in patients with multiple myeloma who have had high doses of doxarubisone followed by long periods of alpha-Interferon,

and that also applies to non-Hodgkins lymphoma, and there has not been any known evidence of an interaction between alpha-Interferon and the anthracyclines.

DR. GHALIE: Dr. Smith, who has some patients who have been treated, would like to comment as well.

DR. SMITH: We have had two patients from Alaska who were started on Mitoxantrone and told us after initiation therapy that their betaseron had been continued until we found that out and stopped it, and there was no difference in their hematologic profile. That was after 2 months in one patient and 3 months in the other patient. So we do have some experience with combined therapy.

DR. GILMAN: Dr. Lacey?

DR. LACEY: You propose if this drug is approved to cap the cumulative dosage of Mitoxantrone. In the United States, considering how medicine is practiced, where both physician and patient are quite mobile, do you expect to do anything other than the patient package insert to help to facilitate this capping of the drug with patients?

DR. GHALIE: As you rightfully mentioned, in the U.S., the physician decides how and when they want to treat their patients. The best we can do as a company is to bring forth the information we have in the package insert and the educational material. In addition, there will be postmarketing databases or studies that will be performed by

Immunex to try to collect postmarket information on safety, and we will be able to tell, if there are some patients who go beyond that dose, what will occur to them if anything. So that will be something that we will be proactively looking at.

DR. LACEY: I guess I am more concerned with the preventive aspect of it going beyond the 140.

DR. GHALIE: The best we can do as a company is make it very clear in the package insert as well as in educational material and publications that will be published.

Dr. Mauch has a comment here.

DR. MAUCH: I would like to make a comment on this very important question you have asked. We manage our patients giving them a sort of "passport." At the start of Novantrone therapy, the patient is handed a passport, and every dosage is registered in this passport, and even if the patient changes to another doctor, he is quite informed about the dosage, about the last leukocyte count, about ECG information, or if echocardiography is executed. And in Germany, the patients are not so mobile as your patients are, but I think this would also be a good idea to manage your patients.

DR. LACEY: So this is something that could possibly be considered as a recommendation.

DR. GILMAN: Yes.

DR. GHALIE: Dr. Ann Hayes, the senior executive in the company, would also like to add her comment to that.

DR. HAYES: Yes, I think I would like to comment that we are trying to be proactive on putting a cap on this to try to indicate that you should not go above this in these patients in our opinion. We fully realize that physicians make a choice and patients make a choice, but I think that as a company, we will certainly try through the MS Society and the various branches to make sure patients are educated, too, on the potential dangers of cardiotoxicity if they go above these doses. So it is not just physician education, it is also going to be patient education.

DR. GHALIE: Dr. Alberts, please.

DR. ALBERTS: Just briefly, I think it is remarkable that etched in the minds of oncologists because of educational programs are the doses for doxarubisone and Mitoxantrone not to go beyond because of cardiotoxicity issues. So that educational program, at least in oncology, I think is very, very successful.

DR. GILMAN: A question from Dr. Lipton, then Dr. Katz, then Dr. Temple, and then Dr. Van Belle.

DR. LIPTON: Given the long survival of people with MS and given the toxicity that we have been talking

about and given the benefit of the 5 mg per meter squared dose in your first study where, if anything, the benefits were numerically superior on EDSS with the lower dose, why did you choose to recommend the higher rather than the lower dose?

DR. GHALIE: This is indeed one of the questions that Dr. Katz raised, and were obviously ready to answer that. You are right to mention that the EDSS evaluation for the 5 mg per meter squared for the results appears to be better than 12 mg per meter squared; although there was no significant differences between the two, they were both better than placebo. That was the only evaluation in fact EDSS where 5 looked better than 12.

If you look at the five primary efficacy endpoints, all five of them were significantly better with Mitoxantrone 12 compared to placebo. Number two, two of the five were significantly better with Mitoxantrone 5. So we recommend now going to 12 mg per meter squared for the following reasons.

One, that was a dose that was always significantly better than placebo. Two, it is the test dose in this pivotal trial. The 5 mg was an exploratory dose; it was not sized for that dose. Three, this is also the dose that was tested in Study 902. As I mentioned, 20 mg fixed dose or 12 mg per meter squared are very similar, so we have

information from two independent studies that this dose worked. We don't have information from independent studies for the 5 mg. And finally, the majority of the experience in cancer patients is based on doses around 12 mg per meter squared. So that is why we recommend 12 as the dose for that indication at present.

DR. LIPTON: The thing that strikes me, though, is that the variables where the 12 mg per meter squared dose has the greatest difference relative to the five are the variables that were rated by an unblinded rater who could be influenced by the greater adverse event profile of the drug. So that is at least part of the context in which I look at these data.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes, one comment and one question. The sponsor was beginning to discuss some possible ways if the drug is approved to prevent its use beyond 140 mg per meter squared--labeling, education, that sort of thing. The Committee will just have to discuss, if you think it is approvable from the effectiveness point of view, whether or not those sorts of warnings and educational efforts will actually prevent its use above 140.

Obviously, we have a number of examples where labeling has been excruciatingly clear about how a particular drug shouldn't be used, and then, of course, it

is used in that way. So that is something that we'd like to hear what the Committee thinks about.

Then I had a question about this so-called passport which you use which accompanies the patient. I just wonder if you have any evidence about how successful it is in informing another physician when the patient does move? You said it works out well--the patient takes the passport, and the next physician is well-informed. Do we know if that's true?

Dr. MAUCH: We try to prevent the patient moving among several doctors. If a patient comes far from our clinic, we try to see that he has a certain doctor and only one doctor who continues therapy. This passport is mainly for information between our clinic and the outside physician, and it is not the intention to let the patient move among a lot of doctors.

DR. KATZ: Okay. So presumably, the success of this passport system is not so much dependent upon the existence of the passport but the fact that the patients are fairly restricted in whom they go to and in terms of the number of physicians they go to.

DR. MAUCH: It does not have the power to restrict a change in doctor; it is intended to have very valid and complete information about therapy, and it is intended that this information is only between treating doctor outside and

the clinic.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: One can imagine a registry system, depending upon how serious one is going to be about this, that actually tried to accumulate dose and perhaps interacted with a patient passport record. Those are probably all things that one should talk about.

I just want to make one observation on the low dose effects. There aren't nominal p-values given for the low dose placebo comparison, but my look at it would say that only the EDSS would be statistically significant if you actually did look. The others are leaning in the right direction, and it is tempting to think that, at least for some people, the lower dose might work. But if one is looking for at least--do we have nominal value--sorry--so the actual values show what I guessed from looking at it--only the EDSS is nominally significant--AI is not so far.

DR. GILMAN: Dr. Van Belle?

DR. VAN BELLE: I was going to discuss the same point mentioned by Dr. Lipton.

Could you put up Slide M-40 for us, please?

DR. GHALIE: Yes. M-40, please.

[Slide.]

DR. VAN BELLE: Just one small point. The 22 percent associated with improved should actually be 28

percent. There is a mistake in that table. So that certainly, the Mito-5 looks at least as good as the 12 dose.

The other thing is that, as was already mentioned before, this index plus the Ambulatory Index, which if you look at the data is virtually identical to the 12 dose, I don't see on the basis of these two blinded outcomes anything to choose between Mito-5 and Mito-12.

DR. GHALIE: We did an additional analysis to determine the dose-response effect, the John Curry [ph.] test, which I do not even want to try to explain, but our statistician will be happy to discuss with you. He explained to me that comparing placebo 5 and 12, there is a trend in the dose-response effect when looking at all patients. That is why we are feeling more confident in recommending a dose of 12 mg per meter squared.

DR. VAN BELLE: Then, I assume that that test was not significant for this particular outcome, for the EDSS?

DR. GHALIE: It was done for the EDSS valuable, and Mike Butan [ph.] may want to comment further on that.

MR. BUTAN: Actually, it was significant for this variable also. I think that that is driven, though, by the low placebo rate. So you are smoothing out that response due to a placebo group. So you have a significant test even though the 5 was numerically higher than the 12.

DR. LIPTON: But I assume you didn't test for

differences between the lower active and higher active dose.

MR. BUTAN: Oh, yes, we did. That was non-significant.

DR. LIPTON: All of them were non-significant?

MR. BUTAN: A few of them were significant, occasionally--I don't recall specifically; we have done so many analyses. I think perhaps one of the time to relapse was significant, but by and large, they were non-significant. We are seeing consistently strong results for 12 versus placebo, and we are seeing very good results for 5 versus placebo, but not nearly the magnitude. So we do see consistent dose response throughout all endpoints.

DR. GILMAN: Dr. Wolinsky?

DR. WOLINSKY: Isn't the time to attack in terms of the dose response very heavily driven by the few attacks which occurred very early in that group, and then the curves are very parallel?

MR. BUTAN: I believe a log ranked [ph.] test is actually going to be more sensitive to sensoring later on in the curve, whereas the Wilcoxin [ph.] would be more sensitive to early ones.

DR. GILMAN: All right. Let's move on to risk-benefit, then, please, Dr. Ghalie.

DR. GHALIE: Yes. I am done with the data, so now it is going to be more a benefit and risk assessment of the

use of Mitoxantrone in patients with multiple sclerosis.

[Slide.]

The acute and long-term adverse events of Mitoxantrone are well-characterized and manageable. I will present guidelines, some of which we have discussed so far, on how to monitor these effects.

Mitoxantrone is effective in a well-defined subset of patients with multiple sclerosis which also I will describe. Overall, we believe that Mitoxantrone's benefits outweigh its risks in patients with progressive forms of multiple sclerosis who have limited therapeutic options.

[Slide.]

The adverse events of Mitoxantrone given at 12 mg per meter squared were well-characterized in the two randomized trials and in thousands of patients with cancer who received this agent.

In general, mild or moderate nausea and/or emesis may occur in about two-thirds of the patients. They do not happen with each course of therapy. That is important to know.

Number two, they tend to resolve a day or two after Mitoxantrone administration. This is not something that persists for the 3 months between courses. They can be managed with standard emetics, and we mentioned the ondansetron before as a potential treatment.

Severe alopecia is not seen, as we have already earlier mentioned, and alopecia usually consists of hair thinning and in many patients resolves after treatment is discontinued.

Severe leukopenia, based on what we have seen in Study 902, occurs in less than 50 percent of patients, and when we have looked in 902 on a weekly basis, we can tell you that leukopenia usually occurs between Days 7 and 14 and tend to resolve by Day 21. During this window of time, based on the two randomized trials we showed you, the risk of neutropenic fever is low. However, it is not impossible to develop neutropenic fever when there is a neutropenia nadir.

[Slide.]

We recommend that patients undergo serum chemistry before each course of therapy, including liver function test, as mentioned by Dr. Swain. We also recommend that a hemogram be performed before each course of therapy. In addition, we recommend that the hemogram be performed at the time of expected leukocyte nadir, meaning anywhere between Day 7, 14 or 21, in a patient who may have evidence, or at least clinic signs or symptoms, suggesting an infection. This is very similar to what the recommendation and experience is in cancer patients.

[Slide.]

Let's now discuss what we are talking about with cardiac toxicity in patients with multiple sclerosis. This risk was well-evaluated in the two randomized trials I have presented to you today. There were no cases of congestive heart failure at doses up to 100 mg per meter squared. We have no evidence and there is no evidence that the risk of congestive heart failure is going to be greater in patients with multiple sclerosis compared to cancer patients.

So a conservative recommendation in our opinion is as follows. We recommend doing a baseline LVEF evaluation and another LVEF evaluation when the patient reaches 100 mg per meter squared, which represents 2 years of treatment with a 3-month schedule.

[Slide.]

DR. GHALIE: Again, as I said, we recommend doing a baseline LVEF examination, and then, when the dose reaches 100 mg per meter squared, which is 2 years of treatment with a 3-month schedule.

Based on the oncology setting we discussed earlier, it may be possible to go beyond this dose. Continuing dosing should be addressed on an individual patient basis, and for each patient, weighing the risk of benefits of continuing therapy and the potential risk of cardiac events.

In this situation, as a company, we recommend

repeating LVEF before each course of therapy. Continuing therapy in patients who have an LVEF that declined by more than 15 percent from the baseline should also be determined on an individual basis. In other words, to state it differently, if you have a patient whose LVEF declined by more than 15 percent, before the next course of therapy, we recommend doing an LVEF evaluation and then deciding whether to continue treatment.

We recommend as a company to discontinue Mitoxantrone in two conditions--if the LVEF declined to less than 50 percent and when the cumulative dose reaches 140 mg per meter squared. We also recommend excluding from therapy--and this was discussed by Dr. Alberts--patients who already have cardiac dysfunction to begin with, who are above the age of 70, who have received chest radiation or doxarubisone, which I recognize the latter two are going to be rare in patients with multiple sclerosis.

[Slide.]

As already indicated in the package insert, Mitoxantrone should not be used in patients who are pregnant or are attempting to become pregnant. That is on the label, and that needs to be known by the physician and by the patient.

[Slide.]

I will now turn to the benefits of Mitoxantrone in

patients with multiple sclerosis. Study 901, the Phase III study, shows that Mitoxantrone slowed the progression of neurologic disability as shown by an EDSS progression reduction by 64 percent compared to placebo. It decreases the number of treated relapses by 69 percent compared to placebo. It also decreases gadolinium-enhancing lesions on the early MRI scan.

[Slide.]

Study 902 in our opinion supports the findings of Study 901. It shows that Mitoxantrone significantly slowed one-point EDSS progression by 83 percent compared to the control arm, decreased the relapse rate by 77 percent, and decreased the number of patients with gadolinium-enhancing lesions by 86 percent compared to the control arm.

Study 903 indicates that with appropriate monitoring, it is possible to use Mitoxantrone in a clinical practice setting.

I would now like to present Immunex' perspective on the question raised by Dr. Katz in his introduction. We have already addressed some of those before, but I will go through them again, one by one.

[Slide.]

First, to the question asked by Dr. Katz, were the two studies presented today adequate and well-controlled, our answer is yes. Study 901 was a randomized, placebo-

controlled trial. It had prospectively-defined entry criteria, efficacy endpoints, study size, and statistical analyses, all prospectively defined.

All five primary efficacy variables consisted of a well-characterized disability scale and standard definition of relapses.

MRI evaluations were prospectively defined to be done in a subset of patients enrolled in the study.

[Slide.]

Study 902 was also a randomized, controlled trial. It had prospectively-defined entry criteria and efficacy endpoints. It had the typical design of an MRI-based trial. It also included evaluation of clinical endpoints, including the EDSS scale and relapse.

[Slide.]

The second question that was raised by Dr. Katz was is there evidence that Mitoxantrone slows the progression of neurologic disability.

DR. GILMAN: Could I interrupt for a second? I actually wanted to stop you there, anyway. But you would agree no doubt that Study 902 was unblinded, and therefore, there has to be some question about the objectivity of those data--clinical data, that is.

DR. GHALIE: In Study 902--to indeed follow up your question--the primary endpoint was masked. The EDSS

and the relapse were unmasked. In our opinion, these results are robust despite this unmasking for the following reasons.

Number one, the magnitude of effect was quite large to be just a coincidence or a bias. Number two, they are consistent with the MRI results, which was a blinded assessment. And number three, if we see the two studies together, the magnitude of effect of Mitoxantrone in both studies is very similar--in fact, the effects on EDSS and on relapse were about the same magnitude--which in our opinion indicates that Study 902 clinical endpoints are also robust, albeit unblinded.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes. Maybe you will get to this, and maybe I should wait, but the first two slides you showed were not in response to any question I had asked.

Just to clarify, the first question I asked was whether or not there was replication or substantial evidence of effectiveness in a particularly well-defined population--progressive MS patients. Maybe you will get to that. But I think we thought that the two trials were adequate and well-controlled. There were certainly clearly blinding questions that we need to talk to you even more about, but as far as their meeting the primary outcome, it wasn't really a question for us.

DR. GHALIE: Indeed, I will be getting to the issue of the patient population.

[Slide.]

The third question to address is is there evidence that Mitoxantrone decreased the relapse rate, since it was done by unmasked physicians. And our answer, based on the two sets of data, is also yes. Now, we recognize, and we have discussed this before, that the treating physician was ummasked to study drug in both studies. However, as I mentioned, despite this unmasking, we believe that the data on relapse is robust, and I have already said that a minute ago, but I will repeat it.

First, the definition of relapse in the two studies, particularly the severe relapse that required treatment, was well-defined, and there is no evidence that the physician did not follow the definition of relapse.

Second, the effect of Mitoxantrone on the number and time to first relapse treated with corticosteroids was highly significant, so it is unlikely that it will be biased just by knowing the arm for which the patients were randomized to.

Third, and as I mentioned earlier for the EDSS, there were very consistent results between the two studies on effect on relapse, which again lends some robustness to the results in both studies.

And lastly, no matter how we look at relapse, whether it is treated relapse, severe relapse, relapse seen by the physician in the clinic, or relapse seen by the physician near home, all the results show Mitoxantrone being better than placebo.

So it is the combination of all the data on relapse that in our opinion provides the robustness to the interpretation of the relapse data in these two studies.

DR. GILMAN: Dr. Temple, a question?

DR. TEMPLE: Do I recall correctly--you don't actually have the descriptions of patients at the time they supposedly had a relapse, so that although you indicated there were criteria, you cannot say on your own--you can trust your investigators, but you can't say on your own--that you know whether the criteria were followed; is that right?

DR. GHALIE: This is always true in a clinical design. We have to trust the investigators to do the right assessment--

DR. TEMPLE: No, no, that isn't--I am not unsympathetic to your point of view necessarily, but what you just said it not true. You could have them fill out a little form explaining how they decided to treat, how it met the criteria; they could check whether the criteria were met. So please don't say that all studies have this lesion.

Yours does.

DR. GHALIE: No, no. I'm going to add to that. I'm sorry.

DR. TEMPLE: Okay.

DR. GHALIE: I hadn't finished my sentence. I was going to say that in addition, there was an audit that was done to determine whether the relapses that were called severe relapse or other were also documented by what we find in the patient case record form.

Thirdly--and this is something that Dr. Hartung would like to describe now--there was a form that was filled out that addressed the description of the relapse in patients randomized in his studies.

So, Dr. Hartung, please clarify how we can be confident with the relapse data.

DR. HARTUNG: All the relapses examined by the treating physician--or the treating physicians in each and every instance recorded the EDSS and then, based on the stipulated criteria, whether this is a severe relapse or not a severe relapse, ticked a box in the CRF.

So the EDSS data is available.

DR. TEMPLE: Now, this was the treating physician's EDSS?

DR. HARTUNG: Treating.

DR. TEMPLE: So that would be different from the

blinded one that was done. But you are saying it could serve to show that the nominal criteria were met.

DR. HARTUNG: Yes.

DR. GILMAN: But it doesn't address the situations in which the physician treating the patient at a long distance was not similar to the treating physician. And we saw there were a fair number of cases in that category.

DR. TEMPLE: No, it doesn't do that. It answers one of the possible questions, namely, that there were standards and that you can say, well, the apparent standards were met. If you don't look, you don't even really for sure know that, although you might believe it because you trust your investigators. That's a different answer, though.

DR. GHALIE: Next, I will discuss the MRI findings in this filing.

[Slide.]

In Study 901, MRIs were performed in a subset of patients who were randomized under the study. Patients were not stratified based on baseline MRI. That was a decision made early on. And the study was not sized to correlate MRI findings with clinical findings as we have already discussed earlier.

However, despite these limitations, there is a clear reduction in the number of patients with gadolinium-enhancing lesions as well as the number of lesions that are

gadolinium-enhancing in this study, and these results were similar, in the mae direction and consistent with the clinical findings of the study.

Taken together, the clinical findings and the MRI findings suggest a biologic effect of Mitoxantrone on the inflammatory process in the CNS in patients with multiple sclerosis.

[Slide.]

Let's look now at Study 902, which had the design typical that we see today for MRI-based clinical trials. The results of the MRI data were highly significant, and they were consistent, as I mentioned, with the clinical results of the study. And the magnitude of the MRI results in both Study 901 and Study 902 are very similar.

So taken together, Studies 901 and 902, in our opinion, provide further support to the activity of Mitoxantrone in multiple sclerosis.

DR. GILMAN: Well, there is the question about the differences in the cases. In 902, you had 15 relapsing remitting cases and 6 progressive cases; whereas in 901, most and essentially all were progressive cases. So there is a difference.

DR. GHALIE: There are differences in the patient eligibility and the type of patients enrolled, and this is what Dr. Lublin is going to discuss in fact imminently. I

will discuss the dose and maybe I can go into the target patient population and why we believe those data are supportive. Is it possible, or would you like me to--

DR. GILMAN: Dr. Grundman?

DR. GRUNDMAN: I have a question regarding the MRI results. Can I refer you to Table 6.1.2.a on page 27 of the FDA review? It is in section 4.

The question has to do again with the comparability of the two groups with respect to their entry into the study. One can see that at the month prior to baseline, the standard deviation of the number of lesions, as well as the median range of the lesions, was much greater in the methylprednisolone-alone group compared to the Mitoxantrone-plus-methylprednisolone group.

I am just wondering to what extent subjects who had many lesions on their MRI, or the lack of many lesions on their MRI, contributed to the mean response that you have seen. Did you make any attempt to stratify the results in terms of the number of lesions that were present either at Month Minus-1 or at Month 1?

DR. GHALIE: This study was not designed to stratify patients based on baseline MRI. Again, that was a 42-patient study, and stratification would have been difficult. And when we look retrospectively at the data, we looked at the data. We have not looked at this analysis

based on the number of lesions at baseline.

Dr. Edan, who designed and conducted this study, has a comment here.

DR. EDAN: We perfectly know that there is a great variation between patients concerning the number of lesions on MRI. This is the reason why the primary endpoint was not a reduction of new MRI lesions, but the percentage of patients with no MRI lesions at all, month after month. What impressed us when we saw the results was that it was month after month that the number of patients without any new activity of MRI increased in the group of patients with Mitoxantrone.

So it is not only the result of mean number of lesions, but we took the most robust primary endpoint for MRI analysis, which was patients with not one MRI lesion, which is much more difficult to reach.

DR. GILMAN: Please continue.

DR. GHALIE: Finally, I will address the issues raised by Dr. Katz about the dose and the target population.

[Slide.]

We propose that the approved dose of 12 mg per meter squared, which is approved in cancer patients, also be approved in patients with multiple sclerosis. The proposed schedule in multiple sclerosis is clearly different than cancer patients; it is going to be once every 3 months

compared to once every 3 weeks, as used in cancer patients. And as I mentioned to you, the rationale for proposing the dose of 12 mg per meter squared is as follows. It was the test dose in the Phase III study; all five primary endpoints and the secondary endpoints were significantly better with this dose compared to placebo. The fixed monthly dose of 20 mg that was tested in Study 902 is essentially identical to 12 mg per meter squared. Again, as I mentioned, this is the dose that we have the largest safety experience with in patients with cancer.

[Slide.]

Based on the results of Study 901, Mitoxantrone in our opinion was shown to be effective in patients with progressive forms of multiple sclerosis excluding primary progressive MS, and they were not tested in this trial.

Dr. Lublin will now address in his remarks current thought about the continuum of patients with multiple sclerosis and the rationale for this proposed patient population. As you know, Dr. Lublin was the lead author in 1996 for the new classification of multiple sclerosis in these four disease categories.

I will come back at the end of Dr. Lublin's presentation to conclude.

DR. GILMAN: Well, again, I have to comment on this last slide. Still, Study 902 consisted primarily of

patients with relapsing remitting.

DR. GHALIE: And I believe this is where Dr. Lublin will be able to shed some information on that specific question that you have.

DR. GILMAN: Thank you very much, Dr. Ghalie.

Dr. Lublin?

DR. LUBLIN: Good afternoon.

In 1993, this panel recommended and subsequently this Agency approved the first treatment for relapsing remitting multiple sclerosis. Since then, two additional agents have been approved for relapsing remitting and relapsing forms of multiple sclerosis. There is currently no approved agent for progressive forms of MS, including the 50 percent of relapsing remitting patients that are expected to convert to the secondary progressive form, especially for those in the higher disability scores.

Multiple sclerosis is a disease that can be categorized into several different clinical course subtypes. These have been derived by a consensus from a survey of physicians specializing in research and treatment in multiple sclerosis and published in 1996. We have heard a bit about this during the course of the day, but let me run through the types for you.

[Slide.]

The commonest course of presentation is relapsing

remitting. This is acute flare-ups, exacerbations of multiple sclerosis followed by a period of disability, followed by improvement which can be either complete, as in the top part here, or incomplete. If the improvement is incomplete, then there is stepwise accrual of disability.

Over time, approximately 50 percent of this group will then convert to the secondary progressive form. The difference between relapsing remitting and the progressive forms of disease is in the baseline between attacks. In relapsing remitting disease, there is a stable baseline between attacks, and in all of the progressive forms, there is gradual worsening.

The secondary progressive form is an outcome from primary progressive where they go into a gradual progressive form either with superimposed exacerbations or without. They start out as relapsing remitting; they are then secondary progressive.

The least common form in this categorization is the progressive relapsing form. They start out as gradual progressive disease punctuated by occasional clear-cut exacerbations, so they have some relapses.

In the primary progressive group, which has not been tested in any of the studies mentioned today, there are no acute exacerbations, just gradual progression, worsening of disease, which may occur at a variable rate.

It is important to not that there are no reliable radiologic, immunologic or biologic markers to distinguish these different types of multiple sclerosis. Some feel that primary progressive may in fact be a distinct subtype, but this is not yet proven. Most recent clinical trials have utilized these designations to obtain better homogeneity of their experimental groups.

Currently-approved therapy for MS is limited to relapsing remitting form or relapsing forms of MS and provides partial benefit as measured by reduction in relapse rate and/or lessened disability. There is no approved agent for progressive forms of disease.

[Slide.]

Worsening of disability in MS occurs via two mechanisms. There is stepwise worsening in the relapsing remitting form which is characterized by incomplete recovery from successive attacks. And then there is the gradual progressive worsening that occurs independent of relapses in the progressive forms of disease. The latter is generally considered to be the greater contributor to patient disability although it is still unclear whether the mechanisms of worsening are actually distinct or not.

[Slide.]

If one looks at the progressive phase of the disease, we don't actually know whether it is truly gradual

progressive disease or rather the summed effect of multiple mini exacerbations, each one of which is not necessarily expressed as clinical disease.

[Slide.]

Despite the lack of proven agents for the more devastating forms of MS, many patients are subjected to treatment with potentially toxic therapies without the benefit of supporting, well-designed, randomized clinical trials. These treatments are administered by well-intentioned clinicians who are confronted with patients who have entered an aggressive phase of deterioration. This is especially troubling for patients who have already failed one of the currently approved therapies such as Interferon-beta and gluteramir acetate [ph.].

[Slide.]

In this slide, we show the groups of patients that would be appropriate for more aggressive forms of therapy and correspond with the groups of patients who are presented here today--that is, patients with relapsing remitting disease who are undergoing stepwise deterioration, patients with secondary progressive disease anywhere along this course, and even patients with progressive relapsing disease which wasn't named until 1996, so it is hard for me to tell, looking back into the database of patients, whether any of these were there or not, but they fit in our hands into a

similar pattern as this. But clearly, these two groups of patients have been included in the studies today, and both are undergoing worsening of their disease.

[Slide.]

The data presented today are consistent and robust. They demonstrate that Mitoxantrone is an effective treatment for slowing disability and reducing relapse rate in patients who are accruing disability and are in the higher range of EDSS. There is no approved, proven effective agent for this group of patients, and thus, Mitoxantrone provides a very reasonable therapeutic option.

Thank you.

DR. GILMAN: Thank you.

Dr. Wolinsky?

DR. WOLINSKY: I wonder if Dr. Lublin could enlighten the Committee as to what kinds of patients were actually included in the pivotal trial for Betaseron, the pivotal trial for Avanex, and the pivotal trial for gluteramir acetate. That is, how would you distinguish the proportion of patients in those trials who were relapsing remitting without accumulated disability, relapsing remitting with some accumulated disability, and relapsing remitting with some amount of progression in between?

DR. LUBLIN: In the Betaseron group, it was all, at least at the start, relapsing remitting, as you will

recall. And they were from--

DR. WOLINSKY: Did we have the wisdom of your definitions then?

DR. LUBLIN: No. In fact, for none of those studies were the current definitions. But the definition that was employed for relapsing remitting disease would have excluded patients who had progressive disease in the Betaseron study.

In the Avanex study, that was not the case, and in fact, when presented here, it was mentioned that there were in fact some patients who they thought could have had progressive disease in addition to relapses, and I think that that in fact affected the labeling. Copaxone, again, the definition was such that I would be confident that those were relapsing remitting patients.

How many ended up accruing disability--they all did. If you look a the Kaplan-Meyer curves, over time, the patients were getting worse in all groups, just less worse in some groups.

DR. GILMAN: Dr. Katz?

DR. KATZ: So as I understand it, your assertion is that the patients in Study 902 were relapsing remitting, but with an accumulating deficit that wasn't resolved. Is that it?

DR. LUBLIN: This again comes from conversations

with Dr. Edan. When you look at his definition, his definition is active relapsing remitting patients having two or more attacks over a year's time, or progressive patients that have increased by two points on the EDSS. HE tells us that in fact in the relapsing remitting group, they were stepwise accruing deficits, but that wasn't necessarily in the definition.

DR. KATZ: No, no. I know it wasn't in the definition, but the assertion at this point after the fact is that in fact they were patients who, although you would still call them relapsing remitting, in fact had an accumulating deficit; they might have been stable between attacks, but--

DR. LUBLIN: That's absolutely correct. That is one of the mechanisms of worsening.

DR. KATZ: I understand that. I'd like to know what the evidence is for that assertion.

DR. LUBLIN: For which assertion?

DR. KATZ: For the fact that these patients were relapsing remitting with an accumulating deficit. As I understand, you're trying to make the point that in some sense, even these patients, even the relapsing remitting patients in Study 902, were progressive. And I am trying to just see what the evidence is to support that.

DR. GHALIE: If i might intervene here, Dr. Edan,

could you repeat again in your protocol the definition of enrollment in the study, which again was written long before the 1996 classification. And as you will hear from Dr. Edan, the way the eligibility criteria was, it will include the patients Dr. Katz has asked about.

DR. EDAN: Yes. We include a category of patients who within the previous 12 months have had at least two relapses with sequelae, and these patients reached the high level of handicap. If you remember, the levels they had after 5 years of the disease, the irreversible EDSS at that time had been at least one month after relapse, were at 4.5, which is very high for a relapsing population 5 years after onset of the disease. So it is clear from my experience and from the study we did that the population who were treated with monthly Mitoxantrone were mostly relapsing remitting patients, with sequelae.

DR. GILMAN: Now I am confused. I thought earlier you said these were all relapsing remitting patients, period, without accumulating disease burden. There were 15--

DR. EDAN: No, no. They were with accumulative disability within the 12 previous months after each relapse.

DR. GILMAN: All of the 15 that were called relapsing remitting.

DR. EDAN: Yes, yes.

DR. GILMAN: All of them were relapsing progressive. Is that what you're saying now?

DR. LUBLIN: No. We like to avoid that term, Dr. Gilman.

DR. EDAN: It is confusing, the term "progressive," I understand, but there was worsening of the EDSS after the relapses.

DR. LUBLIN: Just for clarification, they worsened their EDSS after relapses, and they did not go back.

DR. EDAN: Yes, that's right.

DR. LUBLIN: So they stayed worsened, and then they were--

DR. EDAN: Yes.

DR. LUBLIN: Can I have my first slide?

[Slide.]

DR. LUBLIN: There it is. This group here. This is still relapsing remitting, because the baseline between attacks is stable. But if they don't return to their prior baseline, they are accruing disability. This is what used to be called relapsing progressive by some, but then some also called this relapsing progressive, and that's why we did away with it.

DR. WOLINSKY: Can I again have a little bit more clarification, then, because if we stick to this religiously, then patients who are the top blue line could

only get into a study if, between attacks, they were EDSS zero, and we would only have--this is the way it's shown--

DR. TEMPLE: No. The second line are relapsing remitting, but they don't get back to zero.

DR. WOLINSKY: I understand that they are relapsing remitting with accumulated disability between attacks with stable periods. What I am trying to drive at--and I think this is not trivial, because I actually have a very sympathetic feeling for what I believe the investigators treated in Europe, but I think in terms of trying to help my colleagues in the field, when or if they have this drug, they need to know what to treat. So my problem is that, at least in my own mind, the only way I can really be sure how these groups are different is to know how I cut them by EDSS score and the fact that they at one time or another had enough attacks to get into trial.

DR. LUBLIN: You may very well be right. This is a very common form of MS. Any patients who comes into study with relapsing remitting disease of 1, 2, or 3 has been in here. They haven't returned to a baseline of zero at some point. So you are right, one has to know more than just relapsing remitting disease with accrual of deficit. It is perfectly reasonable to say what else do you have to qualify that with to have aggressive forms of therapy. If that is the point you are getting at, I agree with you.

DR. WOLINSKY: It is very much the point, because the potential extension--and it may be absolutely where we should go; I don't know the answer to this--is to take a patient at first diagnosis and begin Mitoxantrone. But we will hit our cap fairly quickly.

DR. GILMAN: Dr. Temple, do you want to ask your question now?

DR. TEMPLE: I guess for the certified non-neurologist here, to look at those lines between exacerbations and try to figure out whether they are ever so slightly rising or absolutely flat seems a very daunting task. Does everybody really believe you can do that? Again, I know nothing about this; that is important to realize.

DR. GILMAN: I wonder if Dr. Lublin wants to answer that.

DR. LUBLIN: Well, I see some heads shaking no, but yes, I absolutely think you can. We follow these patients, especially the ones on therapy now, so we follow patients a lot more closely, and you have a pretty good idea--even a very good idea--from month- or 3-month to 3-month period whether the patient is changing or not. I don't think this is that difficult a task.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: I guess maybe I'm missing something,

but I don't really see the confusion. I recognize that people in that second line are included in this study, but not all of them. They had to have had more than two relapses in the last 12 months or they had to have had an EDSS progression of greater than or equal to two points. So not everybody on that second line would have gotten into that. It would have been the relapsing remitting patients who didn't return to normal between attacks who had particularly frequent episodes of relapse. So I don't think it's all that complicated--plus the other patients who were in the study were those who were progressing, who had the progressing baseline in between attacks.

So I think that that should be the guideline. I think that what has been proposed is that that group of patients, then, would benefit from this treatment and did seem to benefit from this treatment in Study 902 by MR criteria.

DR. GILMAN: Dr. Lipton?

DR. LIPTON: Yes, but granted what you said, here is my problem as someone who is far from an MS expert. We are being asked to use the evidence in the 902 study to make a judgment about whether or not this treatment works in progressive MS, and some proportion of the patients enrolled in that study have something that we would now call progressive MS, and some of them don't, and in order for me

to apply the data in 902 to the judgment we are being asked to make, I feel the need to know how treatment works in a group that we would call progressive MS, not looking at those who have something else. It sounds like a subgroup analysis to me based on reclassification of patients blind to treatment group.

DR. GILMAN: When I read the narrative that Dr. Katz and the Division prepared, it sounded as if there were 15 patients in Study 902 who had relapsing remitting, and it was undisclosed whether they were the cases that you would see on the first line or on the second line. We now hear that all 15 would match the second line, if I am understanding what the sponsor is telling us. Therefore, it sounds as if all the patients in 902 had a progressive form, even though 15 out of the 21 had relapsing remitting symptoms also.

DR. GHALIE: That is correct. I probably should have been clearer when I presented the patient population and enrollment criteria. Patients, to be enrolled, if they had relapsing remitting, they had to have--as Dr. Edan said, and it was spelled out in the protocol as well--they had to have sequelae, meaning EDSS progression. So they do fit under blue line number two, correct. And this is why as a company we propose the words "progressing forms of MS," which is patients who have the orange line as well as the

second blue line or the yellow line as well, and we clarify excluding primary progressive. So that is really the patient population enrolled in 901 and 902.

DR. GILMAN: Dr. Weiner?

DR. WEINER: Could you put back on Slide M-112?

[Slide.]

DR. WEINER: Okay. I guess I'd like to make a couple points and then ask a question for those who have used the drug. If you look at the forms of MS that one wants to use the Mitoxantrone for, the top one, which is relapsing remitting, and the second one, which is secondary progressive with attacks would actually qualify for treatment with Betaseron or Avanex or Copaxone, because these are people with relapses and remissions, even the progressive relapsing form on one level.

So I am just thinking about the label and the claim that this is just for progressive forms, because those two actually would fit if you wanted to prescribe something for relapsing remitting patients.

The next question that I'd like to ask those who have used the drug--and in this case, what Dr. Wolinsky said in terms of where it really is effective--and I do believe the drug is effective, and I hope it can be approved, and we'll talk about that later, for the appropriate papulation--but I get the feeling that the patients that it really is

effective in are the blue line, the relapsing remitting, and the top line of the secondary progressive people who are having relapses and that the patients who are more slow-chronic-progressive, that secondary progressive, may not be helped as much by this drug. I would be interested in the comments of the physicians who have used it and put people into the studies and what their comments are and the response of the patients in the top two lines and the third line, which is a lot of patients.

DR. LUBLIN: Let me just stress your first issues, Howard. That is why, when I made this slide, I avoided the word "progressing" disease and used "worsening," because I don't know that there is any real difference biologically or any other way between this kind of worsening and this kind of worsening. If someone is ending up with a walker or a wheelchair or whatever, I am looking for something that is going to halt that. So I like "worsening" forms, because it doesn't lock you into anything.

DR. GHALIE: I'd like to address Dr. Weiner's question which was in two parts. We presented earlier this morning a slide that looked at the five primary endpoints including EDSS, Ambulation Index, and the SNS score, based on whether patients had relapsed or not prior to going into the study and whether they were classified as relapsing remitting or secondary progressive. And again, looking at

subset analysis--I did not want to present p-values--these slides show that Mitoxantrone patients were better than placebo whether they had or had not relapsed prior to enrollment. So that is to provide information for you about which one of these patient lines fit.

I'd now like to address and indeed direct my question what you had wanted to hear from physicians who have used this drug in patients to elaborate on how they see which patients fit. So I would first like to have Dr. Hartung, who did Study 901, and after that, Dr. Smith, who is a practicing physician who saw that data and is making decisions now about when to use this treatment in his patients.

DR. HARTUNG: Well, my answer is in two parts. First, the data that I can oversee that has been collected in the trial, and this was both patients in fact with active disease, whether they had relapses or not, but active progressive disease with deterioration.

Second, in my experience with some 30 or so patients who were treated outside the context of the trial, I got the impression that patients with active disease whether or not, again, they had superimposed relapses benefitted from the therapy.

So in my opinion, I think this is a therapeutic option that we should be able to offer patients with any

type of active progressive disease so as to hopefully stabilize them by time--3 years, 4 years, whatever--and perhaps make them responsive again to other kinds of immunomodulatory therapy, although I would very sincerely hope that you can agree that there is a place for Mitoxantrone in the treatment of multiple sclerosis.

DR. WOLINSKY: Peter, if you wouldn't mind elaborating a little bit before we go on to the next. I think I heard using this drug for patients who fail--and I know these are very difficult questions, but of all the people who are going to talk to us, I think you and Dr. Edan have the most experience, practically. So do you see this as your first choice for what kind of patient and your first choice for what other kind of patient? Could you give that to us?

DR. HARTUNG: Again, I think I have to differentiate in my elaborations whether or not I'm talking about data obtained in the trial or experience I collected over the years with the drug. I think we cannot right now, based on the data, say that this drug is also useful in patients who fail to respond to established therapy because we have not tested that in the trial.

However, I have in the meantime seen patients who received--since Beta-Interferon is approved in Europe for the treatment of secondary progressive MS, other than here

in the United States--that patients who did not respond either initially or after wide Beta-Interferon did receive benefit from Mitoxantrone therapy.

So I see in actual fact two scenarios. In patients with very active disease, rapidly progressive, I would consider or at least provide the physician as well as the patient with the option to use Mitoxantrone as a kind of induction and also would consider its use, if you like, as a rescue therapy in those patients--and they are certainly not few--who may have responded initially to Beta-Interferon or any other immunomodulatory therapy but fail to do so. And also, as you know, there are probably nonresponders from the beginning where this would also be an alternative to be considered.

DR. GILMAN: Dr. Penn?

DR. PENN: I think we are getting to the slipper slope at this moment, because what we are asking our colleagues to do is to tell us how they might use this outside of the data that we have for the drug. If we get into this, it will be extremely interesting, but it won't answer the question we have to address as a regulatory advisory committee, and that is: Do we have the data now to approve this drug on the basis of its efficacy and safety for what now, at least in my mind, is becoming fairly clear the clinical situation in which it has been tested.

So I think all of this is what we would do with the drug later on, but we should stick to the point because we can start talking about all sorts of experience, and then we're going to have trouble.

DR. GILMAN: Dr. Katz?

DR. KATZ: That's pretty much what I was going to say. If you do recommend approval, the indication will describe or be closely related to the population that was studied once we think we can define that, and then, as far as second line, if you recommend that it be approved for progressive forms of MS, there is nothing else in this country approved for those forms, so it can't possibly be second line in that case, because once a drug is out there, as you say, people can use it for anybody they want--of course, it is out there, as it turns out, but you get the point.

DR. GILMAN: Dr. Penix?

DR. PENIX: Clearly, there is a problem with semantics. It appears that the sponsor has proposed to have the drug approved for the indication to slow the progression of neurologic disability and reduce the relapse rate in patients with progressive multiple sclerosis. That second progressive is the thing that bothers me, certainly. When I look at the testimonials of the three patients, each of these patients has secondary progressive MS, and two of the

patients have indicated their interest in having a drug, if we agree with the reported claims, to be approved for secondary progressive MS.

Again, I think that certainly, that was my initial concern, and my recommendation would be for us to maybe either get rid of that second progressive or to change it to something like "moderate" or "severe," because clearly, my impression from the patients is that they are thinking that this is an indication for secondary progressive MS.

DR. GILMAN: I'm not sure we're going to be able to change that issue right now.

Dr. Katz?

DR. KATZ: Also, half the patients in the first study were diagnosed with secondary progressive MS, if I am remembering correctly. The other half had something else.

DR. GILMAN: All right, then. Can we turn to Dr. Ghalie for his final comments?

DR. GHALIE: I really essentially concluded my presentation of the data and our view of the role of this agent in the treatment of multiple sclerosis.

What I have tried to present to you today is that we have two studies. They were not identical; they were designed with different endpoints in mind. One has clinical endpoints that it met, and the MRI data supported that. One had an MRI endpoint that it met with the clinical data that

went in the same direction. You have discussed at length what kind of patient population might fit in this disease category.

But in our opinion, we have two well-designed, randomized trials that were conducted that show Mitoxantrone effectiveness and that it is usually well-tolerated in patients with multiple sclerosis.

Based on the data for the Phase III study, when Mitoxantrone is given by short intravenous infusion at a dose of 12 mg per meter squared every 3 months, it slowed progression of neurologic disability, it reduced relapse rate--and that is in patients, not to go into nomenclature, who have progressive forms of multiple sclerosis.

With this dose and schedule, Mitoxantrone can be given for about 2 to 3 years based on the dose that we have decided to propose as a cap.

In our opinion, this will still provide a substantial clinical benefit for patients who have a disease with no therapeutic option available to them and who are suffering from a serious illness.

Thank you. I am ready to take any additional questions you may have.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: The data here are a cornucopia of things you'd like to know but don't yet know. Could you

elaborate a little on any of your future study plans--in particular, the cap at 140 is obviously fairly onerous for people whose lives go on and whose disease goes on. That is potentially susceptible to study, with close monitoring of cardiac function. Do you plan that, or can you say anything about that?

DR. GHALIE: I can tell you about the studies that are currently ongoing and what we have proposed to the agency, in fact, to Dr. Katz' group, about what we intend to do in the future.

We have currently three studies. One was initiated about a year ago when the first of these data were available to investigators. That is a study conducted currently in patients with primary progressive MS. It is a pilot study, an d we have no data to share with you.

The other two studies are pilot studies that are conducted in patients who have--

DR. TEMPLE: Does "pilot" mean no control group? Is that what that means?

DR. GHALIE: It is a placebo-controlled study. It is not powered as a Phase III study, but it is placebo-controlled.

DR. TEMPLE: Okay.

DR. GHALIE: It is a methylene blue, as a matter of fact, controlled.

The other two studies are single-arm studies in patients who have failed Interferons. As you know, there are two Interferons currently available, and each of these studies look at patient populations that have failed Interferon, the first one and the second one. Those studies are really focusing on safety data first, but they include frequent MRI evaluation based on what we have learned from the experts in the field, to try to look at whether there is also efficacy assessed there. There will also be EDSS evaluation.

The other currently ongoing study--and it is presented in the briefing document as well as in our discussion with Dr. Katz' group--as a company, we are willing to do a post-marketing registry to collect data long-term on several hundred patients who receive Mitoxantrone in clinical practice, collect safety information on these patients long-term while on Mitoxantrone or after they completed Mitoxantrone. That hopefully will provide further safety information on this drug as you wish.

DR. TEMPLE: What about doses beyond 140? I think Dr. Alberts said there was some suggestion that a protectant athiol [ph.] might be beneficial. Does that seem like an area you plan to pursue? We may ask you the same question in other fora, but I wonder if you want to say anything

about it now.

DR. GHALIE: Certainly as a company we are interested in looking at potential ways to decrease this cardiotoxicity if we can. These studies, as you know, are very complex to do. Dr. Swain is really the expert here, and she knows how long it takes to be able to collect that information. This is not something we can provide right away. This is something we may have to do prospectively. And that is again something that we are willing to discuss with you as you wish.

DR. TEMPLE: Actually, the candidate group would be people who are getting near their limit, and they probably exist. At that point, you need to randomize to continue treatment, or continue treatment with athiol, or something. But the candidate population doesn't have to be collected; it's out there for you.

DR. GHALIE: As you know, in the U.S., very few patients currently with multiple sclerosis have been treated with Mitoxantrone, so they are not at that point yet. We may go to Europe and try to find out if this patient population exists.

Dr. Alberts has a comment, I understand, presumably about athiol, which is his expertise.

DR. ALBERTS: I would just very briefly reiterate what I said before, that there is a very large chance that

one could go well beyond 140 mg per meter squared, obviously, in a research setting. In this population of people where you exclude people with pre-existing cardiac dysfunction, any prior radiation to the chest, older age, and of course, prior anthracyclines, if you in fact use the population that should be treated, and knowing also--something that I didn't comment on--that dose intensity is involved in the cardiac dysfunction situation with anthracyclines and anthracene dions [ph.], so the point I'd make is that there is every reason to feel that you could go beyond this, and in fact, I think studies need to be designed to look at that. And yes, I think athiol has a real potential role in this area.

DR. GHALIE: Thank you.

DR. GILMAN: Are there any other questions for Dr. Ghalie or the sponsor?

DR. WEINER: I'd just like to ask a question of Dr. Swain. If you--and I don't know if you can answer this or not--but if you took 10,000 people, MS patients, between the ages of 20 and 30, who had no cardiac history or problems, and you treated them with 140 mg per meter squared of Mitoxantrone, how many of those would you expect to get into any cardiac problems?

DR. SWAIN: Well, all I can do is base a number on the information that was presented by Dr. Ghalie. It would

probably be in the one percent range. You're still going to see it even at low doses. You'll occasionally see it idiosyncratically, but it is not going to be high. As Dr. Alberts said, the older age group is more susceptible--although I would have to make a comment that your patients that you treated with this compound, I am sure none or very few of them had radiation, they were not supposed to have low ejection fractions. They didn't have any of the risk factors that he mentioned. So really, this is the group you are going to be treating. It will be present, but it is going to be very low.

DR. GILMAN: All right. Let me ask the sponsor if you have anything further that you would like to present to the Committee.

DR. GHALIE: Not at present, but in case some questions come up later and you would like me to come back, I would be happy to do so.

DR. GILMAN: Let me ask the Division if there is anything further that you would like to tell the Committee.

DR. KATZ: No.

DR. GILMAN: All right. For the Committee, then, there are three questions laid out that we will be voting on; they are in the sheets before you with the agenda. Dr. Katz has posed a series of questions, and I think it is best for the Committee to go back over those questions and see if

we can at least succinctly respond to those issues that were raised.

Yes, Dr. Weiner?

DR. WEINER: I am a non-voting member. If I have comments that I want to make regarding my view of everything, is this the time to say that before we are voting, or will there be a time later?

DR. GILMAN: You are certainly welcome to comment at any time during these deliberations. You are a consultant to the Committee and as such, we would hope you would participate in the discussion. You will not participate as a voting member, however.

DR. WEINER: Right. Are we going to vote now?

DR. GILMAN: No, we are not going to vote now. We are going to go through each of the questions that Dr. Katz wanted us to deliberate.

DR. WEINER: Right. I just want to be able to give some views about it before the voting.

DR. GILMAN: You are certainly welcome to do that.

DR. KATZ: You won't have an opportunity after the voting, so speak now, please.

DR. WEINER: So, do you want me to speak now or wait? I'm just asking that question.

DR. GILMAN: I think it's best if we go through each of the questions that Dr. Katz has posed. We would

like to hear your views if you have any about those questions, and then, when we come to the vote on the three questions before us, perhaps you'd like to make additional comments if you wish, and anybody around the table among the consultants can do so.

Dr. Van Belle?

DR. VAN BELLE: Could we take a short break?

DR. GILMAN: Dr. Van Belle has asked for a short break. It is 25 minutes of 4, and I know there are a lot of airplanes that are going to be taking off shortly that some of our members need to be on. Maybe we should have a very short, 5-minute break. I don't want you to be uncomfortable during the deliberations.

Let's take a very fast break, and please, be back here in 5 minutes.

[Recess.]

DR. GILMAN: Let us start again, please.

Dr. Katz has laid out a series of issues which I have abstracted, and we'll go back through, and we'll take these one at a time.

Of course, he wants to know what our opinion is regarding the controlled trials supporting the sponsor's claim--that is, does Novantrone slow the progression of neurologic disability and reduce the relapse rate in progressive multiple sclerosis.

He expressed the concern that Study 902 included mostly relapsing remitting multiple sclerosis patients, not progressive multiple sclerosis patients, and therefore, he wanted to know whether there are two independent trials that demonstrate efficacy.

So that's a question for the Committee. Now, in light of what we have heard, I believe there are two trials that showed an effect in progressive patients. I am now hearing that 902 cases, even though they are called relapsing remitting, those 15 cases were in fact showing progression.

Is that a debatable question before the Committee, Dr. Katz?

DR. KATZ: Yes. Just a clarification. You said that there are two studies that show an effect in patients with progression. I don't think we're up to the point yet where we know there is an effect--just in terms of keeping things in order.

DR. GILMAN: Thank you.

DR. KATZ: I was first concerned about whether there was an appropriate population enrolled so that a claim, if one was granted, could be made in that population.

DR. GILMAN: Thank you. I didn't say it right. It now appears that in both studies, the patients had progressive multiple sclerosis, and that's the question

before the Committee. Is there a disagreement about that question?

[No response.]

DR. GILMAN: Seeing no objection--good--let's continue on.

Dr. Katz wanted to know whether relapsing remitting and chronic progressive multiple sclerosis constitutes a continuum of disease, or are they distinct pathophysiologically and in their responses to treatment.

You will recall that in the Beta-Interferon studies, the cases were limited to relapsing remitting, and as far as I know, there are no studies as yet of the Beta-Interferons in chronic progressive cases. All the same--

DR. WOLINSKY: I think that's not exactly right, Sid.

DR. GILMAN: Okay. Let's hear about that, then.

DR. WOLINSKY: If what we mean by chronic progressive is secondary progressive, then the answer is that there are studies which are complete and reported, studies which are complete and in the pipeline for reporting, and studies which are complete and under analysis, and studies which are in progress.

DR. GILMAN: Are the results available to us now?

DR. WOLINSKY: The only studies which are in the published public realm that I am aware of at the moment are

the studies in secondary progressive that have been done in primarily Europe and I think with a few Canadian centers with Betaferon, which is basically the European brand name for Betaseron, and those show the now well-expected reduction in attack rate, reduction in MRI activity, and a modest slowing of disease progression.

The studies from Rebif [ph.], which is similar to some other drugs, have been publicly presented in a number of forums but have not yet been published, and those show similar things in terms of relapse rate and in terms of MRI activity but failed as an overall to reach their primary goal of slowing progression. They did show some benefits in subgroups. The other two studies are not available.

DR. GILMAN: Thank you. That is helpful to my own way of thinking. But I'd like to hear further about the question of whether these are different entities, relapsing remitting and the various forms of progressive disease, primarily primary progressive.

I wonder if we could have some discussion about those questions?

DR. WEINER: I think there is a continuum, but I think there is a differential between the relapsing remitting forms and the progressive types of disease that do have either relapses or regular progression with them. And I think another point that helps distinguish them--and we

didn't talk about it--is that if you're looking immunologically, there are certain changes that occur in the immune system in terms of chemokyne [ph.] receptor expression, interferon-gamma secretion in IL-12. It is seem more in the progressive forms of the disease than in the relapsing remitting forms, which would imply that the progressive form from an immunologic standpoint is also more active and may represent a different form or type of the disease.

So I think there is evidence that there are two different broad forms.

DR. GILMAN: Jerry?

DR. WOLINSKY: I could argue it the other way around.

DR. GILMAN: Suffice it to say there is not universal agreement.

DR. WOLINSKY: There is no question, at least in my mind, that as one gets into patients who have increased amounts of clinical disability, they have increased burdens of disease on their MRI, less of the acute measures of activity that we are used to seeing, like gadolinium enhancement and easily-defined clinical attacks, and probably--my bias--have accumulated more easily-found abnormalities in their immune system.

DR. GILMAN: Does any other Committee member or

consultant want to address that question?

[No response].

DR. GILMAN: Well, Dr. Katz, you have heard the two sides of this.

DR. KATZ: Yes. In my view, anyway, I think the question takes on a little less urgency given that the Committee has answered the first question in the affirmative. In other words, the question about how close they are pathophysiologically was designed to get at the question of if these were two different patient populations studied, could we take strength from one, from the relapsing remitting, to make an overall claim for progressive patients. But I gather the Committee thinks that both studies included progressive patients, which was the primary question I was concerned about.

If I could just back up to that question, if I could just hear some discussion about what the evidence is on which you would base your conclusion that the patients in 902 were progressive, whether you call it relapsing progressive or--well, they would be called relapsing remitting--but is it the EDSS at baseline?

DR. GILMAN: As I heard the presentation by the sponsor, these patients had an EDSS that increased, that worsened over time. In other words, these patients did not return to baseline and therefore would be viewed as having

progression--worsening.

DR. WOLINSKY: I think it's fair to say that these patients have aggressive disease in the mid-portion of the EDSS scoring range. It is very hard to differentiate beyond that in group data.

DR. WEINER: I would think that one could easily argue and be confident that there was a progressive component to the 902 as well when you define progression as accumulated disability in a disease that is moving in the individual patient, causing more neurologic impairment. And that's what progression is.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: I'm sorry--I thought I had learned that there was a difference between people who go up, up, and stay up, and people who inch up slowly. You are saying that a) that is hard to discover and b) it may not matter so much?

DR. WEINER: I am saying that obviously, there is a semantic issue here, and obviously, you are in a transitional phase, and because you are in a transitional phase, it is not going to be all one or all the other. But if you are talking about treating an MS patient, and you are talking about the fact that the problem with the disease is that it is a progressive accumulation of neurologic disability, even though we may argue about the semantics of

an attack and coming back or whatever, in my view, the people in the 902 are progressive in the sense that they are getting a progressive neurologic accumulation disability.

DR. TEMPLE: So they are transitional.

DR. WEINER: They are worsening.

DR. TEMPLE: And we don't want them to worsen.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: But at the same time, I am also hearing that this treatment is not advocated for the patient who has a relapsing and remitting--not all patients who have a relapsing and remitting course who have accumulated an abnormal Kurtzke score--in other words, the patient who has a hemiparesis and doesn't completely return to normal--there has to be some amount of disease activity over the last year in the sense of multiple attacks.

To me--and I guess that's what I am struggle with, is whether that needs to be spelled out--and to me, the key conceptual slot is the one that Dr. Lublin presented where he was showing the fact that the progressing slope can be either an intermittent one or a progressive one, but it is sort of the fact that patients are deteriorating or progressing, and I think we are struggling, or at least I am struggling, with how to get the proper wording for that.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: My understanding was that half of the

people in 901 did not in fact have exacerbations in the last year, although they were in one way or another worsening or had achieved a state where they were reasonably bad off, but they didn't actually have attacks. Isn't that correct--that you could divide it into two groups--although the mean number of attacks was in the neighborhood of one-and-a-half, half of the population didn't not have any during the preceding year?

DR. GROTTA: But they were worsening.

DR. TEMPLE: Oh, yes.

DR. GROTTA: In other words, they were going up on a steady way, or they were going stepwise.

DR. TEMPLE: Right, right.

DR. GROTTA: But the fact is that over the last year, they were getting worse.

DR. TEMPLE: Yes. I thought I heard you say that they had had exacerbations, but if you didn't, forget it.

DR. GILMAN: Dr. Penix?

DR. PENIX: The study was performed with specific exclusion of patients with primary progressive MS. There is evidence that some patients with relapsing remitting MS may benefit from this. And again, I hate to belabor this, but I am having a problem with this indication in patients with progressive multiple sclerosis. Perhaps, since we have a subtype of MS that is called secondary progressive MS, and

it appears that these patients will benefit from the drug, I just wonder if there will be confusion--obviously, there may be some confusion from the patients who presented their testimonials, because they specifically say that they want us to look at this drug for treatment of secondary progressive MS. And again, you say that you excluded patients with primary progressive MS.

So again, perhaps patients with worsening MS would help solve some of these issues.

DR. GILMAN: Dr. Katz:

DR. KATZ: Well, yes. What I wanted to hear was whether or not, whatever you call these patients, there is general agreement that the studies looked at the population that was worsening or progressive. Knowing that, we can work on the actual--assuming that you recommend approval and that we approve it--we can work on the specific language. But we will try to make clear in labeling who these patients were.

DR. GILMAN: All right. The next question is whether these two trials show slowing of progression. And again, Dr. Katz is referring to a design that specifically shows slowing of progression, that is, by having an effect upon the fundamental pathology in the disease, in which case one would expect to see a trial that went on after cessation of drug, with an evaluation of the patients at endpoints

post-drug administration, to determine whether the placebo group ran in parallel to the drug-treated group, or did the two connect very quickly after cessation of the trial, suggesting a symptomatic treatment alone, or symptomatic effect alone. Let's have some discussion about that from our consultants.

Dr. Penn?

DR. PENN: Yes. I feel moderately comfortable with that data, but clearly, if we were going to look carefully at that, it would take more patients and a study design that, as far as I am concerned, can't be done very easily. That leaves us with a clear-cut dilemma of do we say on the basis of not really solid facts, just on one study, whether or not looking at that one-year period that we have, that is enough for us to feel that that is the case.

My general impression is that, yes, I would be willing to give them that, but I think we're going to vary in the Committee about our judgments on that.

DR. GILMAN: Dr. Lipton?

DR. LIPTON: The evidence that we have before us that speaks to that issue is the evidence from the blinded assessments of the disability scales, the evidence that following open-label withdrawal, there wasn't exacerbation, and if we accept the MRI as a surrogate marker, the evidence

that accumulation of MRI lesions was slowed.

The one thing I would want to see that is missing is blinded withdrawal as opposed to open-label withdrawal from treatment, and the evidence is sufficient for me, although I would like to see that blinded withdrawal piece.

DR. GILMAN: Yes. The MRI will be another set of questions for us, actually.

Dr. Temple?

DR. TEMPLE: I'm not sure how critical that question is, so you are hearing a slight disagreement between us. The question of whether you change the course of the disease has arisen principally when there was a pharmacologic effect that made some sense as a possible source of the improvement.

Treating someone's lymphocytes doesn't make a really persuasive case for improving the neurologic symptoms of something. So I am not as obsessed with that as I usually am.

I do want to observe, though, that the fact that there is a limitation on dose currently at 140 gives a perfect opportunity to test this very question, because we don't know yet whether it's better to keep treating after 140 or not, so you get a chance to see something about the persistence of effects afterward, the possible benefits of continued therapy, and a whole raft of things.

So I want to push again for the possibility that that is something that can be explored rigorously.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes, there probably is a little bit of a disagreement between Dr. Temple and myself, because as I said earlier, I am hesitant to make a claim for a particular phenomenon, let's say progression, based on what we think we understand about how the drug is working, because we never really understand that very well, and that's why I would prefer some sort of an operational definition, some sort of a study design that will just get at that question empirically, without having to rely on assumptions that we can have a test. So perhaps there is a disagreement.

I think the question of the progression is an important one, because it will have an important effect on how the thing gets labeled if it is approved and subsequent marketing and everything else.

DR. GILMAN: I have a similar view to Dr. Katz, but perhaps after we discuss MRI as a surrogate marker, we could get back to this question, because I think the evidence is pretty good that MRI is a good surrogate marker, and we are finding an effect upon MRI. Therefore, it does appear that there is an effect upon disease progression as indicated from the MRI. But I think we should next turn to the MRI.

Dr. Dahut?

DR. DAHUT: I too would agree with Dr. Katz, especially when you have a drug which at this point we believe we can only give for a fixed period of time at a fixed dose. If, 2 to 3 years after the drug is stopped, regardless of what therapy people went on, if people came back to thes mae point, it would be tough to justify using the drug, particularly--although the toxicity profile in this study was very good--we have to remember the patients were young; 45 was the top of one group, 55 in the other--and eventually, there will be older patients who will want the drug. In the prostate trials, there was 20 percent incidence of congestive heart failure; in an older population, I understand. So if, 2 to 3 years after the drug, basically, the curves came together at that point, any type of lifelong toxicity would be tougher to justify. So I think it is an important issue.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: How long the effect lasts, whether it persists, whether there is a catch-up phase--those are all very interesting questions, and I certainly would not dismiss them. But it is not easy for me to see how a drug that affects your lymphocytes and things like that can be doing anything but slowing progression during the time it is being taken. That is in contrast with a drug that has a

pharmacologic effect where it might be doing nothing at all to the underlying disease, and you still might look better. Maybe you think this is a distinction without a difference and isn't worth talking about too much, which is also a possible interpretation.

DR. GILMAN: Dr. Katz:

DR. KATZ: Yes, I think that's just a different definition of progression. To say that it prevents progression while it is being given, I would not view that as a progression sort of claim. It could very well be what I would call a symptomatic effect.

DR. TEMPLE: Let me give you an analogy, and then I'll forget it. If you could show that an antibiotic could slow the progress of coronary artery disease, which is a hypothesis that is going on right now, it would not be plausible to think that the symptoms of coronary artery disease, like angina and things like that, were being treated by the antibiotic, because an antibiotic affects bugs, not people. The effect might be short-lived. The bugs might grow back as soon as you stop the drug. That would mean maybe you wouldn't think it was very good because you would have to be on the antibiotic all the time, but it would challenge the question of whether you had slowed progression; you have just slowed progression while the drug was there.

In contrast, if you slow heart failure by giving an ACE inhibitor, someone is entitled to ask you are you merely treating the heart failure before it got there, which is a slightly different issue and really goes to the question of whether you are preventing actual changes in the heart muscle.

I think they are two fundamentally different situations, but it may not matter that much.

DR. GILMAN: All right. The intermediate question before we get to the question about MR scanning is that the trials were unblinded, in a sense. Study 901 used blinded evaluators, and 902 did not. Diagnosis of relapses in 902 is made by neurologists aware of treatment assignment. So the question posed to us is what is the effect of unblinding on treatment outcomes in these two studies.

Dr. Grotta?

DR. GROTTA: Well, I think we'd all rather have all of the endpoints blinded, but the primary endpoints of both studies seem to me to have been blinded and were robustly positive. So for instance, the clinical scales in the first study and the MRI reading in the second study were both done in a blinded fashion. So I am not that bothered by the blinding issue.

DR. GILMAN: Let me leap ahead to the question of whether there are two well-controlled, placebo-controlled

trials, with appropriate blinding, then, that show clinical efficacy in that one of the trials, 901, had blinding to clinical outcome, and 902 did not.

Dr. Katz?

DR. KATZ: Yes, 901 we learned did not have blinding with regard to relapses, and since the sponsor is requesting sort of two indications, in a sense, an effect on progression, which we will get back to, and an effect on relapses. So I asked the question whether there is a bonafide effect here on relapses. Both studies are unblinded with regard to relapses.

So if you could discuss that matter first, I'd like to hear that. The other thing--and Dr. Grotta has already given his opinion on this--the other measures in 901 were ostensibly blinded--the EDSS, the Ambulation Index. The treatment effect sizes were relatively small, and there were some that people have discussed, some potential breaks in the blind because of very high instances, for example, of nausea, vomiting--or, nausea, anyway--alopecia, amenorrhea.

So when we are dealing with treatment effect sizes that are in the range, let's say, with regard to the means, anyway, that we have seen in 901, I would be interested to know what people think about the potential effects of unblinding even on those. But first, if we could look at the relapse question, that would be my preference.

DR. GILMAN: All right. Let's deal with the relapse question. That is just fine. I think it has to be said that neither trial had blinding for relapses. That is what we have heard, anyway. I don't think there is going to be disagreement on that point, and I see asset around the table, so I think that's the answer to your question.

DR. KATZ: Well, yes, that's a factual--but does the Committee think that nonetheless they should be entitled to a claim to treat relapses?

DR. GILMAN: Well, I think we should get to that question, ultimately, that is obviously before us.

Dr. Grotta?

DR. GROTTA: Well, I agree that the clinical relapse rate was unblinded, and I guess I'd like to hear from the MS authorities as to how closely--and I think we heard at least a beginning discussion--as to how closely does the MRI appearance of gadolinium enhancement correlate with clinical relapses, because we did see a significant reduction in the incidence of new gadolinium lesions on the MRI scan in the second study that was a blinded assessment, and one could argue that the appearance of gadolinium-enhancing lesions is a form of relapse.

DR. GILMAN: Dr. Weiner, Dr. Wolinsky?

DR. WOLINSKY: Probably the data that speaks to this test is a meta analysis that Ludwig Kapos and other

investigators have done across fairly large datasets in which serial MRI is available, or MRIs at baseline and relapse rates. So the relative risk--whether you want to look at relative risks or whether you want to look at correlations, there is a correlation between the amount of enhancement you see on a particular scan and the likelihood of a subsequent relapse--but it is not high.

DR. WEINER: First of all, if you look at all the studies of correlation between MRI and clinical outcomes in multiple sclerosis, the strongest correlation that is seen in virtually every study is a correlation between gadolinium-enhancing lesions and relapses. There is some debate in terms of T2 volume and progression and other things, but the strongest correlation, although it may not be perfect, because there are silent areas, is between gadolinium-enhancing and relapses, and that's something that we saw in our study as well.

DR. GILMAN: Dr. Lipton, then Dr. Katz.

DR. LIPTON: I guess my question to the MS experts--since I don't do MS trials, I don't know this--is to what extent do you think relapse can be assessed in open-label fashion without bias. How powerfully could knowledge of treatment influence the assessment of relapse in this setting?

DR. WEINER: You're talking about the clinical

relapse, not the MRI?

DR. LIPTON: Clinical relapse.

DR. WEINER: Yes. Of course, it depends on how the relapse is defined, but I think that if the relapse is rigorous defined as it was defined here, and there are clear neurologic findings like intranuclear ophthalmaplegias [ph.] and optic neuritis and ataxia or whatever, I think that it is pretty clear.

DR. WOLINSKY: I think we have seen an effect on what are called severe attacks, and I am convinced that those are the ones that are easy enough to count, hard enough to get too confused about. If the only effects we saw were on, quote, "mild" attacks, those can be much more easily affected by the extent of blinding.

I think the fact that there was a bonafide attempt to provide some level of blinding, even though it will never be perfect in any study, assures me. And while I don't like the tightness of the connection between the activity on the MRI, that is, gadolinium activity, and relapse rate, the fact that both of them are going in the same direction is quite reassuring.

DR. GILMAN: With respect to the problems in blinding clinically when a patient being treated has nausea, vomiting, hair loss, I don't think any trial could possibly deal with that, no matter how large the series, in a drug

such as this. So the point is a good one, Dr. Katz, but I don't believe that the sponsor could be expected to do a perfect study in the light of those side effects.

Let me ask our oncology consultants if they have any other comments about that?

DR. SWAIN: No. I would agree with you. You don't want to give the placebo group something metagenic just to make it unblinded--or blinded.

DR. GILMAN: Dr. Dahut?

DR. DAHUT: I would point out at least in the blinded trial of Sermin [ph.] in prostate cancer--and Sermin is a drug where there is a well-known side effect--about 30 percent of the patients were wrong, and the physicians were often wrong, too.

So there is a very powerful placebo group. People will often develop side effects that they believe the drug has. So I think it can be done. If there is total alopecia, and there is not, that's fine. But I think that actually, it can be blinded, but it is going to still be a minority of the patients.

DR. GILMAN: Dr. Katz:

DR. KATZ: I had a question for Dr. Wolinsky. Suppose a study is done that has no MRI in patients with exacerbations. Would you be comfortable in the future permitting a trial or concluding a trial, in effect, on

relapses if it was unblinded?

DR. WOLINSKY: I would have to look very,k very carefully at the design and the conduct. I might, but then I would also look very carefully at the magnitude of the outcome. And if you are saying there is no comparator group, as opposed to unblinded, no, I have no confidence in that whatsoever.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Just to be sure I am hearing it right, what I heard was at least some view that if the exacerbations are reasonably well-defined and are serious ones, it is at least moderately credible that blinding would not influence that outcome too much and that people are at least somewhat buttressed in their slightly warm feeling about that by the MRI data. And we should tell everybody that you should try to blind the determination from now on about whether an exacerbation has occurred. It is possible to do it--it is a little more difficult--but it ends a lot of questions.

DR. GILMAN: It would make our task easier, I must say.

All right. Coming back to the question about unblinded trials, I believe we have one trial in which clinical outcome was blinded, or clinical status was blinded, and one in which it was not. I wonder if there is

any debate about that question?

[No response.]

DR. GILMAN: All right. Let's move along, then. The next question has to do with use of MRI as a surrogate marker.

Dr. Katz mentioned that it has not been validated--that is, an effect on the MRI has not been shown to predict clinical effect. Can we hear something about that? You have touched on it slightly, but not specifically to this kind of question.

Dr. Weiner or Dr. Wolinsky?

DR. WOLINSKY: I think it depends on how you look at it. I think we have had a number of trials now, both successful and, unfortunately, unsuccessful trials in which the MRI correlates with clinical effects have been very good. We have had an occasional trial where the correlates are not so good--that is, where an effect, particularly on gadolinium enhancement, seemed not to support a clinical effect as there was no clinical effect.

The question, though, that I think you are raising is a much more complicated question, and that is can we take to the bank--at least, this is the way I would see it--the data from 902 which showed an almost complete ablation of enhancement activity after the course of 3 months of treatment, to believe that that will always correlate with

good outcome one or two or three years later. I don't think we have any data that speak to that. And that is a predictive surrogate rather than a surrogate which is, if you will, just a supportive piece of evidence of drug effect.

DR. GILMAN: Dr. Weiner?

DR. WEINER: I don't know what the question is exactly in terms of the surrogate or the MRI. I guess the question is with the changes on the MRI, does one expect that to translate into benefit for the patient--is that the question?

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes. Basically, the predictive surrogate is the sort that the regulation talks about and that in general people talk about, but here, there is no sense from the sponsor, anyway, that they had anticipated that it would be a surrogate in the sense of predicting what happens two or three years down the road. That is why we talked about the concept of the so-called contemporaneous surrogate, which is is it a reflection of the underlying pathology at the moment, and at that moment--let's say at six months--does that mean the patients are better off given the response on the MRI, clinically, importantly.

DR. WEINER: I think the answer to that is yes, in my mind, anyway. And there is data that is accumulating

that the MRI is also a predictive surrogate; some studies that look at MRI lesion burden, et cetera, and how the patient is 10 years later, and there are correlations that patients whose MRIs have more lesion burdening, et cetera, 10 years later don't do as well. So those aren't perfect studies, but that data is beginning to accumulate, so things are moving in that direction, and I think I can confidently say in my own mind, anyway, that what was shown in the study here with MRI shows that during the time of treatment, the disease process itself was lessened.

DR. GILMAN: Well, that becomes key, because 902 did not have blinding to clinical status, and if we are hearing that in fact the MRI serves as a good contemporaneous surrogate for disease and therefore clinical status, then some of our concerns about the lack of blinding in Study 902 are somewhat assuaged.

DR. WOLINSKY: I think the level of understanding or insight into what MRI is telling us--I think we are far enough along to be able to say, particularly with where we think a drug like Mitoxantrone would be working, and what we are seeing on the MRI evidence in these cases is that the influx of new cells into the brain to initiate a new lesion and create a new T-2-weighted abnormality is clearly being stopped. It doesn't say anything is getting into the brain, and of course, the level of MRI analysis here was not

adequate to tell us whether we are having any effects on pre-existing lesions.

DR. WEINER: I would just like to turn your comment around, Russ, in terms of a study that only had clinical. I think we are beyond that. I don't think there can ever be a study now testing a drug that has a putative anti-inflammatory action in multiple sclerosis without MRI. I think it has come that far.

DR. KATZ: Let me just ask a question that's not necessarily on the table for this application. Have we come far enough to say that if you had a trial that showed an effect on MRI and did not show an effect on clinical outcome that that would be--

DR. WEINER: You were at the meeting. We had a big meeting to discuss that in terms of the MRI as surrogate marker here in Washington. The feeling of most of the people who came was that as far as gadolinium-enhancing lesions, they felt that that did reflect attacks, et cetera. There was still some debate on some of the others. But I would predict, rightly or wrongly, that we will one day get to the point where the MRI could be a surrogate marker and that it will be, because it will be linked, and it will not be possible to have changes on MRI not linked to clinical.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: That all seems like a really

important discussion, and because of the people listening, it seems worth saying that the potential use of MRI here in this case is in support of one study that has a clinically meaningful endpoint. That is very different from the conclusion that the MRI data alone, without any clinical data, might support approval, and I wouldn't want anybody out there to forget that distinction.

Before you can accept a surrogate, you have to have some idea of the quantitative relationship. You have to know what a given change might mean clinically--otherwise, how can you weigh it against the risks? So that's a significant additional step.

The burden the surrogate is being asked to support here is considerably less. I'm sure everybody here knows that. I just worry about the outside world.

DR. GILMAN: Thank you.

Dr. Grotta?

DR. GROTTA: I'd just like to make the plea that--I'd hate to see trials, certainly in stroke, and I would think in MS, too, to be done without a clinical correlate. And I don't really want to spend the time to debate this at this point because I have a plane to catch. But the fact of the matter is we need to know what to go back and tell our patients about the effect of a drug. I can say from Study 901 that if one of these patients of the two who had the

secondary progressive, and perhaps the third one, who testified before us today, received this drug--that those patients had a 25 percent chance of deteriorating by one or more points on the Kurtzke scale in the next two years with placebo, and with this treatment, they have an 8 percent chance of deteriorating one or more point on the Kurtzke scale. To me, that is understandable; that is something patients understand. They don't understand the number of MRI lesions. I think we need to keep the clinical scores.

DR. GILMAN: Let me turn to a subset of those issues, which is that the treatment may interfere with the measurement itself. That is, is there any evidence, or are we suspicious at all that the drug interfered or interacted with the lesion or the MR scan itself, namely, with the gadolinium, I guess is the question. I don't know of any such evidence. Can anybody comment on that question?

DR. WOLINSKY: I think that sets a new hypothesis that is for me beyond belief.

DR. GILMAN: Theoretically, it is possible. Is there any other comments about that?

[No response.]

DR. GILMAN: I think we will leave it there, then. The third subset question is the drug conceivably could have a benefit on the surrogate marker but not on the disease itself. That is, the drug could conceivably even benefit

the surrogate but worsen the disease.

As I have seen the data, there is no evidence of that in these two trials, but I want to hear from the rest of the Committee about that question.

DR. LIPTON: I thought it was a valuable cautionary note, that in a context where the surrogate and the clinical measures improve together, it seems unparsimonious to think that's what is operating here.

DR. WEINER: I would agree. Just getting back to your question and your comment as well, I agree 100 percent that all of our trials need to have a clinical outcome. There is no question about that. I think the surrogates can be used in Phase I and Phase II. Also, the point I was making is that I would be very reluctant to approve something in multiple sclerosis in Phase III that didn't also show something on MRI in addition to the clinical. And I don't think that necessarily would happen, but I agree with what you and Dr. Katz said about the clinical.

DR. GILMAN: The next subset of that set of questions would be what specific MRI measure reflects what specific brain pathology. In other words, what are we seeing when we see gadolinium enhancement was the question.

I think the answer is that it shows a breakdown of the blood brain barrier. Are there other comments about that question?

DR. WOLINSKY: This is picking up some measure of the inflammatory process that we currently believe is an important early event in lesion formation, at least for some lesions. And there is good histologic evidence for that now, and there is good correlative pathologic evidence. It probably doesn't pick up all lesion development early.

DR. WEINER: I would agree with that.

DR. GILMAN: Thank you.

Next is the hypothetical situation in which the effect of the surrogate marker is so small that it can never be reflected in a meaningful clinical benefit, irrespective of the sensitivity of the marker. As a consequence, what are the Committee's views on the utility of MRI as a marker?

I think we have addressed that issue pretty well thus far, unless there is any other comment about that. There clearly was a set of changes in the MR scanning with 902 as a blinded study, and the effects were fairly substantial.

Dr. Grundman?

DR. GRUNDMAN: Just one quick question. Can anybody explain to me why going from Month Zero to Month One, the number of mean MRI lesions could double, say, from 5 to 12 in Study 902, but the EDSS score only went up by 0.01 point, if the correlation is that good.

DR. WOLINSKY: The correlation is not that good,

and I could show you many patients that we followed with serial imaging and spectroscopy where the total enhanced tissue volume has been in excess of 7 mls, which is more than the T2 lesion burden in many of the patients in the study, and they have had no symptoms at the time.

DR. GILMAN: It's an anatomical issue, isn't it? It depends upon where the lesion is located with respect to the principal motor and sensory pathways.

DR. WOLINSKY: With all due respect, Dr. Gilman, it is much more complicated than that.

DR. WEINER: I was going to make another point that we haven't discussed that I think is very important. It is not only an anatomical issue, but the brain has a lot of plasticity, so that if you have damage to one area, other areas can then take over. So if you look at someone with optic neuritis who recovers, and you do functional imaging, there are other parts of the brain that are now picking it up. So what is happening is that you are using other parts of the brain, but then, as the disease progresses, you go over that threshold, and then you get an irreversible deficit. So I think things are happening and putting the patient at risk later on for neurologic disease or deficits.

DR. GILMAN: All right. Is there any other discussion about MRI as a surrogate marker or the results of theses studies?

[No response.]

DR. GILMAN: All right. hearing none, Dr. Katz, I believe we are close to asking the question whether the sponsor has proven efficacy, and I am ready to address these questions. So, are there other issues that you want to ask us about?

DR. KATZ: Yes. You were going to get back to the question of progression of disability claim after the MRI discussion.

DR. GILMAN: Thank you. You are quite right.

Then, just to paraphrase, in fact, is there evidence of a chance in progression from what you have heard--let me ask the consultants and let me ask the Committee also, if the consultants want to comment first about the claim of a change in progression contemporaneous.

DR. WOLINSKY: There was a lesser amount of accumulated disability at the end of the study than there was in the beginning of the study in the patients who were treated. This concept of progression is a very thorny issue, and I am not sure exactly how to define it.

I do know that the EDSS scores were different, and I think that's all I could say. I am not clear about the concept of progression. It is likely that there was some meaningful, statistically meaningful, and perhaps for the patients, important, change in the tempo of their disease

that happened temporarily with treatment.

DR. WEINER: Yes, I think there was an effect on progression. I actually liked Dr. Lublin's slide--and maybe this is some wording we might get into, or it might be recommended--that rather than an effect on secondary or progressive disease, worsening forms of relapsing and progressing disease. I think that that's the key--it is the worsening of the disease and the worsening form of both the relapsing or the progressive disease, and I think that that was shown.

DR. GILMAN: Dr. Katz?

DR. KATZ: Again, the word "progression" has been thrown around a lot, and it occurs two places in effect in the sponsor's proposed labeling. I think we have already dealt with the question of who the patients are and what sort of disease they have. We can figure out a word to describe them. What I'm talking about here is the effect of the drug on the disease, and the use of the word "progression" could describe that.

I agree with you, and obviously, I think Dr. Temple and I even have a disagreement about how it best ought to be defined or at least looked for. So it's a complicated matter.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: Somewhat in that same vein, I am a

little bit surprised that I am about to say I have come to the conclusion that this drug probably does have a clinical effect. But I don't understand how it is different from the clinical effect for the drugs that are already approved for MS right now, and I wanted to ask the two MS experts on our panel if, when they are talking about progression and that there is an effect on progression of functional disability or progression of whatever, is that different from the other drugs that are available? Is this a different effect on the disease, or do you think we are looking at something similar to the Interferon in terms of clinical significance and magnitude?

DR. WEINER: Well, I think if the disease is one disease or a subset of diseases, and there are immunomodulatory therapies that are affecting it, they ultimately have to be working through similar pathways. And I would believe or like to believe, and there are theories, that the way the Interferons are working or the way the Copaxone is working or the way the Mitoxantrone is working will ultimately be in a similar area, whether it is decreasing IL-12 [ph.], whether it is decreasing migration of lymphocytes, whether it is decreasing TNF, if we believe the immune hypothesis of the disease, which is what the current feeling is.

So I think that they ultimately have to be working

in a similar way. Where does it fit in terms of the other drugs? We only would know that if they were compared directly against the other drugs. There is some suggestion from the data presented that the Mitoxantrone might have stronger clinical effects because it was used in more active patients. Whether that will be shown to be true if you compare them directly to the other drugs, I don't know. We'd have to see a direct comparison.

DR. KAWAS: So, by your definition of progression, does Betaseron affect progression?

DR. WEINER: Betaseron--I would use the word "worsening" and progression, and I would say yes.

DR. KAWAS: Thanks.

DR. GILMAN: You'd say yes, based on what?

DR. WEINER: This is again a hypothetical question, but I would say yes based on the fact that, for example, if you look--again, we are not now talking about controlled trials, which is comparing one thing to the other--but if you look, there are linkages, for example, between the number of attacks people have and later disease progression or predicted value of how they are doing. And although it may be a certain article of faith that if you are decreasing relapse trait or whatever, you are affecting progression. Again, I interpreted the question as more of what I thought or what I would postulate, not what

necessarily the hard evidence is, and that hard evidence only comes with direct comparison and long-term studies. But there are linkages between number of attacks and how people do later on in their disease; there are linkages between MRI lesions and how people do later. So I think the disease-modifying drugs, although imperfect, if they are affecting gadolinium lesions and if they are affecting T2 volumes, and those are shown to be linked, although imperfectly, they ultimately are going to affect progression or worsening of the disease.

DR. GILMAN: That may be, but what we have seen in the two trials, the Avanex and the Betaseron trial, has been reflected in only relapses, not in progression, except for the study that Dr. Wolinsky mentioned.

Go ahead.

DR. WOLINSKY: I think it depends on what the various review committees accepted as a definition of progression when those particular studies were presented in a room like this. I think it is fair to say in the Betaseron trial, the original one, that there was a trend that suggested a reduction in accumulated disability--I'll use the same term I used a while ago--but the size of the study was probably inadequate to be statistically significant.

I think the trial for gluteramir acetate showed a

magnitude of an effect which is very similar to what we are seeing today, but we are looking across slightly different patient sets, so I don't know how translatable that data is.

The European secondary progressive trial reached statistical significance for this kind of outcome measure. So in my own mind, because of my problems in how I define progression, feel that we probably are seeing a third class of immunomodulator, one with very respectable toxicity, or toxicity to be respected, which provides another alternative for trying to modify the disease course in patients with MS, and it will be our problem, I hope, to figure out how wisely to use these.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: We like most what's actually in the labeling, and Copaxone does not have any claim to reduce the level of disability. You could say that they were moderately close to such a claim, but they weren't given it. And one of the Beta-Interferons has a claim for prevention of progression or whatever you want to call it, but only in relapsing remitting disease.

Now, to the extent that that's a mixed bag, who knows what they really have, but at least at the moment, there isn't anybody who has a claim for prevention of whatever this is in worsening disease--not yet. That doesn't mean those don't have an effect, it's just that they

are not labeled that way.

DR. WOLINSKY: That's why I tried to be very careful with that answer.

DR. GILMAN: Dr. Dahut?

DR. DAHUT: Just one quick comment on this. I think Slide M-39, which shows the number of patients in each group whose EDSS showed a greater than 1.0-point deterioration over 6 months, is probably the most important group in my mind, because we said earlier that a one-point deterioration was meaningful clinically, and this was for 6 months, so I think that's an important endpoint.

Now, it is important to know that while it was statistically significant, it was at 0.045, and you have small numbers, which means if you had one more patient in the Mitoxantrone arm who didn't reach that, it wouldn't have reached statistical significance.

So I think we have to be aware that we only have 62 patients treated in the 2-3-month treatment arm, and just one or two patients a few ways may change our perception of the data. So while I think there is sort of a bias and an accumulation of information that something good is probably going on, it is certainly not overwhelming under any one particular test.

DR. GILMAN: All right. We're going to come next to the three questions before us unless there is anything

else, Dr. Katz, Dr. Temple, that you wanted to hear from the Committee.

DR. KATZ: Yes. Again, just on the progression, I am trying to get a sense of how the Committee in general feels about that. I don't think I got a clear sense about that.

DR. PENN: Shall we just take a vote on whether we think there is some evidence, substantial evidence?

DR. KATZ: Well, the first question asks if you think they have substantial evidence to support their proposed claim and if you think--

DR. PENN: And that is part of their claim.

DR. KATZ: --that is part of their claim--so if you think it does, and you think relapses are involved in that--

DR. TEMPLE: Would people be happier if it said "neurologic progression" or something like that? Does that remove the implication of something eternal? I mean, what else--that doesn't make any difference?

DR. GILMAN: No, no. The request for approval is to slow progression of neurological disability--the first part of the statement.

Dr. Grotta?

DR. GROTTA: I think the problem is still the use of the word "progression," and I think--and I don't want to

put words in your mouth--but I think what you are wrestling with is that that implies a biological effect on the disease, and we are talking about a clinical change. I think that probably if you just change that first progression to some other term, and Jerry suggested "accumulated neurological disability," but I guess you're going to wrestle with the wording of the claim.

DR. GILMAN: Right.

DR. GROTTA: I guess my point is that I feel comfortable with the notion that it affects and reduces the accumulated neurologic deficit, the clinical progression. I don't know about the biological progression, but I don't care.

DR. KATZ: Okay, but I care. From the point of view of labeling, I think it's important. I want to know whether or not the Committee thinks that there is an effect on the underlying biology, pathophysiology, structural, if you will, effect and whether you think there is evidence that that effect is transient, and when you take the drug away, it goes back to the way it was had you never been on drug, or whether you think that's a permanent change.

DR. GILMAN: We don't have data that bear on that question, in my opinion.

DR. WOLINSKY: I can't answer the second part of that in terms of whether or not it goes away. The MRI data

convinces me that there is an effect on a fundamental aspect of the underlying pathology. If that's what we use, which is not what patients really care about, then yes, they've got it.

DR. GILMAN: Dr. Grundman?

DR. GRUNDMAN: I would agree. I don't think there is evidence presented here that it affects the underlying structure. So if the word "progression" is an issue, I could live with the idea of reduction in clinical disability compared to the control group if I actually believed that, and I'm not sure I believe that because I still have problems with the blinding of the study overall, and also with the clinical remissions, as long as we are on the subject. Despite what we have heard here, I don't know if we want to set the bar that low for future studies that we would approve a drug for relapses that weren't conducted in a blinded fashion.

DR. GILMAN: Dr. Penn?

DR. PENN: Okay. I think that an MRI that shows a hole in the head shows something about the biology. Let's put it that simply--that a gadolinium positive scan does say something about biology.

I live in the world of dealing with these scans and deciding whether to do surgery or not on the basis of them, for example. So I don't think there is a question

about that. But we would all like to have evidence of how it works biologically that would make us feel happier about it, and we have some sense of immune responses and so forth that are modified. In fact, that's why we think it might work like the other drugs work, but we don't have comparable evidence with the other drugs. As I thought I said before, we have some moderate evidence that meets your operational criterion of stopping progression--that is, the one-year-out study that was not blinded--so I find that, plus the MRI evidence, which I really give strong weight to, convincing enough to give them the phrase affecting progression of disease as well as we can define it now.

But that's a very forceful "pro" statement, and I'm not sure that all my colleagues would agree with that in that form.

DR. GILMAN: We'll soon find out.

Are there any other comments about that question? Yes, please.

DR. WEINER: Since I don't vote, let me just--and I won't take a long time--tell you my own personal view of the data and where I think it fits in terms of multiple sclerosis as someone who has been treating patients with the disease for 25 years and has actually used other chemotherapy agents that can only be used for short periods of time, et cetera.

First, in my own mind, I don't think there's any question that the Mitoxantrone affects the underlying pathology of the disease while it's given, and also is beneficial clinically.

Second, there is also no question my mind that it will add something to the armamentarium of the neurologist who is confronted with MS patients, especially--and I liked these words--the worsening forms of relapsing remitting or progressive disease. We hope--if you put someone on Copaxone or one of the other drugs, and they do well and don't need anything else, that's fine, but we know that that's not true, and Mitoxantrone will serve a need.

I also want to warn that I think this is going to create false hopes among multiple sclerosis patients. There are going to be MS patients who are severely disabled or who have very slow progression or are not that actively progressive who now think that there is a drug that is going to have a major impact on their disease. There are lots of people that that won't happen. So I would put a word of caution to both the MS Society and to the company, who I applaud for all their work, to be careful about this, because actually, if you look at Table 40, you will see that it doesn't stop things in everybody; there are people who are worse, most people are basically stable, and the number of improved is not that great.

The other thing I would mention to you as someone who deals with the disease and doesn't just see patients for 2 years but sees patients over 10 or 20 years, the ultimate issue is to keep a 25-year-old person stable and without disability over the long course of their disease, and I think that the Mitoxantrone will give us the opportunity to help stop the disease early, and the fact that it can only be given for 2 years is a weakness. However, the strength of the biologic effect will it to be used in combination not necessarily with other drugs being given, but other drugs being given sequentially. And we know in medicine, whether it is cancer or any other disease, that we often use drugs in sequence or in combination. So I think it is going to have an effect in that particular way.

DR. GILMAN: Thank you.

Are there any other comments?

Dr. Wolinsky?

DR. WOLINSKY: No.

DR. GILMAN: Dr. Lipton?

DR. LIPTON: At the risk of perseverating, I continue to be impressed with the fact that the evidence that the 12 mg per meter squared is not demonstrably better than the lower dose and that the lower dose might well address your issue of you only get 2 years of treatment. So in some way, I would like that reflected in the plans going

forward.

DR. GILMAN: That was true of the EDSS, but it was not true for the other markers that they used, whereas with the 12 mg per meter squared, in fact, it was true with most of the other markers for their primary outcome.

DR. LIPTON: Yes. The summary measure was significant for both, and EDSS was significant, as were relapses treated with steroids, and time to first relapse--so three of them were significant, and the primary was significant, and the others weren't different.

DR. WOLINSKY: If I could add, because of the differences in the two studies, because of the differences in the patients, because of the differences in doses, although I am convinced about the biological effect they have shown, I am not sure but what one couldn't get the same effect with 3 months of treatment as was done in the French study alone.

DR. GILMAN: Dr. Grotta?

DR. GROTTA: Just to remind the group, we are not being asked to answer that question. We are being asked is this dose that they propose effective or not. Further study could determine whether there is a better dose or a better way to give the drug.

DR. WOLINSKY: I agree with that, Jim. I just wanted to go on record as saying there is still a lot of

room for potential safer use of this drug.

DR. GILMAN: Dr. Katz?

DR. KATZ: I think that's right, but there is a dose-related, if you will, question that was not up on my slide and might not even be in the book, but I talk about it, which is the fact that these two studies used widely disparate dosing regimens, and the MRI data, which is most impressive, comes from one in which the drug was given every month for 6 months. To the extent that that data makes you feel comfortable about the clinical data in the first study, what can we say about what dose ought to be recommended?

DR. WOLINSKY: I think you can't say very much.

DR. KATZ: Well, you have to.

DR. WOLINSKY: That's why I'm not voting.

DR. GILMAN: No--you are not voting because you are a consultant.

The sponsor has asked for approval of 12 mg per meter squared, and the data that we have are complete for that dose--every three months, yes. Thank you.

DR. GRUNDMAN: Every 3 months for what period of time?

DR. GILMAN: Up to a total dose of 140, they are telling us today. At 100, they do an echocardiogram, but their total dose, they are telling us, is 140.

DR. GRUNDMAN: So this would be approved as a

treatment regimen for 12 mg per meter squared every 3 months up until 100--whatever--is reached?

DR. GILMAN: Well, up until 140, which is their absolute top dose, they have told us today. There will be points at which the echocardiogram would be examined.

DR. GRUNDMAN: And would there be any point before that that we would stop the medication, or would it just be that's the regimen, up to 2 years' worth of treatment?

DR. GILMAN: I believe that would be up to the treating physician.

DR. GRUNDMAN: Because remember, after 6 months' worth of treatment, it was no better than placebo in the first study at 12 mg every 3 months. So two doses didn't seem to matter too much, so it seems like you'd have to continue dosing them for maybe up to 2 years to ensure that you are going to get the effect that you are after.

DR. GILMAN: They were showing an effect already at the third month, and that effect improved in the 901 study. It continued to improve, if I recall the data correctly.

DR. PENN: At six months.

DR. GILMAN: At six months. Thank you. Okay.

Dr. Katz, I think, was first, then Dr. Temple, then Dr. Grotta.

DR. KATZ: I'd like to hear from the voting

members, then, what they think about the proposed dosing regimen. I'd just like to get a sense.

DR. GILMAN: Dr. Grotta, you fill that bill.

DR. GROTTA: Well, I'm not really bothered by it too much. I think in our current health care system, it's much more likely that people are going to get too little of this drug than too much of it, and I think that you're going to spell out the caveats of when toxicity is likely to occur. I think the data that we have seen today show that in the dosing regimen that is being recommended with the safeguards that are recommended that the likelihood of cardiac toxicity is very low, and I think the cancer data would support that, too. So I think we have to worry more about patients being able to have their insurance cover the drug.

DR. GILMAN: I would agree with that assessment that the dose of 12 mg per meter squared appears to have some toxic effects but no "serious" or life-threatening toxic effects.

DR. KATZ: I'm not really concerned, for purposes of this question, about the toxic effects. I am wondering whether, if you think the MRI findings are very persuasive--most of those persuasive findings come from 902, where the dosing was more intensive--and I am wondering whether you think you need that dosing regimen to confer the benefit.