London, where Dr. Miller reviewed the scans at the end of the study.

DR. GRUNDMAN: And this was done at the end of the study.

DR. GHALIE: Right.

DR. GRUNDMAN: And how was the order of those scans given to the rater? Was there some sort of deliberate randomization process, or were they just given in order of subject number?

DR. GHALIE: They were sent in two batches. The first series was for about half of the patients enrolled in the study, and the other series was for the other half. And they were all analyzed at the end of the study. And again, the patients were identified only by their initials or a coding system, not by what treatment arm they were in.

In the efficacy results I will present to you today, we are going to focus on Month 6 at the end of the study as the primary comparison for some of the p values--but in fact I will present all the data, so you can look at all the data.

[Slide.]

I will present first, then, data on patient disposition and demographics. Forty-four patients were randomized onto the randomized part of the study. Two patients, one from each group, withdrew from the study after

the first course of therapy and before they underwent their first MRI evaluation. Therefore, these patients did not have efficacy evaluation available.

Thus, 42 patients of these 44 are evaluable for efficacy, 21 in each of the two groups. Of these 42 patients, 37 completed the 6 months of treatment and all associated procedures. All 21 patients were randomized to mitoxantrone plus methylprednisolone, and 16 patients were randomized to methylprednisolone alone. Five patients were randomized to methylprednisolone who discontinued treatment and withdrew from the study before completing the six courses of treatment. They withdrew at Month 4 or Month 5. All of these five patients withdrew due to lack of efficacy and symptomatic and neurologic deterioration.

[Slide.]

There is no difference in demographics at baseline between the two groups.

DR. GILMAN: Excuse me for one second.

Dr. Kawas?

DR. KAWAS: Just a quick question. The patients who withdraw from the prednisolone group because of lack of efficacy--did they know that they were in the controlled group, essentially?

DR. GHALIE: Yes, indeed. These patients were not blinded, because there was a group that was receiving the

blue chemotherapy and methylprednisolone, and the other group methylprednisolone. So here, the patients and the physicians were unmasked, so they knew which treatment. However, when they withdrew from study, there was clear evidence that they had a high number of relapse, and EDSS worsening, and therefore, the physicians treating these patients decided it was time to withdraw them from study. We have data on these five patients.

DR. KAWAS: Thank you.

DR. GHALIE: Again, these are the baseline demographics that show there was no significant difference between the two groups at baseline. About 80 percent of the patients were considered retrospectively as having relapsing remitting multiple sclerosis based on the fact that at the time of enrollment, they had at least two relapses in the preceding 12 months. These patients, even though they had relapse and were considered relapsing remitting, also had progression of their EDSS as well. The other 20 percent of the patients were considered to have secondary progressive MS because their reason for being enrolled in the study was a 2-point EDSS progression in the preceding 12 months.

A typical patient enrolled in the study was a 31-year-old patient who had a disease history of about 6 years. The patient population as a whole had an average of three

relapses in the year preceding enrollment, and the mean baseline EDSS was 4.5, which, as in the Phase III study, represents a disability severe enough to impair full-day activity.

[Slide.]

I will now turn to the efficacy endpoints of the study, beginning with the primary efficacy endpoint. Again, that is the number of patients with new gadolinium-enhancing lesions during the 6 months of treatment.

Fewer patients in the mitoxantrone group had new gadolinium-enhancing lesions over time. This became evident, as you can see on this slide, at Month 2 and persisted for the remaining period of their treatment.

[Slide.]

If we look now at Month 6, two of 21 patients randomized to mitoxantrone plus methylprednisolone, which is 10 percent of the patients, here in yellow, had new gadolinium-enhancing lesions compared to previous months, compared to 11 of the 16 patients randomized to methylprednisolone who were still on study. That is 69 percent of the patients.

This difference represents an 86 percent decrease in the number of patients with new gadolinium-enhancing lesions at Month 6, and the p-value for Month 6 is presented here as p equals 0.001.

[Slide.]

If we turn to the secondary MRI endpoint, which is the mean number of new gadolinium-enhancing lesions, again, one can see that in the mitoxantrone group, it steadily declined from Month 1 to Month 6, in yellow. In the placebo group, it was more or less unchanged. And again, if one looks at the p-value at Month 6 for the mean number of new lesions, p equals 0.001.

Again, this is a primary and secondary endpoint of MRI done by masked evaluators.

Dr. WOLINSKY: Can you tell me--usually, when one does a study like this, somehow or another, one or more scans don't get done that should have been done. So how much of the data are we looking at? Did you actually have all of it? And the other question which goes along with that is for those patients who withdrew, I assume there was no last observation carried forward, and if there was a missing scan, was there a last observation carried forward or not?

DR. GHALIE: To the first question, for this study, we have data for every cycle where the patient was on study, so it is really a full database for all the months where a patient went on study.

To question number two, what did we do for those five patients who dropped out--we did both analyses. The

analysis I presented to you today is having the patient with last value available presented, and for the month where they withdrew, they were not included in the presentation. That's the most conservative way.

If we included now for these patients last value carried forward, the difference becomes even larger, because those patients were getting worse when they withdrew. But we haven't presented that. The data is available, and again, it shows even more significant difference.

DR. WOLINSKY: You don't know whether they would have gotten worse--they would have gotten worse clinically, but you don't know what the MR showed.

DR. GILMAN: They withdrew indeed because clinically, they were getting worse--correct--it was felt at that time that one could not keep them on treatment with worsening EDSS--

DR. WOLINSKY: I understand, but you can't make any assumption about the MR changes, because they weren't done.

DR. GHALIE: Right. And this is why we felt the most appropriate evaluation to show was for those patient with the MRI data available.

[Slide.]

Now I will turn to the clinical evaluation in the study, beginning with EDSS. In the mitoxantrone group, the

mean EDSS score improved by 1.1 point, from baseline at Month 0 to Month 6. Mean EDSS remained more or less unchanged in patients randomized to methylprednisolone. And again, I would like to add what I mentioned before, that patients who withdrew in Months 4 and 5 in the methylprednisolone group, that data is not included here as last value carried forward, so it is exactly the patients who remained on study who are shown here.

The p-value for this comparison at Month 6 is equal to 0.013.

DR. GILMAN: Let me ask a question about that--go ahead, Dr. Van Belle.

DR. VAN BELLE: Clearly, one issue is whether the clinical scores are correlated at all with the physiological scores. Did you do any correlation at all of the EDSS with such things as the number of lesions?

DR. GHALIE: We did in fact two analyses, and one of them was for each patient--and there are 42 patients here--a correlation on individual patients between the number of gadolinium-enhancing lesions--so any gadolinium-enhancing lesion--and their EDSS score at that month. So for each patient, we had a correlation for that series of values. And then, we did the average for these 42 patients, and we compared that between the two groups. There was a correlation between EDSS value and the number of new

lesions, and this is available on a slide if you would like to look at it.

We also looked at another analysis, a much simpler analysis--and I recognize that with a small number of patients, it is hard to draw a conclusion, but at least we looked at it--where we looked at patients who had EDSS worsening by one point or less, and whether they had gadolinium-enhancing lesions or not. We did this table, and again, with a small number of patients, it is hard to draw any conclusion, but that data is available if you wish to look at it.

DR. GILMAN: I wonder if you would address the question that Dr. Katz raised, which is--as I recall the numbers, 15 of these patients had relapsing remitting, and 6 had progressive MS--how does that play with your request that the drug be approved for progressive multiple sclerosis?

DR. GHALIE: Really, what we are looking at in this study and when the study was designed, the rationale behind designing the study as it was designed was to take patients who really had very active disease and to be able to treat them with the treatment and see very quickly whether these patients had any effect with mitoxantrone. Therefore, they elected to take patients who had very active diseases, and therefore, patients who had a lot of relapses

were more readily available to enroll in that study.

In fact, that had to triage 85 patients to end up with 44 patients who were randomized and 42 who were evaluable.

Now, to answer your question specifically, the majority of the patients who were called relapsing remitting also had EDSS worsening. It is not like their EDSS was stable over the preceding year. Clearly, patients who had secondary progressive, which was 20 percent of the patients, had at least a 2-point EDSS progression.

DR. GILMAN: Wait, now--are you saying that these were remitting progressive patients, or that they were relapsing remitting, some of whom had progression?

DR. GHALIE: They were really defined as relapsing. Again, this study--just to make a small parenthesis--was also designed before the new classification of MS in 1996, so the patients were defined as having a number of relapses of at least two, or EDSS progression of at least 2 points.

DR. GILMAN: That still doesn't address the question. The question specifically is whether the 15 patients who were defined as relapsing remitting did have progression month-to-month. In other words, in the current classification, were they remitting progressive?

DR. GHALIE: These patients were defined, again,

based on their relapse, but they again had some progression of disability. Dr. Edan, who was the study chair, would also like to comment on that, please.

DR. EDAN: We studied relapsing patients at the very bad period of their disease. These patients were selected as having at least two relapses within the previous 12 months, relapses with sequelae, which means worsening of EDSS during that time, or secondary progressive patients with an increase of at least 2 points EDSS, whatever the number of relapses during this 12-month period.

So the way to select the patients was really to-- all the patients started their disease with relapses, and we selected a group of relapsing patients at a very bad period of their disease. They were in at least two different situations. Either they had at least two relapses with sequelae within the previous 12 months, or they moved to secondary progressive with rapid worsening of EDSS.

DR. GILMAN: Well, I am still struggling to understand this. You had 15 cases that had relapsing remitting disease. Which number of this 15 had what in current terminology would be relapsing progressive disease?

DR. EDAN: They were relapsing remitting disease with worsening of EDSS after the relapse within these 12 months.

DR. GILMAN: But subsequently, did their EDSS

return to its previous level?

DR. EDAN: No--they had an increase of their EDSS during that period compared with the 12 months before, for most of the patients.

DR. WOLINSKY: Probably Dr. Lublin will help us with our confusion later, Sid, but I think we are going to stay confused on this forever.

DR. WEINER: I would just make a point. I think there is this transition period in MS where people are moving from many relapses into the secondary progressive stage, and I think this is an important point that we will discuss later, because you have people who might be called secondary progressive who aren't really having relapses, who are slowly progressing, and the issue is whether those patients are different from the patients who are having relapses. Also on MRI scan, the patients who enter the secondary progressive stage and are slowly progressing do not have as many MRI-enhancing lesions, and I think this will become an important point in terms of if the drug is approved, what is it really approved for in terms of which patients are going to be treated. But I would also echo what Jerry said, and Fred has struggled with this--the MS Society has tried to segregate into different categories, but it may not be that possible.

But I guess if we were to ask--and we could ask

the presenters or whatever--if you had to classify the patients in this trial as either relapsing remitting or secondary progressive, would they be more in the relapsing remitting category or would they be secondary progressive?

DR. EDAN: They would be relapsing remitting MS.

DR. GHALIE: Eighty percent are the relapsing remitting.

DR. EDAN: Eighty percent, correct.

DR. GILMAN: So we have to remain with the numbers, that 15 of these 21 patients were relapsing remitting, and 6 were progressive; correct?

DR. EDAN: Yes.

DR. GILMAN: I think we have to take that series of numbers.

DR. GHALIE: I think Dr. Lublin, who was going to comment on that later, may also add a little bit. We can introduce that topic right now and then come back to it later as well.

DR. LUBLIN: Yes. When I do, I can go through the whole classification and tell you where I think these patients fit in, but I think that what Drs. Weiner and Wolinsky have said is essentially correct, and the conclusion is that those 15 patients are relapsing remitting patients. And then I'll show you how that fits in terms of the worsening and so on.

DR. GILMAN: Thank you.

Dr. Lipton?

DR. LIPTON: Actually, I just wanted to take the presenter up on his offer to show us the relationship between the clinical measures and the MR measures.

DR. GHALIE: Okay. I would like to have Slide B-130, and then we will look at Slide B-131, which looks at the correlation.

[Slide.]

DR. GHALIE: Again, with these small numbers, it is hard to make a determination, but again, this is EDSS deterioration during these 6 months. Patients who did not have a deterioration, in the methylprednisolone group, 4 had negative scans, 11 had positive scans at month 6. For the mitoxantrone group, they did not have deterioration in EDSS during the 6-month period; 17 had negative scans, and 3 at some time had positive scans.

So the negative-negative seems to be a reasonably good correlation. When we look at positive-positive, 6 patients in the methylprednisolone group worsened, and their scans were positive. Only one patient worsened, if you recall--actually, I will present the data in a moment; you haven't seen that--and this patient's scan was negative.

So again, this is a very small number, and it is hard to make a determination based on that, but I think

perhaps the clearer evaluation is when we did the correlation, which is actually the next slide, B-131.

[Slide.]

DR. GHALIE: As I mentioned, for each patient--now, we have more data--for each patient, we look at the correlation between their MRI results and their EDSS gadolinium-enhancing lesions, any type of lesions, and we then average these 42 patients for which we had data. The mean correlation for all the groups together was 0.21, and the p-value was significant. So in other words, when there was gadolinium-enhancing lesion, the EDSS seemed to be higher, and where there was no gadolinium-enhancing lesion, EDSS seemed to be lower.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes. I just want to remind the committee that the clinical data with which the MRI has been correlated is unblinded data.

The first slide you showed, the one prior to this, looked at the--

DR. GHALIE: B-130.

[Slide.]

DR. KATZ: I just want to make sure I read it correctly. It looked at patients who had a one-point deterioration--not more than one point, just one point--is that correct. The other question I had was, as in the first

trial, do we have data on what the nature of the relapses was in this? We apparently didn't have that data for the first trial. Do we know what the nature of the relapses was in this trial?

DR. GHALIE: This protocol also defined clearly the three categories of relapse, whether mild, moderate or severe, and also determined when to treat them.

DR. KATZ: I understand that, but I mean the actual relapses that occurred. Do we know--

DR. GHALIE: The numbers?

DR. KATZ: Well, beyond the numbers--do we know clinically what these people looked like? I gather we didn't have that information for the first study, and I am just wondering whether we have it--

DR. GHALIE: Maybe Dr. Edan would like to describe what was a typical patient with relapse in his study, but again, I can also show you the slide showing how it was defined in the protocol.

Dr. Edan, would you like to tell us in your study how you defined relapse and give us an idea about these patients' relapses?

DR. EDAN: We defined relapse according to the consequences of the relapse on daily life and the consequences on EDSS, and we separated mild, moderate, and severe groups according to these two criteria.

DR. KATZ: Do we know how many were in each category in this study? Again, I gather you didn't know that the first time around in the first study.

DR. EDAN: Yes, we should know that.

DR. GILMAN: Dr. Katz, what was your question?

DR. KATZ: Do we know--I mean, there is moderate, there is severe,, and there are different criteria for diagnosing--I am just wondering how many patients met what criteria, and how many were moderate, how many were severe, that sort of thing. I am just trying to get a sense of--again, because blind is an issue here--are we talking about minor changes that are potentially questionable, or are we talking about big league changes?

DR. EDAN: Only patients with moderate or severe relapses received methylprednisolone for 3 days. We have the exact number of patients who were treated with methylprednisolone in each group.

DR. KATZ: I don't want to beat a dead horse, but in the first study, there were at least two criteria by which a severe relapse could be diagnosed--either a new lesion with an increase of at least 2 points in the Kurtzke, or a worsening by only one point in a previously existing sign. And again, we didn't know the breakdown of which relapses met which definition in the first study, and I'm just trying to get a handle on whether we have that sort of

data for this study or whether we do not.

DR. EDAN: Our goal was not to treat patients with light relapses, so the physician had to measure the consequences of the relapse on daily life and on EDSS, and only if they considered that relapse had consequences on daily life, with a significant change in EDSS, did he decide to treat the patient. We have this data in the publication.

DR. GHALIE: Slide B-135 in fact describes the number of patients who received corticosteroid for the relapse, as well as the number of corticosteroid-treated relapses. So if one follows what Dr. Edan said, they treated only patients who in their opinion had a severe relapse.

This is for the methylprednisolone group. Eleven patients received corticosteroid, and they received 21 courses. In the mitoxantrone group, six patients received corticosteroid--and again, this was during the 6-month period--for a total of seven courses. So one patient had two courses.

So that addresses a little bit your question about what was the severity and the degree of relapse in this patient population, and these are the corticosteroid-treated relapses.

DR. GILMAN: Dr. Wolinsky?

DR. WOLINSKY: If I could ask a couple more

questions about these relapses, especially when patients are seen monthly--I guess I would like to know how many of these relapses occurred between visits, and how many of them wound up being defined at visits and whether or not the neurologist who was declaring these relapses and deciding whether or not to treat them was making reference to the MRIs which were done on these visits.

DR. GHALIE: Dr. Edan, please answer.

DR. EDAN: We had some patients who had their relapses at the time of the MRI, but for practical reasons, it was impossible to change the date of the MRI. So we performed the MRI even if the patient had received methylprednisolone 2 or 3 days before. And remember that most of the patients were in the group with methylprednisolone, so this should have improved the results in the group with methylprednisolone, as we know that methylprednisolone the day of the injection did decrease the number of lesions if the MRI is performed at the same time as methylprednisolone.

So doing so did not break down the validity of the MRI analysis--on the contrary.

DR. WOLINSKY: The question actually was a little bit different, and that is did the physician who was declaring a relapse have access to the MRIs which were done, and did that influence whether or not a relapse was

declared?

DR. EDAN: No. He didn't have access to the MRI data. He decided only on a clinical basis.

DR. WOLINSKY: So that the MRIs were kept from the investigators at the site and just shipped off to London; is that correct?

DR. EDAN: Yes.

DR. WOLINSKY: Thank you.

DR. GHALIE: I would like to continue the presentation.

[Slide.]

The next slide looks at another measures that physicians like to see for EDSS deterioration, which is they categorized one-point EDSS change as to whether it improved, remained stable, or worsened by one point or more.

[Slide.]

Again, there was a difference seen between patients randomized to mitoxantrone plus methylprednisolone compared to the control group. One patient on mitoxantrone worsened by one point during this time period versus six on methylprednisolone. This is the p-value.

If we look now at patients who had improved EDSS by one point during the 6-month period, again, we see a significant difference between the two groups, 57 percent versus 14 percent.

[Slide.]

And to come back now to the issue of relapse assessment which we already approached earlier, here again, one can show a significant difference with mitoxantrone plus methylprednisolone, compared to methylprednisolone alone, and that is looking at the annualized relapse rate. Here, I have put the baseline in the first row to compare, so you can look at how it was at entry, and then the annualized relapse rate on study, which is the second row, and you can see that there is a significant difference between the two groups. The annualized relapse rate dropped in the patients with mitoxantrone from a 3.1 mean relapse rate per year in the year preceding enrollment to 0.7 for the year they were on study--rather, for the 6 months on study--whereas it was unchanged for methylprednisolone. And the p-value here is a comparison between the two groups, 0.7 versus 3.0.

And if we look at patients who remained free of relapse during this 6-month period of study, again, there were 67 percent of patients randomized to mitoxantrone versus 33 randomized to placebo, a doubling of the proportion, and the p-value was also significant.

[Slide.]

So in conclusion, this study, Study 902, shows that mitoxantrone plus methylprednisolone given every month for 6 months significantly reduced gadolinium-enhancing

lesions at monthly MRI scans; slowed neurologic impairment, as seen by EDSS evaluation; and decreased the relapse rate. This is in patients with highly active or rapidly deteriorating multiple sclerosis.

I would now like to turn to the safety data on the use of mitoxantrone for patients with multiple sclerosis.

DR. GILMAN: I wonder if you would handle a few questions now related to the data you have just covered for the two studies, 02 and 01.

DR. GHALIE: Certainly.

DR. GILMAN: Dr. Katz asked whether you had actually shown a change in basic progression of the disorder, and he made the point in his narrative that if there were a change in progression, to evaluate this, you would have to look at the patients after they had stopped the medication and look to see whether the group that was on drug returned to the level of the placebo-treated group or whether they formed parallel measures over time.

Would you address that question?

DR. GHALIE: I will begin with Study 902 and say that the data is not available. So let's go to Study 901, which is our Phase III study.

During the 2 years on treatment, clearly, patients who were on mitoxantrone had less EDSS progression and the other Ambulation Index. But we also have data on Month 36.

Almost all patients who completed Year 2 ended up coming at Year 3 for their evaluation, and as I have shown you on that slide, patients who were randomized on placebo still had less EDSS progression between baseline and Month 36 than patients who were randomized to placebo. And that was true for the EDSS, the Ambulation Index, and the SNS scores. We can come back to that slide, if you wish, to make the point.

DR. GILMAN: Please do.

DR. GHALIE: That is Slide M-43.

[Slide.]

DR. GILMAN: Dr. Katz has another question.

DR. KATZ: Just two points about that. One, in the design that you are talking about and that I have mentioned, as you point out, in order for a true effect on progression, at least by this paradigm, you would have to maintain that parallelism that you talked about. The question here, as we will see, is whether they were still different at 36 months or whether they were approaching each other. In other words, were they still as different as they were at the end of the double-blind. That is number one.

Number two, again, I will remind the committee that the Month 36 data are unblinded\--I believe that's what were told--so that should be taken into consideration.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: I just want to comment a little

further on that issue. This comes up in cardiovascular evaluations also, where people would like to treat a condition like heart failure with a drug like an ACE inhibitor and find improvement over a period of time, that is, find that some measurement of heart failure is better at the end of a period of time, and suggest that there has been a change in the heart. We have generally said, well, that's nice, but to show that there has been a change in the heart, you need to have people off therapy, because we already know that ACE inhibits treat symptoms. So the fact that you are better at that period could mean that you are treating the symptoms; it doesn't necessarily mean you have changed the heart.

So in response to that, there is a trial of people who have had a heart attack who were given an ACE inhibitor for 6 weeks and were then evaluated at 6 months--that is called the Gissey II [ph.] trial--and it makes the case that ACE inhibitors given early really do have an anatomical effect on the heart.

But it seems worth pointing out that that issue arises when the drug in question has both a potential claim for changing the underlying disease and also has the potential for symptomatic improvement. So that, for example, in Alzheimer's disease, we have been very rigorous in saying that before you want to claim anything other than a

symptomatic benefit, like that we slow the rate of progression, you have to show what the results are off-therapy, and when that was done with Aracept [ph.], there was no effect off-therapy. People came back to the baseline.

It is just worth saying, without trying to prejudge the answer, that how worried you are about that depends a little bit on mechanism. So that if one used an antibiotic, for example, to treat coronary artery disease, it isn't too plausible that an antibiotic has an effect on angina other than on its effect on fundamental atherosclerosis. So the question is a little less forceful when the mechanism doesn't seem to have a potential for symptomatic benefit. Now, you have to make the judgment whether this mechanism has a potential for just improving symptoms transiently, but that does get factored into how important that question is, I think.

DR. GILMAN: Well, I think that clearly this drug would be expected to have a symptomatic effect based on what we know about the immunologic basis of multiple sclerosis and the effectiveness of other immunosuppressive agents.

Dr. Grotta was next, and then Dr. Weiner.

DR. GROTTA: Well, I guess this bears on this question, and that is whether the drug sort of has a nonspecific effect on MRI lesions. Maybe the oncologists

can tell us from the oncology experience in patients who have, say, brain metastasis in whom the drug is given. Is there an effect on the MRI scan, or has that ever been observed, or can we be convinced that the changes that we are seeing in the gadolinium-enhancing lesions are actually an effect on MS activity?

DR. SWAIN: I think that's a very good question, and I don't really know the answer. I actually tried to find out some of this information before I came, and one question I had was how much of the Mitoxantrone actually gets into the CNS and into intracerebral tumors, and the data is very minimal and it shows actually it doesn't get into the tumors very much; it is more in the surrounding brain tissue. And if there is not a disrupted blood brain barrier, it actually doesn't get in much at all. And I assume that in MS, you do have a disrupted blood brain barrier, so you would get drug in there, but I wanted to later have the company comment on that.

For Mitoxantrone particularly, I don't know of any data looking specifically at brain metastasis in a study.

DR. GHALIE: I would like to have Dr. Alberts comment on that, and then I will come back and answer your question, Dr. Swain, about the systemic effect versus the central nervous effect of Mitoxantrone.

Dr. Alberts?

DR. ALBERTS: I think Dr. Swain is on target here. The studies that we have suggest that Mitoxantrone does not get through the blood brain barrier to any extent. The effects on MS, on the other hand, are not related to the Mitoxantrone effects directly on the lesion; they are related to the immunologic effects that they are having.

So I don't think that we have any data to suggest that Mitoxantrone directly would affect lesions seen on MRI scan.

DR. GILMAN: But the lesions on the MR scan reflect breakdown of the blood brain barrier, so is there a possibility that the drug has an effect upon the vessels rather than the nervous system?

DR. ALBERTS: Well, I think we are in a very gray zone area of the pharmacology of Mitoxantrone and, for that matter, most of the antineoplastic drugs. I think the only real data that bear on this are looking at CNS levels or actually cerebrospinal fluid levels of Mitoxantrone after intravenous injection, and in fact, studies have not been able to determine levels or pick up levels of the drug in cerebrospinal fluid in cancer patients. I think that's the closest I can come to answering the question about whether it's really getting into the brain itself.

DR. GILMAN: Thank you.

Dr. Penn, then Dr. Weiner.

DR. PENN: I had a follow-up immunology question and then I had another question I wanted to raise. Is there any data in MS patients--and I know some of this was presented earlier--regarding levels of Interferon gamma or TNF or other regulatory-type cytokines, et cetera, in patients treated with Mitoxantrone in multiple sclerosis? Do we have any data on that?

DR. GHALIE: There are data available both in animal models and in patients. There is a lot of data from the models that were done in the seventies and eighties that show effect on cytokine, and there is data also on patients that shows a decrease in B-lymphocytes, a significant decrease in B-lymphocytes, to a lesser extent a decrease in T-lymphocytes, particularly T-helper lymphocyte, CD4. There is also data, although more limited--and Dr. Hartung is intending to do this in his own Phase III study--looking at cytokine, where there is also a decrease IL-2, Interferon gamma and TNF alpha.

DR. WEINER: So there is a decrease in IL-2, Interferon and TNF alpha. That was done in--

DR. GHALIE: In a small number of patients.

DR. WEINER: Another question that I have--if there is a shift--with some of the other chemotherapy drugs, for example, cyclophosphamide, where you have a decrease of Interferon gamma, et cetera, and you might have a shift more

toward a TH-2 or TH-3 response, in the bloodstream, there is actually an increased number of eosinophils which is seen on the white blood count which would indicate an immunologic effect. Was there a change in eocynofils [ph.], or was that looked at in MS patients treated with Mitoxantrone?

DR. GHALIE: We have no information on eocynofil [ph.] counts. That may be something we can look at later.

DR. WEINER: Okay. That was just a follow-up immunologic question. The other question I'd like to address is related to the 901 study, and it relates to page 081 which was provided by Immunex to the committee, where analysis is done based on the type of MS. There, from the 901 study, we have remitting progressive patients and secondary progressive patients, and they are broken out. I have a number of questions I'd like to ask.

First of all, based on the classification of patients as remitting progressive or secondary progressive, how many patients, then, in the 901 study were classified as relapsing remitting?

DR. GHALIE: Yes, that's something we addressed earlier in the morning. Remitting progressive are patients in that study defined as patients who have relapsing remitting disease with incomplete neurologic recovery after relapse. That represents about half of the patients enrolled in the study.

DR. WEINER: The other question I wanted to ask, and I don't know if any statistics are presented, is is there a statistical difference between the placebo and the Mitoxantrone 12 mg per meter squared in the secondary progressives when you compare placebo 23 versus Mitoxantrone 15?

DR. GHALIE: With respect to which endpoint? I'm sorry.

DR. WEINER: Well, there are a number of endpoints listed--EDSS, AI--

DR. GHALIE: Okay, for the efficacy endpoint, no, there was no difference in baseline between the two groups. As far as treatment effect, again, we are talking about patient subsets here, and there were no significant differences, but there was a trend, as you can see, in favor of Mitoxantrone 12 mg per meter squared.

DR. WEINER: The last question I would like to ask is a very important issue in terms of patients with secondary progressive disease is that the longer they have secondary progressive disease, the less likely they may be to respond to immunomodulatory therapy, and if this is used in patients with secondary progressive disease, some patients who have had disease for long periods of time might be treated.

Do you have any data on the response in terms of

subgroups in terms of how long the patients were secondary progressive--in other words, those who were progressive for a year or two years versus those who might have been progressive for five years? Do you have any data on that?

DR. GHALIE: We have read, Dr. Weiner, your paper which was published in December 1999, and I knew that was going to come up as a question. The data was not collected, so unfortunately, I will not be able to answer whether there is a relationship between duration of the secondary progressive part of their disease. We have the duration of their disease overall, and here there was no relationship. But as far as the duration of secondary progressive, we don't have that information. That may be something that Dr. Hartung may have some information on.

DR. HARTUNG: Yes. This is obviously an important question bearing on the possible differentiation of differences between the various forms of progressive MS. We have tried to go back and look at the 14 patients enrolled in the Wurzberg [ph.] Center, and we found, if I remember correctly, that those patients classified as secondary progressive had disease for something between 1.5 and close to 4 years. We don't have information from all the centers, but I am trying to somehow retrospectively get that data.

DR. WEINER: Thank you.

DR. GILMAN: Dr. Penn, then Dr. Grotta.

DR. PENN: I just want to make sure that I am clear on a few points. I think the committee is going to have a lot of discussion about the claim of progression and whether your drug helps to avoid progression of the disease. Is the only data that supports that the 36-month data which you show on your Meyer-Kaplan curves? Is there anything else that we should consider other than mechanistic types of arguments that you don't have data for that we should take into account as we debate that point?

DR. GILMAN: Can we see that slide as you answer the question, please?

DR. GHALIE: The only data I can present to you today on a slide is this Month 36, and again, we can go back to that slide.

[Slide.]

DR. GHALIE: Again, I mentioned in the beginning for full disclosure that our protocol allowed physicians and patients to be unmasked to study drug during the third year of follow-up. That was the most conservative way, and in fact, in many centers, that was not done. In other words, patients and the EDSS disability assessor remained masked. But I can't add to that how many were.

So that's the only data we have for that study. We don't have follow-up beyond Month 36. In fact, this is happening these days beyond 36. So this data is not

available.

There are two other sets of information that are available that were not submitted to FDA, so I cannot present it to you as fact with a slide, but at least I can mention it to you.

There is one publication that I referenced very early in my presentation by Nili Firini [ph.] and collaborators. This is a study that was done in Italy published in 1997, a randomized trial with 57 patients with relapsing remitting disease who were randomized to receive Mitoxantrone or placebo. In that study, patients were given Mitoxantrone or placebo on a monthly basis for one year, and they had EDSS assessment relapse and MRI results. The patients were seen a year later at Month 24--and again, in this publication which is in the briefing document you have received--at Month 24, there was still a difference between the two groups in EDSS progression. Again, that is one year after stopping treatment. I don't have the raw data to share with you, but that was in the publication.

DR. KAWAS: Was that study masked?

DR. GHALIE: This was masked. It was a placebo, and the EDSS evaluator was masked; correct. It is in the paper.

DR. GILMAN: How do those scores compare with the status at Month 24--the SNS, the AI, the EDSS, for example?

DR. GHALIE: What I am hearing is that you would like to see what happened between Month 24 and Month 36.

DR. GILMAN: The differences between treated at 12 mg per meter squared and placebo.

DR. GHALIE: It is Slide B-25.

[Slide.]

DR. GHALIE: Now, this is only in the year of treatment, Month 24, again in the three groups. For the SNS, Ambulation Index, and EDSS--and that is EDSS progression during the third year of treatment for those patients followed for a total of 3 years. That's the mean change also, not total EDSS.

DR. GILMAN: So there is essentially no change in EDSS between Months 24 and 36?

DR. GHALIE: They were relatively stable, correct, the three groups, here for EDSS, Ambulation Index, and then SNS was higher in the placebo.

Dr. Lublin has a comment here.

DR. LUBLIN: Thank you.

Let me alter the perspective. This is a relatively new definition of progression in the field of MS that Dr. Katz has posed. So what you are looking at is the very best data extant in any study done anywhere in MS that matches the criteria he is trying to put up.

The nature of this agent is such that none of us

would have thought of this as being a symptomatic therapy in the way we used symptomatic therapy, such as baclofen and tisadidine [ph.] and things that alter things. And the nature of EDSS is also such that we don't view it as a measure of symptoms in MS.

The thing that we get worried about that this panel has been worried about in the past is whether the change that we are seeing over time in EDSS is reflective of true alteration of the underlying disease or alteration of intercurrent relapses. And that's why we've used the sustained EDSS to try to take the issue of relapses out. But we have never thought of it in terms of disease coming back. That's something that we just don't expect to see, either with the measure of the EDSS in this type of disease and over this time period or with this type of agent.

DR. GHALIE: I would like to complete my answer to Dr. Penn. You had asked if there is other data out that I have not presented. In fact, there is also data from Dr. Edan's Study 902. In his own site, there were 17 patients enrolled in this study, half of whom were treated with Mitoxantrone, half with placebo. He had looked at these patients long-term now, obviously--these are his patients. Clearly, we can't present these data today because they were never submitted to the FDA, but Dr. Edan had shown us the data yesterday, and he had graphs on those where he showed

in these graphs that once he stopped treatment with Mitoxantrone--and again, it is 6-month treatment--up to 3 years post-treatment for those patients who have 36-month follow-up, the EDSS was stable compared to what it was at the time he stopped treatment for patients with secondary progressive MS.

So there is some information accumulating suggesting that patients who stop Novantrone do not have a disease rebound; it stays where it is. How long this is going to persist will be addressed by following patients longer in the future.

DR. GILMAN: We have some questions now. First, Dr. Katz, then Dr. Wolinsky--were you through, Dick?

DR. PENN: I think we ought to discuss this topic as much as possible, and then I want to ask another question after that on a different topic.

DR. GILMAN: Let's stay with this topic, then.

Dr. Katz?

DR. KATZ: Again, I would just point out that all this post-treatment data when we're talking about rebound is unblinded data, so that has to be factored in.

Also, when we talk about progression or symptomatic, I am a little nervous when people talk about what their expectations are in terms of how the drug is working or what sort of effects it has based on what we

think we know about what it's doing, and what the EDSS reflects and what we think that reflects. That's why it is useful to have some sort of an operational definition of progression that you think makes sense, like this blinded withdrawal sort of phase, and see whether or not the disease returns under those conditions.

This way, we don't have to worry about the mechanism of action, because we don't really know, as was pointed out earlier, what the mechanism of action is. That's why I think we ought to--I mean, it's worth discussion, but I don't think it is absolutely germane to the question, because it is based on a whole bunch of assumptions for which we don't really know the truth.

DR. WOLINSKY: Maybe I got confused, particularly around these issues of what we are calling these patients, because I think you just referred to Dr. Edan's subset of patients in the French study as secondary progressive, when I was under the impression that he had referred to them as relapsing remitting, some with accumulating disability. This is not a small issue.

Now, as I look across these two studies, one of the things that strikes me, since one of the things that is in common is at least a baseline MRI, is that the group of patients selected to be included in the French study were, albeit enriched for the presence of an enhancement on one of

the two MRIs coming into the trial, they did what I would expect patients with relapsing remitting disease to do, that is, based on the clinical criteria, about half of them had an enhancement.

What strikes me in the other study--the multinational study--is that the enhancement frequency was only about 24 percent even though the patients were stated to be rather aggressive in their phase of disease. This surprises me. I would have thought it would have been closer to 40, 50 percent.

Again, trying to get a feel for what kind of patients we really want to hopefully approved these drugs for, what are the similarities and differences between the patients who were entered into these two trials in terms of type.

DR. GHALIE: Let me first address your first questions about Dr. Edan's patients. And again, I feel uncomfortable talking about this, because this is data which was not submitted to the agency, and we have not analyzed it. This is follow-up data that Dr. Edan-

DR. WOLINSKY: What they were when they started is submitted.

DR. GHALIE: No, no--I'm saying that in the data we looked at, he had data on patients who were classified as relapsing remitting, patients defined as primary

progressive, and patients defined as secondary progressive. So it is not only the patients in Study 902, it is the patients in his practice. And I don't want to talk any longer about that; I would like Dr. Edan to comment briefly about that. But I didn't want to give the impression that it is only 902. It is 902 plus other patients he has in his practice. And again, we don't have the data to show you, and I apologize for that; I think we could do that. But Dr. Edan, very briefly, if you could tell us.

DR. EDAN: Yes; it shows our experience. At the present time, in the MS clinical frame, we have the experience of 106 patients who were treated with Mitoxantrone monthly for 6 months. Our concern was to know what happened with these patients after the induction treatment, and we found 52 relapsing remitting patients; 35 secondary progressive patients, and 19 primary progressive patients.

We had a follow-up period of 3 years, and what we observed openly is a clear-cut effect of Mitoxantrone during the induction treatment, allowing the patient to improve quite a lot the EDSS level, beneficial for the next 3 years.

But I have to confess that most of these patients were treated after the induction treatment also by immunosuppressive or immunomodulatory agents. They were treated by betaseron, they were treated by methyltrexate.

So just to tell you my experience with the effect of an induction treatment for 6 months, followed by less aggressive treatment, we have very clear-cut, good results for a 3-year period after this attitude.

DR. GILMAN: These were not blinded cases; you were not blinded?

DR. EDAN: No, no. It is our experience. It is not a study; it is the experience of my center.

DR. WOLINSKY: To follow up on that just a small amount, so in the patients in 902, who obviously didn't disappear from France at the end of the study--

DR. EDAN: No.

DR. WOLINSKY: --and even though this is anecdotal, and we don't have the same level of rigorous anecdote that we have from the multinational study, what happened to them?

DR. EDAN: Yes. We published that two years ago at a meeting in Stockholm. In the five French centers, we had two different attitudes. Half of the patients were then treated with Mitoxantrone every 3 months for 2 years, and another attitude was to give no treatment at all--that was for the patients included in the trial.

What we observed were quite similar results for the two groups of patients. It was the reason why some of the French centers decided not to continue to treat every 3

months with Mitoxantrone in that group of patients after that.

DR. WOLINSKY: That brings me back to a question I had before, which is what is the appropriate way to use Mitoxantrone in patients with, to use newer terms, transitional or very active MS.

DR. GHALIE: That is something that we would like indeed to discuss as I go along in our presentation. But in a capsule, what I am getting to is the two studies that I am presenting to you today, in our opinion, show that Mitoxantrone has an effect on patients with multiple sclerosis. These two studies were designed differently. The drug was given on a different schedule. But what we are seeing is an effect on EDSS progression as well as relapse and MRI.

And in our opinion, where we are proposing the use of Mitoxantrone, it is to slow neurologic disability in patients who have what we call progressive forms of multiple sclerosis. And I don't want to add a new classification to MS; that's what Dr. Lublin will address.

Really, it is, in our opinion, what was tested in the Phase III study--patients with secondary progressive MS or patients with relapsing remitting MS with accruing disability following relapses. In our opinion, that's where we had the strongest data about the role of Mitoxantrone,

and that's what we propose as an indication.

DR. GILMAN: Dr. Grundman first, then Dr. Grotta.

DR. GRUNDMAN: I think the question of dosing is actually a key question. If you look at Slide M-38 in the main presentation book, you can see that after 6 months of treatment with Mitoxantrone at 12 mg per meter squared, they perform no better than placebo.

Now, when you use the induction phase that was just described and which was performed in the 902 study, there was an effect, so kind of an interesting question, getting back to Dr. Wolinsky's point is what is the appropriate way to treat these patients, and I'm not sure we know.

DR. GHALIE: The data we have on the larger study, the randomized trial, the one that has the blinded EDSS evaluation, is the one where it was given every 3 months. And I am not sure I follow what you said, but the placebo patients are the ones in gray, so indeed, at the 3-month evaluation, which is only after one course, there was no difference between the two groups, but after that, the line separates.

DR. GRUNDMAN: I thought it said 6 months there.

DR. GHALIE: This is 3 months after one course; this is 6 months after two courses; and after that, the curves do separate, and the patients on placebo get worse,

and the patients on Mitoxantrone improve. So it could be that one needs one or two courses of Mitoxantrone for a population of patients with MS to separate. For individual patients, some of them may respond sooner; some may not respond. It is always hard to do on a mean result, but clearly, the curves separate at that point.

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

DR. GROTTA: Notwithstanding some of these confusions we have just been discussing, at least from my perspective, I am becoming convinced that there is some clinical effect here, but I need to come back to the MR data, because that's what you are presenting from the second study as confirmatory evidence, and I'm still not certain about this.

I am still bothered by the fact that the main outcome you were looking at in the MR studies were gadolinium enhancement, and it bothers me that these patients were getting monthly high-dose steroids in both groups and that that is not a nonspecific effect. So I would like to--and this reflects my own ignorance of what is the best thing to follow on MRI, but to me, when you see T2 abnormalities, long-term differences, that might be somewhat convincing.

I noticed in Study 901 that while it wasn't significant--this is on your Slide M-50--there appeared to

be some changes in the T2-weighted lesion load in the first study, 901, and I wondered whether the same thing was looked at in Study 902 and whether any of those were looked at long-term even beyond the end of the dosing period and whether maybe you even combined the data from Study 901 and Study 902 to increase your numbers.

DR. GILMAN: As you point out, in Study 901, we present the T2-weighted lesion data, and there was at least a trend that one can see. In the Mitoxantrone group, they were stable, and in placebo, they were worsening.

I did not present the data for Study 902 because it was not written in the protocol as one of the secondary endpoints. However, it was done, and the look at the data was available to us. In fact, it is on Slide B-129. This is the data for T2-weighted lesions, and they are small lesions, and that changed in T2-weighted lesions at baseline versus Month 6 at the end of the study. And the lesions were classified as small, moderate, and large in size, and then, the combination of all these lesions.

If one looks at the change between--we have mean and median shown for you here--in the Mitoxantrone group, for the small lesion, it had increased by 0.6, and for the methylprednisolone, 1.7.

Now, if one looks at moderate to large lesions, the difference is more significant, and these are the p-

values.

Again, those are the data. I didn't want to present them up front because they were not part of the protocol-defined criteria, but clearly, that was looked at.

As far as your first question, or at least the introduction to your question, about the effect of methylprednisolone on MRI results, this is something that I would like to have our consultant comment on, but my first answer to that is that methylprednisolone may have an effect on MRI when it is given immediately before, within maybe a day or two prior to, doing the MRI. In this study, MRI was done, and then methylprednisolone was given. Then, the patients were scanned another month later. So any potential effect of methylprednisolone on MRI is not going to be a month later.

DR. GROTTA: I thought that that was what the protocol stated, that if the patients deteriorated or had a relapse during that month, the physician might have given them steroids for symptomatic treatment prior to their coming in for their MRI scan. I guess I'm just not--maybe it's just me--but I'm just not 100 percent certain that the gadolinium enhancement done monthly was that precise a measure of disease activity.

DR. GHALIE: Actually, I would like to follow your reasoning. Indeed, there are a few patients who may have

had methylprednisolone given to them prior to MRI, within a few days, but if you recall the data I presented to you, there were more patients in the methylprednisolone group who had relapse treated with corticosteroid. So if it is in any way going to impact the study results, it is going to be in favor of methylprednisolone. Again, this is an observation that one can think of.

DR. GILMAN: Dr. Temple, do you still have a question?

DR. TEMPLE: Yes. I just wanted to get back to the dose question. The second study does, as was pointed out, appear to show a neurologic difference as early as Month 1, and it raises the question of whether there is still more to explore about how best to use this agent.

You have evidence that you have provided that makes you believe, anyway, that the effect is long-lasting--that is, even after you stop the drug, you still see improvement relative to the untreated patients even in the year after treatment--now, that's not blinded; leaving aside those reservations. It really does raise a question of whether a loading dose approach in the long run is better and actually leads to more rapid benefit and perhaps even less toxicity in the long run. I mean, one doesn't really know until one looks.

Do you have further studies ongoing of any of

these questions, or plans?

DR. GHALIE: Allow me to answer your question in two parts. Number one, on why this schedule was selected, every 3 months, there were a number of rationales. One of them was that the pilot studies which were done and were published in the early nineties showed that every 3 months works. And the investigators knew that this was a treatment that eventually had a cumulative dose that you cannot exceed, so they wanted to stretch treatment as much as possible, and every 3 months seemed to work, so it made sense to do it in the Phase III study, and this is the data we have, and we would like, at least for the time being, to consider this as the appropriate dose and schedule for Mitoxantrone.

Now, to answer your question number two, whether there are currently ongoing studies to evaluate other schedules, Dr. Edan indeed and investigators in France and Italy are currently conducting a study which looks at this induction regimen with Mitoxantrone for six courses, monthly for six courses, and then, either stopping Mitoxantrone and going to Interferon; and the other arm is Interferon alone.

So in his group--and it just started recently--there were about 25 patients enrolled out of 200--the question of induction regimen will be studied.

We are also having requests now from investigators

who would like to investigate the role of Mitoxantrone, obviously, as you can imagine. We have an investigator who is evaluating an induction dose with 12 mg per meter squared every 3 months, going down to 5 mg per meter squared on a different schedule.

So these are things that we will be looking at in post-marketing if we are given this opportunity. But at present, the strongest data is what Dr. Hartung's trial showed on the every-3-month schedule.

Later on, we will get to Dr. Mauch's retrospective analysis and his experience with 500 patients, and as I will describe to you, there is an alternate way that he has given Mitoxantrone that can also tell you about some of these methods one can use. But again, we would like to focus on our Phase III trial as at least the dose and schedule.

DR. GILMAN: Dr. Penn, then Dr. Penix.

DR. PENN: I see the other major thing that we are going to be debating is the relationship between our surrogate marker, or so-called surrogate marker, and clinical progression, and I am wondering whether at this point you might want to speak not with your own data but present something that will either convince us or not convince us that this is a good surrogate.

DR. GHALIE: Really, I would like to refer this to the neurologist experts at this table; I would not like to

myself get into that debate which, as you may know, is ongoing in the neurology field.

So I would like perhaps to hear first from Dr. Lublin about how he views the MRI and how can this be viewed as a surrogate marker for pathology of MS, and after that, Dr. Panitch, please, and then Dr. Smith.

DR. PENN: It isn't just as a surrogate marker for pathology, which is, of course, very interesting, but also clinical progression.

DR. GILMAN: Okay. Dr. Lublin, please.

DR. LUBLIN: Let me start with that issue first, because this is one that has become an issue of great interest for us in the MS community and a source of considerable discussion.

My view is that the fairest way to view MRI is that in fact it is reflective of the underlying neuropathology, and that the clinical scales that we use are also reflective of the underlying pathology. We have had this discourse, because some of the regulations say you have to show clinical benefit and such, and that is of course very important, but some of us have the underlying bias that any changes going on in the brain are bad for you, and that the most reflective measure of those changes, at least demyelinating disease, is the MRI scan.

Having said that, there are a number of studies

which show correlations between, for example, gadolinium-enhancing lesions early in disease and time to different levels of disability, even in individuals who have not yet made the clinical diagnosis of MS, but with the first symptom, what percentage are going to go on and have it, and that data is not bad.

There is also in the literature relatively unimpressive correlations between, say, T2 lesion load and levels of disability, and we have been arguing over that as to what that means as well. But I think again, if one goes back and says, well, it is showing us the underlying neuropathology, that most would agree that growing white spots in your brain are inherently a bad thing, and that is the view we take.

The other issue, of course--and I'm sure some of your experts here are going to bring this up as well--is each different measure is looking for something different. So the gadolinium-enhancing lesions are measuring breakdown of the blood brain barrier. In MS, that is thought to be the equivalent of inflammatory lesions.

T2 lesions, which we also have a measure of here, are a measure of a number of things--inflammation, demyelination, astrocytosis, edema--a whole bunch of different things. So it is a little hard to pin that down. There are other more recent measures that have come into use

but that weren't either available or weren't part of these studies, so they don't give us any added information.

DR. GILMAN: Nevertheless the point remains that the location of the multiple sclerosis lesion, the new lesion, is absolutely key with respect to clinical presentation--that is--and Dr. Katz has said this in his narrative--if a lesion happens to cut across the corticospinal fibers someplace, the patient is going to clearly become symptomatic. Should it be up in the prefrontal region, there may not be a clinical manifestation of that lesion.

DR. LUBLIN: There may not be an immediately obvious clinical manifestation of that lesion. But for example, the best correlate that I know of for white spots presumably representing demyelination in the brain is neuropsychological testing. So that each one of those is in fact taking its toll; it's a matter of when you are able to measure it with a clinical correlate.

DR. WEINER: Let me say a word to your question in terms of how it relates. We just finished a study that is going to be coming out, and it was NIH contract where we took progressive patients and relapsing remitting patients untreated who were imagined on MRI as many as 22 times over a year; they were analyzed by three-dimensional imaging and quantitative imaging, both in terms of gadolinium-enhancing

lesions and in terms of T2 volume. And we do indeed find a correlation between disability as measured by EDSS and Ambulation Index with T2 volume and with disability and relapses as far as gadolinium-enhancing lesions.

So I am becoming more and more convinced that the MRI does indeed reflect not only what is going on in the brain but what is happening in terms of disability. Because there are silent areas of the brain, the R values are not 1; they are somewhat in the middle. Although we also have positive data, some of it published, some of it we are now putting together, that there are correlations between T2 lesion and volume and cognitive changes by a very sophisticated measure.

So my own feeling is that indeed the MRI does reflect not only the pathology but clinical manifestations.

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

DR. KATZ: Yes. An important part of the utility of a surrogate from the point of view of deciding whether or not it is useful for approval of drugs, for example, is not so much only that it correlates with the pathology but that also treatment has the appropriate effect on it and on the clinical outcome of interest.

So everything we have heard so far about the MRI as a valuable surrogate talks about on treated patients and following them and natural history kind of data. But what

is the data--other than the data we have heard this morning for this drug--that in general, treatment has the effect that you want to the surrogate and also the effect, ultimately, on the clinical benefit of interest?

DR. PENN: Well, we are revisiting what we did a number of years ago with the Interferon when we had data on MRI, and it did correlate with progression, as I remember those meetings. So I think there is substantial data. And as a neurosurgeon looking at this, I am very glad to see that things are correlating, and they are correlating better when you use the right test--that is, truly volumetric things and take in cognitive impairment, because of course, most of the brain is cognitive, and we are wiping out sections that may not cause obvious neurological symptoms but which are there anyway.

So the way that I see this discussion going is making this a very powerful surrogate marker, because it is all fitting in the same direction--although we always have to worry about exactly which measures and that it is being done in the same way. That's why I think the fact that it was read blind in England by somebody who is expert in doing this really gives us some power in this particular case.

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

DR. GROTTA: This is very useful. So I am

reassured that these MRI measurements among MS experts, both T2 and gadolinium, are now being recognized as reflective of real disease activity. How dependent is this upon the methodology of carrying out the measurements, and are we convinced that the methodology used in this study is comparative to those carried out in centers like yours, Dr. Weiner, that find these correlations?

DR. WEINER: Are you asking me?

DR. GROTTA: I am asking whoever knows how--do we need to explore how the measurements were made in London; do they do all the three-dimensional measures and things like that, and is it possible that--I look at T2-weighted lesion load, and I see a mean score change of 3 or 4, and I don't know what that means.

DR. WEINER: My analysis of the data that is presenting here is that it was done in an appropriate way, with the appropriate measures, et cetera, and is indeed valid in terms of showing changes, both in terms of T2 volume and in terms of gadolinium lesions.

DR. GILMAN: Dr. Wolinsky?

DR. WOLINSKY: I don't think we can address very easily in this particular meeting the notion of MRI as a surrogate, as I understand the FDA is raising it, and I don't think there is any data here that allows us to look at it as the perfect surrogate. Certainly, nothing that

predicts what these patients are going to do in the future based on what we are seeing across the course of either the short or the longer study.

But I am very encouraged when I see clinical data and MRI data which convincingly goes in the same direction. I would be very bothered by data that goes in opposite directions, and that is the kind of data we are presented today. So I think as much as I would like to argue for the importance of MRI in other arenas, I think the issues for us today are not technical on how do they read this, not do they show effects in both areas, but how in the world are we supposed to use this.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Surrogates are not expected to be perfect substitutes for clinical outcomes--they hardly ever are. People have written a fair amount about this; we have written only a little bit.

The initial hope that a surrogate endpoint or putative surrogate might be useful can never be based on correlation with outcome results, because you do not have any outcome results yet. So in the case you have here, you have only a few drugs that work, and the best you could hope for is a modest degree of association with clinical outcome and the putative surrogate.

Before one gets to that, however, there is a phase

where you look to the available data you have of an epidemiologic nature and see if at least--I think this relates to the last comment--the natural history of the disease seems to serve some correlation with the surrogate and the real outcome. If it didn't do that, then it wouldn't be a very good candidate surrogate.

What I think Dr. Weiner was saying is that he feels there is growing evidence at least at that level that there does seem to be a correlation with outcome and the MRI findings.

The ultimate conclusion that it is a really, really, really solid surrogate sort of depends on looking at a large number of drugs that have effects on both, finding that it always works, showing that patients who have a better response on MRI have a better response clinically, and all kinds of stuff that you can't possibly have yet.

But I want to emphasize that the Committee is a judging group, not just a data analysis group, and that one of the reason we come to you is for your judgment on the quality of a surrogate like that, even with imperfect information which, heaven knows, is what we have.

DR. GILMAN: Are there any other questions from Dr. Ghalie at this point?

[No response.]

DR. GILMAN: If not, Dr. Ghalie, with your

consent, I think it would be good for us to have a lunch break, because at one o'clock, we are expecting some patients to be here, and we don't want to keep them waiting.

Let me ask that the Committee members refrain from any discussion of this agent in any way over lunch. All of our discussion should be in public. There is a place reserved in the dining room for Committee members, so please, let's herd together there.

We'll take a one-hour break and resume at one o'clock.

[Whereupon, at 12 o'clock p.m., the proceedings were recessed, to reconvene at 1:10 p.m. this same day.]

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AFTERNOON SESSION

[1:10 p.m.]

DR. GILMAN: We are now going to hear from three people. The first person who would like to speak is Frank Vanik.

Mr. Vanik, please.

MR. VANIK: Good afternoon. My name is Frank Vanik, and I am diagnosed with secondary progressive multiple sclerosis. I live in White Marsh, Maryland, right outside of Baltimore.

I am here representing the National Multiple Sclerosis Society and the third of a million people it serves annually.

I am having trouble in that one symptom of my MS is that my vision is kind of blurred, so I am going to just put this statement down and talk to you.

I have been an athlete all my life. When I was a senior in college, I noticed that I seemed to step slowly in basketball, and I was tripping a lot over my feet, so I began to worry. I went first to an orthopedic doctor, and to make a long story short, it took three doctors over two years to get the diagnosis of multiple sclerosis at the age of 22.

I graduated from Virginia Tech with a degree in mechanical engineering in 1989 and began work as a

maintenance foreman at Bethlehem Steel. About 2 years after I was diagnosed with MS, I started walking with a cane, and I progressed to where I used canadian crutches, and within 4 years of being diagnosed, at the age of 25, I was using a wheelchair most of the time to conserve my energy.

I had to stop working. It is kind of tough to work in a steel mill in a wheelchair, so I stopped working there and went on to look for a second career of some sort.

MS has changed every dynamic of my life. I tell people off-handedly that the only part of my life my MS has not affected is my appetite. You name it, I have experienced it.

One of the affirming things about living with MS has been that I have found out that I really have a great family. My father brought me here today, and there is not a day that goes by that one of my sisters or my parents or my friends aren't calling and asking me if there is anything they can do--more times than not, there is, so I am very grateful for that.

About 5 years ago, I took a part-time job working for the Maryland Chapter of the MS Society, coordinating recreation and social programs for other people in Maryland with MS. In addition to that job, that paid employment with the MS Society, I have found a lot of good things to talk about that the MS Society does, and I have kind of found

myself appointed as an ambassador of the Maryland Chapter of the MS Society. I would like to mention here that they have been wonderful for me and I am sure for the rest of the folks living with MS in Maryland. If the Maryland Chapter is a reflection of how the national organization treats people, then all over the country, we are in pretty good shape.

One of the things people have asked me about in the past is about my future, and do I want to be a recreation coordinator for the rest of my life, do I want to work part-time for the rest of my life. It is clearly difficult for me to answer any questions like that. It is difficult for anybody--nobody can predict their future--but having multiple sclerosis makes it a little more apparent. It makes it quicker for you to realize that you cannot predict your future and that it is uncertain.

I guess that is one of the nice things I have heard about Novantrone--if that is the right pronunciation--and the other thing I should mention is that it seems that my multiple sclerosis has progressed to the secondary progressive stage, and sure, the ABC drugs are wonderful, and my goodness, I hope they work for everybody who is taking them, but the Novantrone, from what I understand, is the first medication that is tailored specifically to people with secondary progressive multiple sclerosis. And while I

hesitate to speak on behalf of other people with multiple sclerosis, I can speak for myself and tell you that if the clinical trials show that it has an impact on people's lives, I just think it is wonderful what you are doing and what Immunex is doing to possibly get this drug cleared to it can be prescribed for everybody living with secondary progressive multiple sclerosis.

That's about it. I'd like to thank you for having me here and letting me speak. I think you all are doing wonderful work.

Thank you.

DR. GILMAN: Mr. Vanik, thank you for coming today. We greatly appreciate your making the effort to come and talk to us.

Next, we will hear from Mary Elizabeth McNary. We have pictures of your two children that we'll pass among the Committee members.

MS. McNARY: Thank you.

I am Mary Elizabeth McNary, and 5 months ago yesterday, I became the proud mother of a pair of beautiful twins, Aidan and Aisling McNary Hickey. I also work as a counselor at the National Capital Chapter of the National MS Society.

My career has taken a couple of circuitous turns. My 1992 diagnosis of relapsing remitting MS, my marriage

shortly thereafter to Patrick, who is an international policy analyst with the U.S. General Accounting Office, and our subsequent transfer to Germany have been a couple of the major twists and turns.

I have come to believe, however, that everything in life happens for a reason. Back in 1982, I graduated from Harvard with a specialty in romance languages and literature and Latin American affairs. I started out in the direction of a law career. I soon left that path, though, and I worked for several years in the music industry in New York. I used my knowledge of the law to advocate for copyright protection as a grassroots organizer in the creative community.

That experience took me to Washington where I accepted a position with Senator Chris Dodd of Connecticut. I wanted to develop an understanding of effective lobbying while working from the inside on the Hill.

It was here in Washington that I first met Patrick, to whom I remain happily, happily married despite anything that MS has thrown my way.

As a newlywed in Germany, I used to keep the multiple sclerosis a deep, dark secret. But after about a year of silence, I decided to use my own experience with chronic illness to help other people, and I began studying for a master's degree in counseling.

Then, when Patrick and I returned to the States, I accepted a scholarship to study rehabilitation counseling at the University of Maryland. Upon graduation, I was required to work at a nonprofit organization--so what better choice than the MS Society. My work with the Society allows me to provide both information and empathetic understanding to others with MS. I will soon be using my knowledge of foreign languages and law and Latin America to create an outreach program at our local chapter for the Hispanic community, many of whom don't know anything about MS and don't discover anything about it until it hits them, and they read our Spanish language brochures about it.

I have learned to live with the unpredictable symptoms of my MS, where one day fatigue can make me feel like the only thing running through my veins is water, and the next day, perhaps I can't walk a straight line unless someone offers me his or her arm. My vision problems make it impossible for me to drive a car; I most likely wouldn't be here today if Patrick hadn't been kind enough to bring me.

All these symptoms are really frustrating, and they are also hard to explain because I don't really look any different from anybody else. But what fills me with dread is that I have had a relapsing remitting form of MS for some 10 years now, and that makes me a prime candidate

for developing secondary progressive MS.

Half of all the people who are diagnosed with relapsing remitting disease see their MS turn into secondary progress within 10 years, and of these people, nearly 50 percent will require a walking aid, and 10 percent will need a wheelchair within 5 years. If my own MS becomes secondary progressive disease, I want to have a treatment available to me. My babies and my husband need me too much for me to allow this disease to progress untreated.

Therefore, if the panel believes that the results presented here today support the reported claims that Novantrone can affect underlying disease process in MS for those with secondary progress disease, I encourage--no--I implore the FDA to approve this product with all due dispatch.

Thank you.

DR. GILMAN: Thank you very much, Ms. McNary.

Is Pat Redondo here?

MS. REDONDO: I am so sorry I am late. We lost the directions.

My name is Patricia Redondo, and I have been diagnosed with secondary progress multiple sclerosis. I want to give you a little bit of background on myself.

I was diagnosed in 1972. When I was diagnosed, I had just met my future husband, and we had just bought a

house. We decided, since we were both 28, that we wanted to start a family right away. In 9 months minus a day, we had our second child.

Everything was going along great. I was a program coordinator at the University of Maryland Department of Pediatrics Hospital, and I was in the residency program. I did the work to make sure that the house staff were running smoothly. I helped coordinate their beginning and followed them all the way through their third and fourth years. I helped test them and made sure they were on the right track--I was a proctor--and at the end of their 3 or 4 years--those in the fourth year were usually those people who were chief residents--I filled out the paperwork that qualified them to become certified in pediatrics. I did that through the dean's office in the School of Medicine, and through that, they went out into the world.

After about 10 years of working after my diagnosis, I was stricken with what the doctors said was just hip pain. After a year of living with "just hip pain," I was referred to an orthopedist, and the orthopedist diagnosed me, after x-rays and so on, with vascular necrosis. He decided to operate on me, and what he did was pulled blood out of my hip bone, and he decided one of two things--that it was either a success, and I would revascularize on my own; or, two, it would give me the

sponge that I needed to walk comfortably.

I was successfully operated on, and everything went well until I got back to work, and my multiple sclerosis decided to go from relapsing remitting into secondary progressive multiple sclerosis. So that happened, and over the course of the next 10 or 15 years, my disease progressed slowly. Now, I am basically paraplegic from my waist down and almost quadriplegic in that I can't use my left hand and arm; I can barely use my right hand; I can use my computer with two fingers. It is really not a pleasant situation to be in.

As you can tell by my speech, I am also suffering from cognitive impairment in that I can see my notes, I can see what I want to say, but I can't get it out.

I am here to represent what relapsing remitting MS can do to people. There are 300,000 people in the system at the Multiple Sclerosis Society, and somewhere along the line, probably in about 10 years after there diagnosis, there is a good chance that they are going to go into secondary progressive multiple sclerosis, which is what I am in now.

If you can speed up the process of getting this drug on the market so that the people who are yet to go into the relapsing remitting stage can have this drug available to them, they will not have to face what I am facing now. I

have made a good life for myself. I have volunteered very much. I have a supportive husband. He is a saint. My mother says his halo kind of slips because his head must be so heavy. I also have two children who are great and supportive of me, and I also have an aide. I now have to be dressed, I have to be bathed, my hair has to be washed. Fifty percent of the time, somebody has to feed me. I cannot write. I can work on the computer, which is fun. I can still read, and I can still watch television.

But you know, there is a better life out there for people who are struggling with this disease. It is hard enough as it is, but when people go into secondary stages of progressive multiple sclerosis, and you can help them with this new drug, you will be saving so much misery.

I have a good husband, I have good kids, I have support all around me--but is that really all there is? I'm sure not.

So I just want you to consider putting this drug on the fast track. Thank you.

DR. GILMAN: Thank you, Ms. Redondo, very much. I'll ask the panel if there are any questions.

[No response.]

DR. GILMAN: Thank you all again.

Now, Dr. Ghalie, can we resume where we left off? Let me first ask if the panel has any questions

about the efficacy of 901 or 902 before we move on to safety.

[No response.]

DR. GILMAN: All right, then, perhaps we can take up where we left off, then.

DR. GHALIE: I would like to add a personal note here that is not scripted and has nothing to do with the presentation.

I would like to salute the patients who have presented to us today. I admire your courage in the face of adversity; it is an inspiration for me. So I thank you.

I would now like to review a little bit where we left off before lunch, which is the efficacy results, just to put together what I presented to you this morning.

We had presented to you two studies, two randomized trials, that were well-conducted--Study 901, a large, Phase III randomized trial which has as its primary endpoint clinical endpoints. These endpoints were met. There were also MRI results in this study, and they went in the same direction as the clinical endpoints.

There was also another study which we presented to you, Study 902, which is a study typical of MRI-based clinical trials. Its primary MRI endpoints were met. The clinical results also went in the same direction, and we would like you to keep this in mind as you do your

deliberations later.

[Slide.]

This slide is in fact at the back of your package, so you may not be able to find it.

I will now move on to talk about safety.

[Slide.]

The safety information I will present to you today is based on three sets of data--the two randomized trials I presented to you earlier, and then a single-center retrospective analysis. Altogether, this represents data on 603 patients treated with Mitoxantrone.

Let's begin with Study 901. In Study 901, treatment discontinuation due to an adverse event was reported in five patients randomized to Mitoxantrone 12 mg per meter squared, no patients randomized to 5 mg per meter squared, and two patients randomized to placebo. On the slide, you have the month of withdrawal and the reason for withdrawal.

[Slide.]

The next slide demonstrates and describes to you the adverse clinical events that were significantly more frequently observed in the two Mitoxantrone arms compared to the controlled group, the placebo group, with p less than 0.05. Except for nausea, which was graded as Grade 3 or 4 in 5 percent of these patients, all the other adverse events

in the remaining nausea patients had adverse events graded as Grade 1 or 2.

[Slide.]

This next slide, which is a busy slide that you also have in the briefing document, now describes all adverse events that were recorded in 10 percent or more of the patients who were randomized in this study. Here again, most of the adverse events were graded as mild or moderate.

Now, as you have heard before, Mitoxantrone belongs to a class of agents known to have cardiac toxicity that is related to cumulative dose. As a result, the effect of treatment on the heart was evaluated carefully, with clinical evaluation and electrocardiograms performed on an every-3-month basis and echochardiograms that were performed at baseline, end of Year 1, end of Year 2, and end of Year 3.

I will present to you some of these results now.

No patients who were randomized on this study developed congestive heart failure.

[Slide.]

This slide shows the distribution of LVEF, or left ventricular ejection fraction, which I will call LVEF from now on, that was equal to or below 50 percent in the three groups at the end of Year 1, end of Year 2, and end of Year 3. As you can see, there was no significant difference

between the three groups based on this factor.

Now, as you may know, an LVEF of 50 percent, just to clarify what it is, does not represent 50 percent of normal. It says 50 percent of the blood volume that is ejected during cystoly [ph.]. Cardiologists consider an LVEF of less than 50 percent as indicative of decreased myocardial function.

[Slide.]

This is the third year follow-up for those patients who had discontinued treatment at Month 24 and then had LVEF data available at Month 36. There were two patients, one in each of the two Mitoxantrone groups, whose LVEF was above 50 percent at Month 24 and declined to less than 50 percent at Month 36.

There was one patient in the Mitoxantrone 5 mg per meter squared group whose LVEF was less than 50 percent at Month 24, and then, at the Month 36 evaluation went over 50 percent.

[Slide.]

Additional safety information--there were no deaths on study for the 2 years of treatment, and in fact, for the 36-month period. Two pregnancies were reported on study, although women of child-bearing age were requested to take appropriate contraception precautions. One patient randomized to placebo elected to terminate her pregnancy.

One patient randomized to Mitoxantrone 12 mg per meter squared was found to be pregnant during the third course of Mitoxantrone therapy. She discontinued study treatment and had a normal child delivered.

[Slide.]

This slide presents the number of patients with hematologic parameters who were below normal at any time during the 2 years of treatment for the three groups. As you can see, there were no meaningful differences in the number of patients with low platelets or low hemoglobin in the three groups, and there were no transfusions required in the study.

Looking at leukocyte count, there were five patients, 15 patients, and 20 patients with low leukocyte count in the three groups respectively. Now, I must mention right now that leukocyte count decrease in the use of Mitoxantrone is usually transient and reversible. I would also like to add right now that there were no cases of neutropenic fever detected in the study, and there were no differences in these three groups for hospitalization for severe infection.

[Slide.]

Continuing to laboratory results, this slide represents serum chemistries that were above normal at any time in the tour of study between the three groups. And as

you may see again, there were no meaningful differences among the three groups, and here again, most of the adverse events reported were Grade 1 or 2, and they were reversible.

[Slide.]

I will now move to the safety results of Study 902, in which you will recall Mitoxantrone was given on a monthly basis for six courses.

Overall, the type and frequency of adverse events reported in Study 902 were similar to that reported in Study 901 that I presented to you, and they were presented to you in the briefing document. Adverse events were usually graded as mild or moderate in intensity. There were three adverse events graded as severe, and they are listed here. There was one case of amenorrhea, one case of depression with anorexia, and there was one case, called severe, of intolerance to contact lenses. There were no deaths on study, and there was no clinical cardiotoxicity reported.

In this study, echocardiograms were performed at baseline at Month 6, and the electrocardiogram and clinical evaluation were done monthly.

DR. PENN: I'm sorry. I'm a little confused as to why contact lens intolerance is a severe reaction. Didn't you use a standard protocol--

DR. GHALIE: The rating for the severity of adverse events in the study followed the WHO criteria, which

rates from mild to severe, Grades 0 to 4. The investigators decided to call this adverse event as severe. We don't know. In fact, I agree with you--I can't imagine how severe that can be, but--

DR. PENN: I mean, you could buy them a pair of glasses.

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

DR. TEMPLE: In ADR land, there is a distinction between a serious reaction, which is life-threatening or something like that, and a reaction that is not dangerous to you, like nausea, which could be mild, moderate or severe. So this was a severe reaction of this kind. It didn't threaten lives, but that would be called severe, that sort of standard.

DR. GHALIE: This slide shows the percent of patients with Grade 3 or 4 hematologic toxicity using the NCI criteria, Grade 3 or 5 meaning the more severe hematologic toxicity, which you may have interest in knowing.

[Slide.]

DR. GHALIE: In this study, as you may know, hemograms were performed weekly on the Mitoxantrone group for the 6 months of treatment. With monthly courses of Mitoxantrone 48 percent of the patients experienced Grade 3 or 4 leukopenia at any time during the 6 months of

treatment. That does not mean it occurred with every course, but at any time, they may have had a Grade 3 or 4 leukopenia.

Leukopenia usually occurred during the first or the second course after Mitoxantrone administration and tended to result by day 21 after Mitoxantrone administration.

As with Study 901, there were no meaningful differences in serum chemistries between the two groups, and I am not presenting this today, but again, it is in the briefing document.

[Slide.]

To provide additional long-term safety information on the use of Mitoxantrone in patients with multiple sclerosis, we retrospectively collected data from a single MS center where Mitoxantrone was used extensively over the last 10 years. This study, designated 903, took place at the Academic Clinic of Ulm University in Germany under the direction of Professor Mauch, who is here.

This retrospective analysis involved every patient who had received at least one dose of Mitoxantrone in the clinic during the period of November 1998 and September 1998. Four hundred fifty-four patients treated with Mitoxantrone were identified. These patients were not enrolled in clinical trials. They received Mitoxantrone as

part of the standard of care at this clinic. We did not exclude any patients from this analysis.

[Slide.]

A staff that was hired specifically to do the data collection used specifically designed case record forms to collect specific data on safety and efficacy. An effort was made to collect the most recent forms possible from patients who were not actively followed in the clinic.

Information on treatments given off-site during this 10-year period was not collected for this retrospective analysis. Dr. Mauch reviewed each and every one of these case record forms for accuracy.

[Slide.]

In this clinic, Mitoxantrone was usually started at a dose of 12 mg per meter squared and given every 3 months, and that is based, again, on the pilot study published by Dr. Mauch in the early nineties. The dose and the interval between courses were then adjusted in certain patients as needed to take into account hematologic tolerance, adverse events, and also treatment effects.

Treatment was usually discontinued in patients who did not tolerate therapy, in patients who achieved a good MS response and one who stopped treatment, or in women who wanted to become pregnant, and obviously, in patients who elected not to continue treatment.

[Slide.]

Patient demographics are shown on this slide. Mean EDSS for that study was 5.1, which is higher than I have shown in the two randomized trials. In fact, some patients had baseline EDSS of 8 and 9.

Mean follow-up from the first dose to the last contact was 47 months, which is nearly 4 years. Overall, 80 of the 454 patients, which represent 18 percent of the patients, had received six, seven, or eight courses of Mitoxantrone in the study. In addition, 49 patients received more than eight courses. The reason I mention six to eight courses is because that was the range that was studied in the two randomized trials.

[Slide.]

No death reported in this series was temporally related to Mitoxantrone administration. Twenty patients, or 4 percent of the 454 patients, died. The causes are listed here and are the typical causes of death in patients with advanced multiple sclerosis.

I would now like to discuss two specific deaths, the two patients who died from heart failure, knowing your interest in knowing more about that adverse event.

One patient of these two patients who died from heart failure received a single dose at the clinic and then stopped treatment. This patient then died at least 4 years

after receiving this single dose of Mitoxantrone. It is unlikely that this single dose of Mitoxantrone was responsible for this heart failure.

The other patient who died from heart failure had received 90 mg per meter squared of Mitoxantrone in the clinic and then went to his treating physician, and the treating physician near home continued Mitoxantrone administration for additional courses. This patient died later from heart failure. The contribution of Mitoxantrone to this heart failure and death cannot be ruled out.

DR. GILMAN: In that case, do you know the total dose that was administered? It is not in the narrative that I saw.

DR. GHALIE: No, because we were unable to collect data on treatment given off-site. We do not know how many more courses of Mitoxantrone were given to that specific patient. Dr. Mauch intentionally tried to determine that information by calling either the physician treating the patient or the patients themselves to collect that information, and for that specific patient, that information was not available. The family said the patient had multiple courses, but no number could be assigned.

DR. GILMAN: Are you going to talk about the infections?

DR. GHALIE: Certainly.

[Slide.]

Four pregnancies began during Mitoxantrone administration, and five others occurred after the patients started Mitoxantrone with the intent of becoming pregnant. Of these nine pregnancies, six resulted in the birth of a normal child, one was ongoing at the time of data collection, which was a few months ago, and the outcome of the remaining two pregnancies was not available to us for collection.

[Slide.]

Patients underwent cardiac monitoring as expected. An echocardiogram was usually performed when the Mitoxantrone dose reached about 100 mg per meter squared. In addition, patients had additional echocardiograms performed if there was any evidence of signs or symptoms that could be suggestive of cardiac failure. At that time, Dr. Mauch had a consultation with a cardiologist who worked with the clinic, and echocardiograms were performed and evaluated.

A cardiac event that was considered clinically significant by Dr. Mauch in his retrospective analysis was identified in seven patients shown here. Five patients had decreased LVEF of various degrees, and Mitoxantrone cannot be ruled out as the cause of this decreased LVEF. One other patient had mitral valve insufficiency, and it is unlikely

based on what we know from Mitoxantrone in cancer patients that it is due to Mitoxantrone. And one last patient had tachycardia during administration of the first course of chemotherapy with Mitoxantrone. This patient did not continue Mitoxantrone, and again, it is unlikely that Mitoxantrone was the cause of this event.

Additional information is obviously available to us based on the large experience with the use of Mitoxantrone in cancer patients. The information I present to you is available to us based on reviewing Immunex databases, Lederle databases--Lederle was the company that developed this product years ago--and also, publications available in the literature, including the experience of oncology cooperative groups. We also know that the FDA briefing document has an extensive description of this information that is available.

In summary, I can tell you that with a cumulative dose of 140 mg per meter squared, the incidence of congestive heart failure is equal to 2.6 percent, and the incidence of moderate to severe decreased LVEF is 13 percent. That is in patients who have received Mitoxantrone either alone or in combination with other agents who may have received chemotherapy prior to receiving Mitoxantrone or who may have received chest radiation--and that also includes an age group that goes anywhere from children to

older patients.

DR. GILMAN: Dr. Swain?

DR. SWAIN: I had a question regarding where you got this database. Was this reporting in CHFs [ph.], or is it from trials that you have completed?

DR. GHALIE: This is really a compilation of different databases which are also listed in the briefing document. There are really three large publications that were published, by Dukart [ph.], Posner [ph.], and by the Schwab [ph.] Group. They included anywhere between 700 and over 3,000 patients. Those are a compilation of patients enrolled in clinical trials as well as a postmarketing report. These publications were done early after Mitoxantrone was put on the market, and that is really where the aggregate of this information is available. And pretty much nothing new that we know of Mitoxantrone in the last 10 years has changed what we know from that information.

DR. SWAIN: So you have data from case report forms asking specifically about congestive heart failure; this is not a retrospective review of patients--is that correct?

DR. GHALIE: What we have in our record at Immunex will be database from patients who enrolled in the two pivotal trials that led to the approval of Novantrone for leukemia and prostate cancer. There is also the experience

with breast cancer that was collected in the eighties, and as I mentioned, there are all the postmarketing safety reports that were submitted to Immunex over the last few years.

DR. SWAIN: I guess I'm just making the point, is this under-reporting--because I know that if you look at doxorubicin, you will actually see more, if you look very, very carefully, than what is reported in the literature.

DR. GHALIE: This information I present to you here is really what is in the Novantrone/Mitoxantrone package insert, and that was established early on when the drug was approved, which was based mostly on the randomized trials that were available at that time for approval.

[Slide.]

In conclusion, the three studies in Mitoxantrone in multiple sclerosis showed the following. Most adverse events are mild to moderate. They are manageable and reversible. No congestive heart failure was reported for a cumulative dose up to 100 mg per meter squared in the two randomized trial control data we have presented to you today. Marrow suppression is reversible within one to 3 weeks after chemotherapy administration, and it is not associated with an increased incidence of severe infection.

Furthermore, the Month 36 evaluation from Study 901 and the long-term safety database from Professor Mauch

indicate that no unexpected late adverse event occurred after Mitoxantrone administration in patients with multiple sclerosis. In addition, there was no secondary leukemia or myelodysplasia reported in these long-term patients.

I would now like to turn to a benefit and risk assessment--

DR. GILMAN: If I could interrupt before you go on, just to ask two questions. One, Dr. Kawas has reminded me that on page 28 of the FDA Safety Review, there is a paragraph about Subject 281, a 42-year-old male MS patient treated in the clinic with Mitoxantrone, cumulative dose 155 mg over a 2-year period. The patient's family doctor gave an additional 120 mg over a 2-year period. Two months after his last dose, he was admitted for cariogenic shock and died of cardiac insufficiency.

That's a huge dose, 275 total. Is this the patient that you referred to earlier?

DR. GHALIE: Yes.

DR. GILMAN: So we do know the dose, in fact.

DR. GHALIE: We do know; I had forgotten.

DR. GILMAN: Good. Okay, thank you.

Also, I wanted to ask you about infections. Again, the same narrative page 27 of the FDA's Evaluation of Safety, at the bottom of the page, it says "The sponsor reported that 38 percent, or 171 of the patients in the

cohort, had a recognized infection during the observation period. Eighty-six percent of these were classified as urinary tract infections, 2 percent upper respiratory, fewer than 1 percent sinusitis, 12 percent unknown. The sponsor did not report the severity at outcome of the infections and did not state which of these occurred in the setting of decreased white blood cell counts."

That was my question. Do you know the severity of these infections; do you know the outcomes of them; and do you know whether they were post administration of drug, and if so, what were the white blood cell counts associated with them?

DR. GHALIE: Yes. You are referring to Slide C-52, where most of the adverse events in fact called infection adverse events were urinary tract infections and upper respiratory infections. We did not collect in the case record form that have designed to collect in this study if there was a relationship between the episode of infection and if the patient was neutropening [ph.] at that time.

Maybe Dr. Mauch, who reviewed all of these case record forms, could comment on that, please.

DR. MAUCH: Most of our patients had urinary tract infections, and they were completely reversible and had no influence on further disability of patients, and there was no reason to stop treatment.

Also, we collected at every contact the patient had with the clinic the leukocyte counts. I think these data are not available, but sometimes, we could see that we had high leukocyte counts without further information as to what kind of infection it was. That was the majority of these 40 patients with unknown infections.

DR. GILMAN: So if I understand what you just said, the severity was such that the urinary tract infections responded quickly to treatment; is that correct?

DR. MAUCH: Yes. They were treated with antibiotics after we had tested the urine, and they recovered completely from these infections.

DR. GILMAN: And you do not know their white blood cell counts at the time of the infection?

DR. MAUCH: Yes, we do--

DR. GILMAN: You do know?

DR. MAUCH: We do know.

DR. GILMAN: But you have not analyzed the data.

DR. MAUCH: We have not, I think, in the plan to present, but we have in our data also the leukocyte counts.

DR. GILMAN: Can you tell us anything about it? Was the leukocyte count down in most of these patients who had urinary tract infections?

DR. MAUCH: No. In many patients, the leukocyte count was increased.

DR. GILMAN: Increased--you mean within normal limits?

DR. MAUCH: Yes.

DR. GILMAN: Can you tell us about the length of time between the last treatment and the occurrence of the urinary tract infection? Were these often soon after treatment?

DR. MAUCH: I looked through all the data we presented, and it was my impression that we had frequent urinary tract infection in highly disabled patients, and in my impression as a treating physician, the percentage of urinary tract infections did not differ from our treated patients to patients treated only symptomatically for their MS.

DR. GILMAN: That is helpful. And of course, people who were impaired with mobility and so on do develop such infections.

DR. MAUCH: Yes.

DR. GILMAN: The question is whether there is any relationship between the treatment and the onset of the urinary tract infection, the timing.

DR. MAUCH: Yes. There was more relationship between immobility than with therapy.

DR. GILMAN: Dr. Grundman?

DR. GRUNDMAN: Again, I think there was almost a

threefold increase in the frequency of urinary tract infections among patients treated with Novantrone compared to the placebo patients, so wouldn't that prima facie be evidence for an association of the urinary tract infection with the drug treatment?

DR. GILMAN: That would be the impression, but we are not hearing that. I am not sure I am getting the question directly answered, though.

DR. KATZ: There are no placebo patients in this cohort.

DR. GILMAN: No.

DR. GRUNDMAN: I'm sorry. I was referring to page 49 in Study 901, which--

DR. GILMAN: This is retrospective data on treated patients.

DR. GRUNDMAN: Yes, but in their actual study that they presented prospectively, there was a threefold increase in UTIs among the treated patients.

DR. GHALIE: This is something that indeed we have looked at and have presented the data. The cause of that is at present undetermined. Whether that can be due in part because patients had a dip in leukocyte account and therefore had maybe a higher incidence of UTI, or the physicians being unblinded were more susceptible to that and more frequently likely to report this as a UTI than patients

who were not. At present, I don't know what is the interpretation for that observation.

DR. GILMAN: Dr. Swain?

DR. SWAIN: I just have to comment that even though your percent of leukopenia in that 01 study was only 20 percent or something like that, you did not mention nadir count, which you normally do in oncology. It's probably much, much higher than that. In your second study it was extremely high; it was 86 percent. I really find it hard to believe that you had no reports of febrile neutropenia.

DR. GHALIE: I will describe to you how Study 901 was designed and what was asked to be done and where the data was obtained, and then I will move to Study 902.

For Study 901, as you mentioned, there was a CBC that was required before each course of therapy. In addition--and the protocol was very clear about it--there was a requirement to do a CBC at the time of the expected leukocyte nadir--in fact, the treating physicians, as you know, were unmasked, so they knew when the expected leukocyte nadir was--to do repeated CBC in a patient who may have an episode of infection or something that would be suggestive of infection. So even though it was not required to do at Day 14 or 20--and again, those are masked patients that go back home, and they are not necessarily actively seen as oncology patients every 3 to 4 weeks--so that

incidence that we show is for those patients who had a CBC done either every 3 months or at the exact time of neutropenia nadir if they had any episode that was suggestive of infection.

In Study 902, indeed, Mitoxantrone was given on a monthly basis more as when it is used in cancer patients, and indeed, the incidence of neutropenia was higher in this study than in Study 901.

DR. SWAIN: In Study 902, were those patients also followed by their local physicians? Are we missing data here, because I just cannot believe there is no febrile neutropenia.

DR. GHALIE: For Study 902, because the treatments were given on a monthly basis, they were also closer to the site where the treatment was given. Most of the patients came back to that specific clinic to be followed.

I know that Dr. Alberts has a comment here. Dr. Alberts?

DR. ALBERTS: I just wanted to comment that Mitoxantrone came on the market in oncology as the safest drug that we have seen, and I think the reason is that as a single agent, at 12 mg per meter squared, even though you get a nadir, and you can get a very significantly lowered nadir, these nadirs usually last 3 or 4 days at the most. So febrile neutropenia is an extremely rare event, at least

in the cancer patient.

DR. GILMAN: Dr. Wolinsky?

DR. WOLINSKY: If I read it correctly, in the SNS that was done in Study 901 and not in the other studies, one of the scoring systems talked about residual urine volumes. Were those measured by ultrasound, or were they by catheterization, and did manipulation have anything to do with the UTIs in that patient population?

DR. GHALIE: I would like to invite Dr. Hartung to answer that question, please.

DR. HARTUNG: This was done by ultrasound measurement.

DR. GHALIE: I understand your concern as a committee about potential infection in patients with multiple sclerosis and receiving Mitoxantrone, so I would like to ask for Slide C-16, which looked at the randomized Phase III study, which looked at the three groups--placebo, Mitoxantrone 5 and 12 mg per meter squared.

[Slide.]

DR. GHALIE: We have here the two events that are of interest--what happens when the leukocyte count goes down, infection, and potential for bleeding. As you can see, the percent of infection in the three groups--and that includes any type of infection--really is reasonably similar among the three groups.

If we look at severe infections or infections that led to hospitalization--and again, it is unlikely that this is going to be underreported when there is a hospitalization--and you look at the difference among the three groups, it is really minor. And if you can read the little font at the bottom, that tells you what was the reason for hospitalization for each one of these patients--tonsillitis, and for the 12 mg per meter squared group, which is the higher dose of Mitoxantrone, one case of tonsillitis, two cases of urinary tract infection, one case of endometritis.

We looked very carefully at all the patients enrolled in this study to see if there was any episode of neutropenic fever, what oncologists call neutropenic fever, meaning low white cell count, less than 1,000 or 500, and a systemic infection. There was no report in this study of any patient who had neutropenic fever.

It is very likely that the every-3-month schedule is different than the every-3-week schedule as far as patients' tolerance to infection.

DR. GILMAN: Dr. Swain has another question.

DR. SWAIN: Yes, I have a couple more safety questions. In the FDA review, there was a report of six patients who had hyperbilirubinemia. Can you just comment on that, because I know that Mitoxantrone concentrates quite

a bit in the liver.

DR. GHALIE: Yes, you are indeed very right, Dr. Swain. Mitoxantrone is metabolized in part in the liver. And as you also know, the package insert says that patients who have severe liver impairment should not receive Mitoxantrone, or should at least receive a lower dose.

Patients who had increased bilirubin were all Grade 1 or 2. In fact, I can bring up the slide that shows the chemistries of Grades 3/4 in Study 902, which is Slide C-37.

[Slide.]

DR. GHALIE: These are really the Grades 3/4. That is using the WHO, which is similar to NIH criteria. Really, there was one patient who had SGOT increase in each of the two Mitoxantrone arms; no patient who got 3/4 bilirubin. They were mostly Grades 1 and 2, and they eventually came down.

There was one patient in fact in the placebo who had Grade 3, but that was colithiasis [ph.].

DR. SWAIN: So you don't think that the cases reported--I don't remember where they were in the FDA review--were related to drug, that hyperbilirubinemia?

DR. GHALIE: They were not reported in the case record form as drug-related. They may have occurred at different time points during the 3 months between courses.

DR. SWAIN: Then, my last question is on the issue of amenorrhea. I think 63 percent of the patients had amenorrhea. In those situations, how often was it reversible, since you did follow patients for a year later?

DR. GHALIE: I believe we have the month 36 follow-up for the menstruation data on Slide C-40.

[Slide.]

DR. GHALIE: That will give you an idea one year after stopping treatment what was observed. In the three groups--and these are obviously women; that's why the number decreased from what we had for total population--patients with regular menses--and that is percent of patients--29 percent of the women had normal menses at Month 36, and 54 percent of the placebos. So clearly, there are some patients who at least a year later had not recovered their menses. Again, this patient population ranged from 18 to 55; some women were in the stage where they were becoming menopausal. There was irregular menses quite similar between the two groups; amenorrhea higher--that really compliments the first finding. Some patients, we had no data available for, and "Other" meaning mostly dysmenorrhea or some other change in cycle length.

DR. SWAIN: Thank you.

DR. GILMAN: What does "Other" mean at the bottom of that slide?

DR. GHALIE: That's what I was saying. Those are probably dysmenorrhea patients or patients whose cycle was not the regular cycle that you would expect.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: Just now and also in your text, on more than one occasion you made the comment that it might be that these women were supposed to be already perimenopausal. Is that because there was an age effect to the amenorrhea, or is there any data to support that? Is it just that women who were going to be perimenopausal in the next few years might have been hastened, or are these 20-year-olds who are amenorrheic a year later?

DR. GHALIE: There are young women who can become amenorrheic with Mitoxantrone, but in general--and that is in chemotherapy experience, but certainly with Mitoxantrone--the older the woman, the more likely that if she receives Mitoxantrone, particularly if she is close to menopause, it may accelerate her menopause.

DR. KAWAS: And that was also the experience in the study, that it was the older women who were more likely to be amenorrheic?

DR. GHALIE: I have to say I have not analyzed data looking age and what happened with amenorrhea.

Dr. Hartung, do you have any additional information to add here?

DR. HARTUNG: No.

DR. GHALIE: No. We haven't looked at this specifically.

DR. KAWAS: Thank you.

DR. GILMAN: Dr. Weiner?

DR. WEINER: I had a question in terms of the alopecia. How severe was the alopecia in the patients that you treated?

DR. GHALIE: As I mentioned earlier, all adverse events that were reported in the study, more common in the Mitoxantrone group, which includes amenorrhea, were graded as Grades 1 or 2. So in fact when we see amenorrhea in patients receiving Mitoxantrone as a single agent, it is more of hair thinning as opposed to hair loss--alopecia--I am sorry. I will repeat my sentence. When we see alopecia in patients receiving Mitoxantrone, single agent, particularly when it is given every 3 months, it was mostly hair thinning as opposed to complete hair loss.

And if you like, Drs. Hartung and Mauch, who have seen many patients treated like this--do you have anything else to add to that?

DR. HARTUNG: Well, it is my experience that as a physician, I am in most instances unable to detect, being a neurologist and not a dermatologist, alopecia. I have to rely on the patients' recollection of their hair becoming

thinner, but I haven't seen any patchy alopecia or any diffuse, massive alopecia.

DR. GILMAN: Dr. Grundman?

DR. GRUNDMAN: On page 30 of the Immunex document, there is a table which lists the hospitalizations and quality of life. It seems that as far as the patients who were hospitalized, the most patients hospitalized were in the placebo group with corresponding decreases as you go to the 5 mg and 12 mg dose. But the duration of the hospitalization remained stable, or actually, in the case of the 5 mg dose, increased to 49 days. I recognize that the p-value was not significant, but the suggestion is that perhaps the people who are admitted to the hospital have somewhat longer stays for the people in the Mitoxantrone groups.

And there is a footnote which says that many of the hospitalizations were for rehabilitation. So I wonder if you were able to break these up into hospitalizations that were due to adverse events or side effects to determine whether or not there was a longer hospitalization stay for the Mitoxantrone groups due to adverse events.

DR. GHALIE: I would like to have Slide B-109, which in fact allows all of us now to see that data.

[Slide.]

DR. GHALIE: One difference in the management of

MS patients between Europe and the U.S.--and that was really the only one I noticed from reading all the data and talking to experts in the field--is in the hospitalization of patients.

In Europe, patients are hospitalized to treat any complications of MS and for rehabilitation. So when you see duration of hospitalization which goes from 15, 20, 30 days, the bulk of that is really to rehabilitate the patient.

Now, if you look at number of patients hospitalized in the three groups, it was higher in placebo compared to Mitoxantrone. IF you look at the number of hospitalizations, it was higher. And the mean days, as I mentioned, are really very likely here driven by the rehabilitation.

As I mentioned, and I showed you in the prior slide which was also Study 901, the number of hospitalizations for severe infection was very low--in fact, four, two, and one--so this certainly does not drive that duration. And really, most of the hospitalizations, as you can see, were MS-related, 81 of 89, 64 of 85, and 34 of 50.

DR. GRUNDMAN: The piece that I was looking for is actually not on the slide, which is the hospitalizations that were due to other causes and their mean duration in the non-MS.

DR. GHALIE: Unfortunately, I have to see the

document--unless someone who has the document can answer.

MS. HAYES: I think you only looked at the hospitalizations for multiple sclerosis.

DR. GHALIE: Right.

DR. GILMAN: She said that he only looked at the hospitalizations for multiple sclerosis.

Dr. Penix?

DR. PENIX: Are there any recommendations about the total dose that can be given? Since we can anticipate that a relatively young patient who has MS may require drug treatment for many years, I know that in your Study 903, there were 49 patients, or 11 percent of the patients, who got greater than nine doses. In that group, are there any who got doses for several years, and do we have any data on how they did; and also, do we have any data from the cancer treatment patients who may have gotten drug for prolonged periods of time?

DR. GHALIE: To bring together the issue of duration of treatment, Study 901 looked at eight courses; Study 902 looked at six courses. In Dr. Mauch's retrospective analysis, you see the number of patients who went beyond six courses. In fact, there were six patients who went beyond 140 mg per meter squared, and I have data on these patients. We obviously looked at them very carefully. In this subset of patients, these six patients, there was no

cardiac toxicity detected and no severe infection.

Our recommendation, which we are going to present to you in a moment and which I can mention right now, as far as the duration of treatment with Mitoxantrone patients with MS, is to say the following. We have data for two controlled trials for dose up to 100 mg per meter squared. That would be the dose that we would recommend for treatment.

Based on the experience we have from patients with cancer, it is possible to go beyond that dose. For these patients as a company, conservatively, we would like the physicians to do an echocardiogram or at least an LVEF evaluation before each course. We as a company are going to recommend to discontinue treatment for patients who reach the dose of 140 mg per meter squared, just to be on the safe side. The reason for that is because on the cancer experience, we know that once one exceeds a dose of 160 to 180 mg per meter squared, the risk of heart failure takes off. Therefore, to really be conservative, we are recommending to be very cautious at 100 mg, to do monthly or at least before each course echocardiogram, and we recommend not going beyond that. And there will be more recommendations that I can describe as we get to that in my presentation.

DR. PENIX: And those recommendations would be

placed in the package insert?

DR. GHALIE: That will be something we will be discussing with the agency to decide in which format this will be presented. We would like it to be in the package insert. We will also have an educational program when we have this drug on the market for syndication to ensure, hopefully, that physicians get this message and make their decisions based on that.

It is really a question of benefit and risk assessment that is a physician's decision, but that would be the company's recommendation.

DR. GILMAN: Dr. Swain?

DR. SWAIN: I just have to say I totally agree with your recommendation. I absolutely would cap it at 140, because you have a population that really has a normal life span. All of the data that has looked at doxarubisone and injection fractions and trying to figure out who is going to develop congestive heart failure really shows that the serial testing is not effective to predict who will develop CHF. So I don't feel comfortable at all, and I think the company is totally right in capping it and not increasing it any more.

DR. GHALIE: Dr. Alberts, would you like to add something to Dr. Swain's comment?

DR. ALBERTS: Well, in talking to the company

about cardiotoxicity, I think there is one other ingredient to making certain that these MS patients do not get it, and that is to exclude any patient who has had prior anthracyclines, those who have had chest radiation, those who have a prior existing cardiac dysfunction, and those who are 70 years of age or older. Those are the primary risk factors for cardiotoxicity with Mitoxantrone, and in fact if you eliminate that group of subjects, the chance of cardiotoxicity at 140 mg per meter squared is infinitesimally small.

DR. GILMAN: Dr. Weiner?

DR. WEINER: There may not be an answer to this, but I think it is an important question to ask anyway. Is there any experience or any theoretical reason to believe that patients who are on the interferon drugs would have an increased risk of toxicity subsequent to being treated with Mitoxantrone, either cardiac or otherwise?

DR. GHALIE: As I mentioned earlier, the two randomized trials I presented to you today were done in patients who were Interferon-naive. So I do not have data to present to you on that.

However, Dr. Mauch's experience as well as Dr. Hartung's and Edan's, and in fact Dr. Smith in Seattle, have used Mitoxantrone now in patients who failed Interferon, and based on what they will be able to tell us right now, in