

#### **4.0 Efficacy of Mitoxantrone in Multiple Sclerosis**

The efficacy of mitoxantrone in MS was demonstrated in two well-designed, randomized trials: Studies 901 and 902. The study design and efficacy results from these two trials are presented in this section.

#### **4.1 Randomized Phase III Study (Study 901)**

The efficacy and safety of mitoxantrone in patients with active MS were evaluated in a multicenter, double-blind, three-arm, randomized, placebo-controlled Phase III trial. The study was open to enrollment in June 1993 and was closed in July 1997. It was conducted in 17 centers in four European countries (Germany, Belgium, Poland, and Hungary) and was co-chaired by Professors H.P. Hartung and R.R. Gonsette. The German regulatory agency Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) approved the design and conduct of this study. The preliminary results of this study were presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) annual meeting in 1998 (Hartung 1998, Krapf 1998) and were updated in 1999 at the American Academy of Neurology (AAN) annual meeting (Hartung 1999a) and ECTRIMS annual meeting (Hartung 1999b) (see Appendix G, Published Papers).

##### **4.1.1 Study Objectives, Design, and Endpoints**

The objectives of the study were to determine the efficacy and safety of two dose levels of mitoxantrone in comparison to placebo in patients with MS with evidence of disability progression. Treatment efficacy was primarily assessed by its effect on neurologic disability using 3 different scales and on relapse rate and time to relapse. In addition, mitoxantrone effect on the pathology of MS was evaluated by MRI scans performed in a predetermined subgroup of patients enrolled in the study.

Eligibility criteria included patient age of 18 to 55 years, secondary progressive or remitting-progressive\* MS, EDSS between 3 and 6 points, and active disease progression as defined by EDSS deterioration of at least 1.0 point in the preceding 18 months.

Exclusion criteria consisted of primary progressive or benign MS, a relapse in the preceding 8 weeks, corticosteroid treatment during the preceding 8 weeks, prior therapy with mitoxantrone, immunosuppressive therapy during the preceding 9 months, cardiac risk factors (e.g., left ventricular ejection fraction [LVEF]  $\leq$  50%), or any major illness.

Patients were randomized to one of three treatment arms: placebo, mitoxantrone 12 mg/m<sup>2</sup>, or mitoxantrone 5 mg/m<sup>2</sup>. The 5 mg/m<sup>2</sup> dose was included for exploratory purposes to determine whether a lower mitoxantrone dose was effective while potentially reducing treatment toxicity. Doses of mitoxantrone could be reduced using a protocol-specified schedule if hematologic or nonhematologic toxicities occurred. Study drug was administered by 5-minute IV infusion every 3 months for 2 years (a total of eight courses). Methylene blue was used as placebo to mimic mitoxantrone's blue color. Patients who experienced severe disabling relapses were to be treated with short-term (5-day) courses of high-dose (500 mg/day) methylprednisolone. The protocol specified the definition of severe disabling relapse and the conditions for when to treat such relapses. To prevent possible nausea and vomiting, one tablet of ondansetron (8 mg) or a matched placebo (the latter for the placebo group) was given orally 1 hour before study drug infusion and 8 hours later if needed.

Several precautions were taken to reduce risks of bias in the interpretation of the efficacy results. First, the study was placebo-controlled to mask patients and specially trained physicians responsible for the neurological evaluations. At each site, other investigators not masked to study drug were responsible for managing study drug administration and for reporting and grading the adverse events and their relationship to study drug. Second,

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\* In the nomenclature used in this study, "remitting-progressive" indicates patients with relapsing-remitting disease with residual deficits after relapse.

the MRI scans were centrally reviewed at the end of the study by two trained physicians masked to study drugs and clinical outcomes.

Primary efficacy variables were changes in the EDSS, AI, and SNS values at 24 months compared to baseline values; number of relapses requiring corticosteroid treatment; and time to first relapse requiring corticosteroid treatment. The EDSS, AI, and SNS scales are presented in Appendices A, B, and C, respectively.

Secondary efficacy variables included 1.0 point improvement or deterioration in EDSS confirmed at 3 and 6 months; number, time, and type of relapses; quality of life evaluation using the Stanford Health Assessment Questionnaire (HAQ) and the Zung Self-Rating Depression Score (SDS); number of days in hospital; and overall clinical efficacy ratings by the blinded physician. A subset of 110 patients enrolled at specified sites underwent T1-weighted MRI scans with Gd enhancement and T2-weighted MRI scans at baseline, Month 12, and Month 24.

In addition, patients underwent an evaluation at Month 36 (third-year follow-up visit) to collect safety and efficacy data one year after discontinuation of therapy. Treatment for MS during this third year, if needed, was not defined by protocol but was left to the discretion of the investigator or primary care physician.

#### **4.1.2 Planned Statistical Analyses and Number of Patients Required**

The protocol defined the primary efficacy criterion as a single multivariate statistical analysis in one combined hypothesis of five endpoints: changes in EDSS, AI, and SNS between Month 24 and baseline; number of treated relapses; and the time to first treated relapse. The primary efficacy analysis was defined as a comparison between mitoxantrone 12 mg/m<sup>2</sup> and placebo using a multivariate test with  $\alpha = 0.05$  (see Appendix E). If the multivariate test was significant ( $p < 0.05$ ), then univariate tests for each efficacy endpoint were to be performed in a prespecified order comparing mitoxantrone 12 mg/m<sup>2</sup> to placebo, with  $\alpha = 0.05$  for each endpoint.

The number of patients required for the study was calculated to detect a 0.5 point difference in mean EDSS change over 2 years between placebo and mitoxantrone 12 mg/m<sup>2</sup> with a one-sided  $\alpha = 0.05$  and a power of 90%. To achieve this goal, it was estimated that 60 patients were needed per group. These calculations were based on expected ranges of response and standard deviations from previously published studies of mitoxantrone in MS.

#### **4.1.3 Disposition of Patients**

A total of 194 patients were enrolled in the study, of which 149 (77%) completed 2 years of therapy and the required evaluations, and 138 (71%) completed the third-year follow-up evaluations.

Three patients, one from each arm, were found to be ineligible after randomization and were withdrawn before receiving study drug. These three patients are not included in any of the efficacy and safety analyses. Three other patients (one in the mitoxantrone 5 mg/m<sup>2</sup> arm and two in the mitoxantrone 12 mg/m<sup>2</sup> arm) received a single dose of study drug and then discontinued treatment before completing the efficacy evaluations at Month 3. The reasons for withdrawal consisted of an adverse event and disease progression in one case, and patient refusal in two others. These three patients are not included in the intent-to-treat (ITT) efficacy cohort but are included in the safety analyses. Repeating the efficacy analyses with these three patients considered non-responders did not change any of the efficacy conclusions drawn from the study.

Thirty-nine patients discontinued study treatment before completing all eight courses of therapy and the required evaluations: 17 patients in the placebo group, 10 in the mitoxantrone 5 mg/m<sup>2</sup> group, and 12 in the mitoxantrone 12 mg/m<sup>2</sup> group. The following table summarizes the disposition of patients on the study.

### Study 901 - Disposition of Patients

Disposition	Placebo	Mitoxantrone		Total No. of patients
		5 mg/m <sup>2</sup>	12 mg/m <sup>2</sup>	
Patients randomized	65	66	63	194
No treatment	1	1	1	3
No follow-up after first course	0	1	2	3
ITT efficacy cohort	64	64	60	188
Early treatment discontinuations (total)	17	10	12	39
Lack of efficacy	8	3	4	15
Patient refusal	6	3	2	11
Lost to follow-up	1	3	0	4
Adverse event	2	0	5	7
Other	0	1	1	2
Patients completing 2 years of therapy	47 (71%)	54 (82%)	48 (76%)	149 (77%)
Patients with 3rd-year follow-up data	43 (66%)	53 (80%)	42 (67%)	138 (71%)

ITT = intent to treat.

Efficacy analyses while on therapy were performed on the 188 patients who comprised the ITT population. Safety analyses while on therapy were performed on the 191 patients who received at least one dose of study drug. Efficacy and safety information is also presented here on all patients evaluated at the third-year follow-up visit.

#### 4.1.4 Demographic and Disease Characteristics

Mean patient age was 40 years. Ninety-eight (52.1%) were female and 90 (47.9%) were male. There were no significant differences between treatment groups in physical and disease characteristics, as shown in the following table. The patients generally exhibited features of moderately severe MS.

#### Study 901 - Demographic and Disease Characteristics

Characteristic	Placebo (N = 64)	Mitoxantrone	
		5 mg/m <sup>2</sup> (N = 64)	12 mg/m <sup>2</sup> (N = 60)
Female/male (no. of patients)	31/33	39/25	28/32
SP/RP (no. of patients)	35/29	27/37	32/28
Mean values:			
Age (years)	40.02	39.92	39.94
Duration of MS (years)	10.27	9.03	9.63
EDSS score at entry	4.69	4.64	4.45
EDSS increase in preceding 18 months	1.58	1.62	1.50
AI at entry	2.63	2.52	2.52
SNS at entry	20.94	18.88	19.33
No. relapses in preceding 12 months	1.31	1.42	1.27

SP = secondary progressive multiple sclerosis.  
RP = remitting progressive multiple sclerosis.

#### **4.1.5 Efficacy Results**

The study results showed that mitoxantrone given at a dose of 12 mg/m<sup>2</sup> every 3 months was significantly better than placebo in all primary and most secondary efficacy variables. Mitoxantrone given at this dose schedule significantly slowed the progression of neurologic impairment and decreased the relapse rate in patients with progressive MS. The efficacy of mitoxantrone 5 mg/m<sup>2</sup> was usually intermediate between placebo and mitoxantrone 12 mg/m<sup>2</sup>. Because the primary endpoint was a comparison between mitoxantrone 12 mg/m<sup>2</sup> and placebo, only the p-values for this comparison are provided in this document.

##### **4.1.5.1 Primary Efficacy Endpoint**

The protocol for Study 901 defined one primary efficacy criterion, described as a multivariate analysis of five primary efficacy variables comparing placebo to mitoxantrone 12 mg/m<sup>2</sup> (see Appendix E, Statistical Methodology for the Primary Efficacy Analysis in Study 901). These variables evaluated the cumulative effect of treatment given over 24 months on the progression of neurologic disability (i.e., the effect on EDSS, AI, and SNS), on the number of relapses requiring corticosteroid treatment, and on the time to the first treated relapse.

The primary criterion was met in this trial. Patients treated with mitoxantrone 12 mg/m<sup>2</sup> showed significantly better results after 24 months of treatment than patients receiving placebo ( $p < 0.0001$  for the global multivariate test). Therefore, per protocol, each of the five primary efficacy variables was evaluated individually following an order defined in the protocol. Mitoxantrone 12 mg/m<sup>2</sup> was significantly better than placebo in all five primary variables, as shown in the table that follows. Except for mean EDSS change, the effect of mitoxantrone 5 mg/m<sup>2</sup> was intermediate between placebo and mitoxantrone 12 mg/m<sup>2</sup>.

**Study 901 - Primary Efficacy Endpoint at 2 Years**

Endpoint	Placebo N = 64	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 64	12 mg/m <sup>2</sup> N = 60	
Effect on disability (mean, M24 minus baseline)**				
EDSS change (SD)	0.23 (1.01)	-0.23 (1.10)	-0.13 (0.90)	0.0194 <sup>†</sup>
AI change (SD)	0.77 (1.26)	0.41 (1.40)	0.30 (1.24)	0.0306 <sup>†</sup>
SNS change (SD)	0.77 (6.79)	-0.38 (7.27)	-1.07 (8.61)	0.0269 <sup>†</sup>
Effect on steroid-treated relapses				
No. of relapses (total, adjusted for early withdrawals)	76.77	46.88	24.08	0.0002 <sup>‡</sup>
Time to 1st relapse (median months)	14.2	NR	NR	0.0004 <sup>‡</sup>

M24 = Month 24 (last evaluation carried forward for early drop-outs); NR = Not reached during the 2-year evaluation time.

\* Mitoxantrone 12 mg/m<sup>2</sup> group compared to placebo group, 2-sided test.

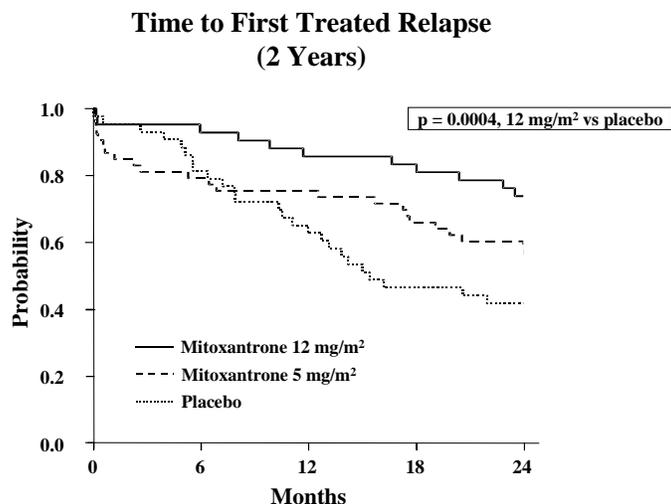
\*\* Negative value denotes improvement and positive value indicates worsening.

<sup>†</sup> Wilcoxon test.

<sup>‡</sup> Log-rank test.

The number of treated relapses was adjusted to take into account early study drug discontinuation. A conservative approach was taken in the data analysis. Adjustment was performed using the relapse rate observed in the placebo group as follows. The study duration was divided into four 6-month intervals and the daily relapse rate for placebo calculated for each of these intervals. For patients in the two mitoxantrone arms who discontinued study drug prematurely, the relapse rate was calculated as the observed relapse rate for the observed period plus the relapse rate in the placebo arm prorated for the number of days off study.

The graph that follows presents Kaplan-Meier estimates of the time to first treated relapse in the three groups.



There was a significant difference in time to first treated relapse between the placebo and mitoxantrone 12 mg/m<sup>2</sup> groups (p = 0.0004). The curves for mitoxantrone 12 mg/m<sup>2</sup> and placebo separate as early as the first evaluation at the 3-month time point. The median time to first treated relapse was 14.2 months for the placebo group, but was not reached within 24 months by either mitoxantrone group.

#### 4.1.5.2 Secondary Endpoints

Mitoxantrone 12 mg/m<sup>2</sup> was superior to placebo in secondary efficacy parameters evaluating neurologic disability, relapse, quality of life, and hospitalizations. There was a trend toward superior results with mitoxantrone 12 mg/m<sup>2</sup> compared to mitoxantrone 5 mg/m<sup>2</sup>. The results for all protocol-defined secondary parameters evaluating treatment effect on disability are summarized in the table that follows.

**Study 901 - Effect of Mitoxantrone on Neurologic Disability**

Endpoint	Placebo N = 64 n (%)	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 64 n (%)	12 mg/m <sup>2</sup> N = 60 n (%)	
No. patients (%) with ≥ 1 point EDSS deterioration:				
At any time after baseline (single assessment)	16 (25)	10 (16)	5 (8)	0.013 †
Confirmed 3 months later (≥2 assessments)	14 (22)	9 (14)	5 (8)	0.036 †
Confirmed 6 months later (≥2 assessments)	12 (19)	6 (9)	4 (7)	0.045 †
No. patients (%) requiring wheelchair	7 (11)	5 (8)	3 (5)	0.225 †
Time to wheelchair (median)	NR	NR	NR	0.195 ‡

NR = not reached during the 2-year observation time.

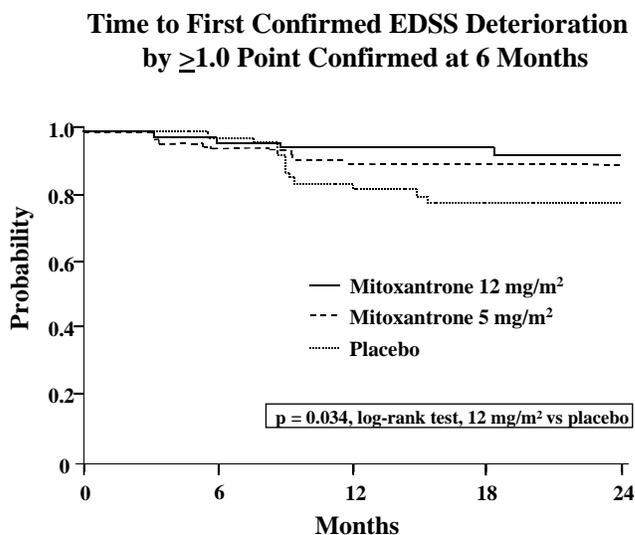
\* Mitoxantrone 12 mg/m<sup>2</sup> compared to placebo.

† Chi-square test.

‡ Log-rank test.

A categorical evaluation classifying EDSS results at Month 24 as deterioration of at least 1 point, no change, or improvement of at least 1 point also showed significantly better results with mitoxantrone 12 mg/m<sup>2</sup> (p = 0.030). More patients in the placebo group had an EDSS deterioration of at least 1 point compared to patients in the mitoxantrone 12 mg/m<sup>2</sup> group (25% vs. 8%, p = 0.013). In the other direction, more patients in the mitoxantrone 12 mg/m<sup>2</sup> group had at least 1 point improvement in EDSS compared to placebo (20% vs. 11%, p = 0.161).

The graph that follows presents Kaplan-Meier estimates of the time to first EDSS deterioration by ≥ 1.0 point confirmed 6 months later in the three groups. An EDSS deterioration by 1.0 point is generally considered as indicative of consequential progression of neurologic impairment.



As shown in the table that follows, mitoxantrone had a significant positive effect on variables related to relapses.

**Study 901 - Effect of Mitoxantrone on Relapses**

Endpoint	Placebo N = 64	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 64	12 mg/m <sup>2</sup> N = 60	
Time to first relapse (median months)	8.3	15.0	NR	0.009 †
Time to first severe** relapse (median months)	15.01	NR	NR	0.0009 †
No. relapses (total, adjusted for early withdrawals)	129.4	77.4	48.2	0.0002 ‡
No. patients (%) without relapses	23 (36)	25 (39)	34 (57)	0.021 ††
No. of relapses (mean)	1.77	1.09	0.65	0.0009 ‡
No. of treated relapses (mean)	1.03	0.66	0.30	0.0002 ‡
No. of severe relapses (mean)	0.94	0.56	0.28	0.0008 ‡

NR = not reached during the 2-year observation time.

\* 12 mg/m<sup>2</sup> compared to placebo.

\*\* Defined per protocol.

† Log-rank test.

‡ Wilcoxon test.

†† Chi-square test.

As shown in the table that follows, the annualized relapse rate was also notably lower in the mitoxantrone 12 mg/m<sup>2</sup> group, with a 66% reduction in relapse rate over 2 years.

### Study 901 - Annualized Relapse Rates

Relapse rate	Placebo N = 64	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 64	12 mg/m <sup>2</sup> N = 60	
Year 1	1.15	0.658	0.424	< 0.0001
Year 2	0.853	0.488	0.269	0.0001
Overall	1.02	0.58	0.35	0.0002

\* Exact test of homogeneity of Poisson rate using StatXact software, 12 mg/m<sup>2</sup> vs placebo

As shown in the table that follows, patients receiving mitoxantrone 12 mg/m<sup>2</sup> compared to patients receiving placebo had significantly better quality of life assessments, fewer hospitalizations, and better overall clinical rating of efficacy by the masked evaluator. In particular, there was no increase of depression as assessed by the self-rating depression scale in the mitoxantrone groups.

### Study 901 – Evaluation of Quality of Life, Hospitalizations, and Overall Clinical Rating

Endpoint	Placebo N = 64	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 64	12 mg/m <sup>2</sup> N = 60	
Change in HAQ (mean M24 – baseline) **	0.26	0.01	0.09	0.0243 <sup>a</sup>
No. patients (%) with HAQ deterioration	41 (64)	25 (39)	25 (42)	0.012 <sup>b</sup>
Change in SDS (mean M24 – baseline)	1.01	0.08	-0.19	0.5852 <sup>a</sup>
No. patients (%) hospitalized †	43 (67)	36 (56)	24 (40)	0.002 <sup>b</sup>
Duration of hospitalization (mean days)	32.0	49.0	35.2	0.6051 <sup>a</sup>
No. patients (%) with rating of “good” or “very good” ‡	11 (17)	27 (42)	26 (43)	0.001 <sup>b</sup>

HAQ = Health Assessment Questionnaire; M24 = Month 24 (last evaluation carried forward for early drop-outs); SDS = Zung Self-Rating Depression Scale.

\* Mitoxantrone 12 mg/m<sup>2</sup> vs placebo.

\*\* Positive change indicates worsening HAQ.

† Excludes hospitalization for study drug administration. Many hospitalizations were also for rehabilitation.

‡ Overall rating by blinded observer.

<sup>a</sup> Wilcoxon test.

<sup>b</sup> Chi-square test.

In summary, patients treated with mitoxantrone 12 mg/m<sup>2</sup> had significantly better clinical outcomes than patients receiving placebo for all primary efficacy criteria and for most secondary efficacy parameters. The effect of mitoxantrone 5 mg/m<sup>2</sup> was generally intermediate between mitoxantrone 12 mg/m<sup>2</sup> and placebo, indicating a dose-response effect and supporting the evidence of biological activity of mitoxantrone in MS.

Mitoxantrone slowed the progression of neurologic disability, decreased the relapse rate, and had favorable effect on quality of life measures.

#### **4.1.5.3 Sensitivity Analyses**

Post-hoc sensitivity analyses using standard subset populations were performed to confirm the efficacy of mitoxantrone. These subset analyses evaluated:

- Center effect.
- Gender effect.
- Age effect, i.e., above or below the median age of 40 for the study population.
- Baseline EDSS effect, i.e., baseline of 3 or 4 points versus 5 or 6 points.
- Type of MS, i.e., remitting progressive disease versus secondary progressive disease.
- Presence or absence of relapse in the year preceding study drug treatment.
- Completion of the study as per protocol, i.e., received eight courses of study drug and completed all evaluations or did not completed the eight courses.

The results from these sensitivity analyses were consistent with the efficacy results seen in the population as a whole and confirmed the superiority of mitoxantrone compared to placebo. Appendix F summarizes the results for the analyses conducted on gender, age, type of MS, relapse in the year preceding the study, and planned completion of study.

#### **4.1.5.4 MRI Results**

In addition to demonstrating favorable clinical efficacy, mitoxantrone had an effect on the inflammatory process associated with MS in a subset of 110 patients who underwent T1-weighted Gd-enhancing and T2-weighted MRI scans at baseline, Month 12, and Month 24. Total lesion load on T2-weighted scans was calculated manually using a scale from 1 to 5, where a score of 1 indicated a lesion diameter of < 3 mm, 2 indicated a diameter of 3-5 mm, 3 indicated a diameter of 6-10 mm, 4 indicated a diameter of 11-20 mm, and 5 indicated a diameter of > 20 mm.

Patients were not stratified at enrollment on the basis of MRI results, which resulted in differences in the mean numbers of lesions at baseline between mitoxantrone 5 mg/m<sup>2</sup> and the 2 other groups (see table that follows).

**Study 901 - Baseline Gd-Enhancing and T2-Weighted Lesions**

Endpoint	Placebo N = 36	Mitoxantrone	
		5 mg/m <sup>2</sup> N = 40	12 mg/m <sup>2</sup> N = 34
No. of patients (%) with Gd-enhancing lesions	8 (22)	19 (48)	10 (29)
No. of Gd-enhancing lesions per patient (mean)	0.44	3.23	1.88
T2-weighted lesion load per patient (mean)	34.5	51.5	39.7

As a result, comparison of MRI results were performed between mitoxantrone 12 mg/m<sup>2</sup> and placebo only. The results are summarized in the table that follows.

**Study 901 - T2-Weighted Gd-Enhancing MRI Results**

Endpoint	Placebo N = 36	Mitoxantrone		p-value**
		5 mg/m <sup>2</sup> N = 40	12 mg/m <sup>2</sup> N = 34	
No. patients (%) with new Gd+ lesions				
Month 12	7 (19)	6 (15)	4 (12)	0.378 †
Month 24	5 (16)	4 (11)	0 (0)	0.022 †
Mean change in number of Gd+ lesions *				
Month 12 vs baseline	-0.14	-2.93	-1.74	0.1795 ‡
Month 24 vs baseline	-0.19	-3.27	-2.03	0.1048 ‡
Percent change at Month 24	-35%	-78%	-90%	

Gd+ = Gd-enhancing.

\* Negative value indicates decrease in number of lesions.

\*\* mitoxantrone 12 mg/m<sup>2</sup> vs placebo.

† Chi-square test.

‡ Wilcoxon test.

There was a substantial reduction over time in the number of patients with Gd-enhancing lesions and in the mean number of Gd-enhancing lesions in the mitoxantrone 12 mg/m<sup>2</sup> group versus placebo, indicating an effect on active inflammatory lesions in the CNS.

### Study 901 - T2-Weighted MRI Results

Endpoint	Placebo N = 36	Mitoxantrone		p-value*
		5 mg/m <sup>2</sup> N = 40	12 mg/m <sup>2</sup> N = 34	
No. of lesions (mean)				
Baseline	34.5	51.5	39.7	0.1745
Month 12	35.7	48.8	39.6	0.2957
Month 24	34.0	49.2	39.6	0.1635
Change in no. of lesions (mean)				
Month 12 vs baseline	1.17	0.66	0.24	0.0697
Month 24 vs baseline	1.94	0.68	0.29	0.0272
Total lesion load (mean)				
Baseline	60.8	94.2	73.5	0.1483
Month 12	63.2	88.9	73.2	0.3043
Month 24	61.3	89.0	73.3	0.1751
Change in lesion load (mean)				
Month 12 vs baseline	2.36	0.32	0.58	0.3323
Month 24 vs baseline	4.28	0.0	0.64	0.1228

\* 12 mg/m<sup>2</sup> vs placebo (Wilcoxon test).

There was a significant difference in lesion load on T2-weighted MRI scans, suggesting an effect of mitoxantrone 12 mg/m<sup>2</sup> on chronically established MS lesions in the CNS.

#### 4.1.6 Results of the Third-Year Follow-Up Evaluations

A total of 138 patients completed the third-year (Month 36) evaluation: 42 patients in the mitoxantrone 12 mg/m<sup>2</sup> group, 53 patients in the mitoxantrone 5 mg/m<sup>2</sup> group, and 43 patients in the placebo group. At Year 3, there was a continuing difference in the clinical outcome between the mitoxantrone and placebo groups. Patients who had received mitoxantrone had less neurologic impairment 1 year after stopping study drug treatment compared to patients who had received placebo, as evidenced by better EDSS, AI, and SNS results (see table below).

### Study 901 - Assessment of Neurological Impairment at Month 36

Endpoint	Baseline to Month 36			p-values Mitox 12 vs placebo†
	Placebo (N = 43)	Mitox 5 mg/m <sup>2</sup> (N = 53)	Mitox 12 mg/m <sup>2</sup> (N = 42)	
Change from baseline (mean)*				
EDSS	0.46	0.04	0.10	0.1141
SNS	3.28	1.51	0.19	0.0383
AI	1.13	0.55	0.61	0.0650

Mitox = mitoxantrone

\* Negative values indicate improvement of this scale.

† Wilcoxon test.

The number of relapses, treated relapses, and severe relapses reported at Month 36 continued to be lower in the mitoxantrone groups than the placebo group, as was observed during the first 2 years of the study. The table below summarizes by treatment group the relapse results at Month 36.

### Study 901 - Relapse Results at Month 36

Endpoint	Placebo (N = 43)	Mitox 5 mg/m <sup>2</sup> (N = 52)	Mitox 12 mg/m <sup>2</sup> (N = 42)	p-values Mitox 12 vs. placebo
Month 24 to Month 36				
Number of relapses (mean)	0.77	0.46	0.50	0.1377 <sup>a</sup>
Number of treated relapses (mean)	0.56	0.33	0.33	0.1712 <sup>a</sup>
Baseline to Month 36				
Time to 1st relapse (median months)*	8.67	15.05	29.96	0.0407 <sup>b</sup>
Time to 1st treated relapse (median months)	15.38	26.97	NR*	0.0206 <sup>b</sup>

Mitox = mitoxantrone, NR = not reached.

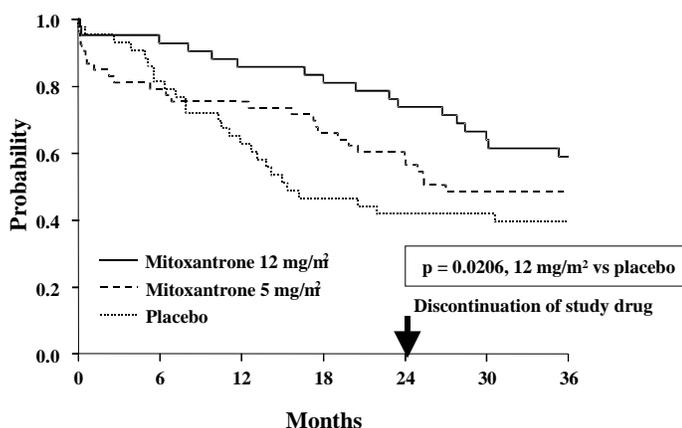
\* Not reached within 36 months.

a Wilcoxon test.

b Log-rank test.

The graph that follows presents Kaplan-Meier estimates of third-year results for time to first treated relapse in the three groups.

### Time to First Treated Relapse



At the Month 36 evaluation, time to first treated relapse continued to be longer for patients in the mitoxantrone 12 mg/m<sup>2</sup> group compared to patients in the mitoxantrone 5 mg/m<sup>2</sup> and placebo groups.

As at Month 24, a greater number of patients in the two mitoxantrone groups showed improvement at Month 36 in both the HAQ and SDS compared to the placebo group, as shown in the following table.

**Study 901 - Quality of Life and Depression Scale Results at Month 36**

<b>Parameter</b>	<b>Placebo (N = 43)</b>	<b>Mitox 5 (N = 53)</b>	<b>Mitox 12 (N = 42)</b>
Change from baseline in HAQ (mean)*	0.48	0.17	0.13
Change in HAQ status (n [%])			
Deterioration	23 (66)	19 (45)	14 (44)
No change	6 (17)	7 (17)	6 (19)
Improvement	6 (17)	16 (38)	12 (38)
Change from baseline in SDS (mean)*	4.40	0.17	-1.55
Change in SDS status (n [%])			
Deterioration	19 (54)	17 (39)	12 (36)
No change	7 (20)	10 (23)	6 (18)
Improvement	9 (26)	17 (39)	15 (45)

\* Higher number = worsening score

**4.1.7 Efficacy Conclusions for Study 901**

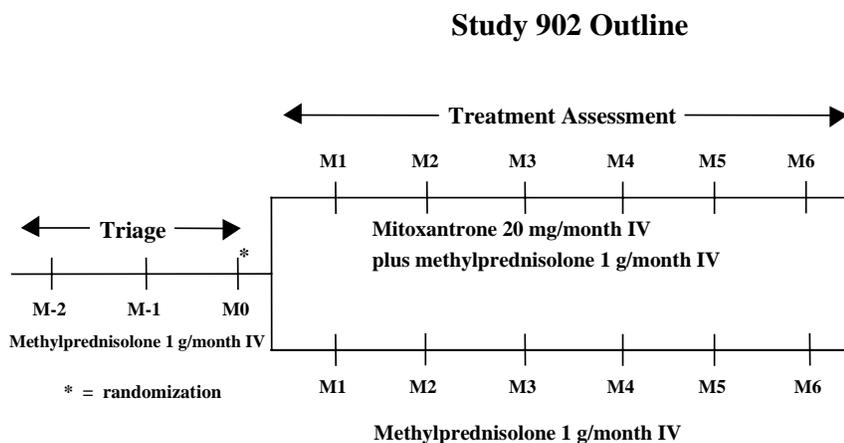
Mitoxantrone 12 mg/m<sup>2</sup> was significantly better than placebo in all primary efficacy endpoints and all secondary endpoints evaluating neurologic disability and relapses. The dose-dependent trend of superior results with mitoxantrone 12 mg/m<sup>2</sup> compared to 5 mg/m<sup>2</sup> indicates a biologic effect of mitoxantrone. The MRI findings support the hypothesis that mitoxantrone decreases the inflammatory process in the CNS. At Year 3, there was a continuing difference between the mitoxantrone and placebo groups.

## 4.2 Randomized Phase II Study (Study 902)

A multicenter, randomized, open-label study evaluating the efficacy of mitoxantrone plus methylprednisolone versus methylprednisolone alone was conducted in patients with highly active MS. The study was chaired by Prof. G Edan and conducted in five French academic medical centers. It was opened to enrollment in April 1992 and was completed in March 1995. The results from this study were published in 1997 (Edan 1997, see Appendix G).

### 4.2.1 Study Objectives, Design, and Endpoints

The objective of the study was to evaluate the efficacy of mitoxantrone in patients with highly active MS by assessing the development of CNS inflammatory brain lesions using MRI with Gd enhancement. This was a two-part trial, as shown in the figure that follows.



The first part was a 2-month triage period (Month -2 to Month 0), during which Gd-enhancing MRI scans were performed monthly, and methylprednisolone was administered IV monthly as a single dose of 1 g following each MRI scan. It was not expected that methylprednisolone would affect the MRI scans obtained 1 month later. The objective of the triage period was to use MRI scans to screen patients with active

disease to ascertain eligibility for the second part of the study, a 6-month treatment period (Month 0 to 6).

At Month 0, patients who met MRI criteria for active disease, as defined by the development of at least one new Gd-enhancing brain lesion, were randomized (centrally in a blinded fashion by a third party) to receive six monthly courses of methylprednisolone (1 g/month IV) alone or methylprednisolone (1 g/month IV) plus mitoxantrone (20 mg/month IV). The mitoxantrone fixed dose of 20 mg is similar to a dose of 12 mg/m<sup>2</sup> in an adult of average size.

Patients with MS were eligible for triage if they were between the ages of 18 and 45 years, had a clinical diagnosis of MS using the Poser criteria, and had an EDSS of ≤ 6.0. Patients had to have experienced at least two relapses or a 2-point increase in the EDSS in the preceding 12 months. They could not have been treated with immunosuppressive agents in the 3 months prior to triage or with corticosteroids within 1 month prior to triage. To be eligible for randomization, patients must have developed at least one new Gd-enhancing MRI brain lesion during the triage period (Month -2 to Month 0).

The primary efficacy criterion was the number of patients without new Gd-enhancing brain lesions on MRI scan during the treatment period (Month 0 to Month 6). To provide an unbiased analysis of the primary endpoint, MRIs were reviewed centrally by observers who were blinded to study drug and to clinical and therapeutic data. Secondary efficacy criteria included the number of new and persisting Gd-enhancing lesions on MRI scan, clinical results assessed by EDSS score, and number of relapses.

#### **4.2.2 Disposition of Patients**

Eighty-five patients fulfilled the clinical criteria for inclusion in the triage phase of the study. Forty-one of these patients were excluded after the 2-month triage period because they did not meet MRI criteria for randomization and treatment with study drug, and 44 patients were randomized to a treatment group. This number of patients was estimated to

be sufficient to demonstrate a 50% reduction in the proportion of patients with new Gd-enhancing lesions over a 6-month period (2-sided alpha = 5%, power = 90%).

Two patients were randomized, received one course of therapy, and were then discontinued from study before undergoing any efficacy evaluations. One patient in the mitoxantrone-plus-methylprednisolone arm discontinued treatment due to an increase in liver enzymes (discontinued on Day 1; considered by the investigator to be due to fluoxetine treatment and unrelated to study drug) and one patient in the methylprednisolone arm discontinued treatment due to rapid disease progression (discontinued on Day 16). These 2 patients were not included in the efficacy analyses.

Thus, 42 of the patients who were randomized continued into the treatment phase: 21 received mitoxantrone plus methylprednisolone and 21 received methylprednisolone alone. These 42 patients served as a basis for the efficacy and safety evaluations. Including the patient who withdrew from the mitoxantrone-plus-methylprednisolone group as a non-responder did not change the efficacy conclusions of this study.

Five of the 42 patients discontinued study drug before completing all six courses of therapy. All had highly active disease as measured by both clinical and MRI criteria, i.e., a mean of three relapses over 6 months, mean EDSS deterioration of 1.6 points, 33-34 active lesions on MRI scan, with a mean of 9 new lesions per scan. All five were in the methylprednisolone-alone group and they discontinued study drug due to worsening MS and lack of therapy effectiveness.

#### **4.2.3 Demographics and Disease Characteristics**

Of the 42 patients randomized and included in these analyses, 26 were female and 16 were male, the mean age was 32 years, and all patients except one were Caucasians. The patients exhibited the features of highly active, moderately severe MS. There were no significant differences between the two treatment groups in regard to demographic and disease characteristics, as shown in the following table.

**Study 902 - Mean Demographic and Disease Characteristics**

<b>Parameter</b>	<b>mP (N = 21)</b>	<b>Mitoxantrone + mP (N = 21)</b>
Age (years)	32.2	31.4
Gender (female/male)	11/10	15/6
Mean values:		
Age at onset of MS (years)	26.6	25.1
Duration of MS (years)	5.7	6.9
No. relapses since MS onset	6.1	7.4
No. relapses in preceding 12 months	2.4	3.1
No. patients with RR/SP MS	15/6	17/4
EDSS score	4.7	4.4
Walking scale	2.9	2.9

mP = methylprednisolone  
 RR = relapsing-remitting  
 SP = secondary progressive

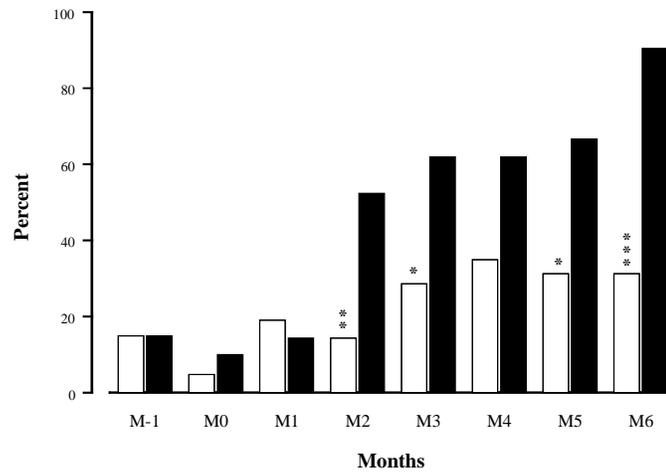
**4.2.4 Efficacy Results**

The study showed that mitoxantrone plus methylprednisolone was significantly better than methylprednisolone alone in the primary and all secondary efficacy endpoints defined in the protocol.

**4.2.4.1 Primary Endpoint**

The primary endpoint of the study was met, with significantly more patients randomized to mitoxantrone-plus-methylprednisolone improving, as defined by negative Gd-enhancing scans at Month 6 compared to methylprednisolone alone (p = 0.001). During the treatment period (Month 0 to 6), the percentage of patients free of new Gd-enhancing lesions in the mitoxantrone plus methylprednisolone group increased progressively to 90% (19/21) at Month 6. In the methylprednisolone-alone group, the percentage of patients free of new MRI Gd-enhancing lesions increased to 31% (5/16). As shown in the figure that follows, mitoxantrone-plus-methylprednisolone was consistently better than methylprednisolone alone from Month 2 to 6, and differences between the two groups were significant at Month 2 (p = 0.009), Month 3 (p = 0.03), Month 5 (p = 0.033), and Month 6 (p = 0.001). The gradual improvement of the MRI scans from Month 2 to 6 in the mitoxantrone-plus-methylprednisolone group suggests a direct effect of mitoxantrone on the pathological lesions of MS rather than an effect on the blood-brain barrier.

**Percent of Patients Free of New MRI Gd-Enhancing Lesions  
During the 6-Month Treatment Period**

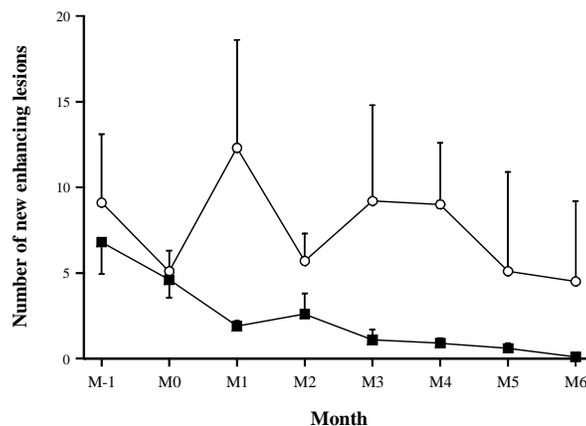


Mitoxantrone + methylprednisolone = ■; methylprednisolone = □.  
M-1 = 1 month before starting study drug; M0 = beginning of study drug.  
M1 to M6 = 1 to 6 months after starting study drug.  
\*  $p \leq 0.033$ ; \*\*  $p = 0.009$ ; \*\*\*  $p = 0.001$

**4.2.4.2 Secondary MRI Endpoints**

As shown in the figure that follows, the mean number of new Gd-enhancing brain lesions was significantly lower in the mitoxantrone-plus-methylprednisolone group every month from Month 1 through Month 6 ( $p = 0.001$  at Month 6).

**Mean Number ( $\pm$  SEM) of New Gd-Enhancing Lesions**



Mitoxantrone + methylprednisolone = ■; methylprednisolone alone = ○.  
 M-1 = 1 month before starting study drug; M0 = beginning of study drug.  
 M1 to M6 = 1 to 6 months after starting study drug.

The mean numbers of all Gd-enhancing brain lesions (new lesions plus persisting lesions) were also significantly lower by Month 6 in the mitoxantrone-plus-methylprednisolone group compared to the methylprednisolone-alone group ( $p = 0.0001$ ).

New T2-weighted lesions were categorized as small, moderate, or large. At Month 0, the mean number of new T2-weighted lesions was comparable between the two treatment groups. During the treatment period, the mean number of new T2-weighted lesions was consistently lower in the mitoxantrone-plus-methylprednisolone group, and the difference was statistically significant for all new lesions (1.1 versus 5.5,  $p = 0.024$ ) and for the moderate ( $p = 0.036$ ) and large ( $p = 0.001$ ) new lesions.

**4.2.4.3 Clinical Efficacy Endpoints**

Effect on EDSS. There was a significant improvement in neurologic disability in the mitoxantrone-plus-methylprednisolone group during the treatment period. Mitoxantrone-plus-methylprednisolone had a continued effect on improving EDSS score. Mean

monthly EDSS values were consistently lower in the mitoxantrone-plus-methylprednisolone group for all 6 months of treatment compared to methylprednisolone alone (data not shown). Mean EDSS changes from baseline were significantly better in the mitoxantrone-plus-methylprednisolone group each month from Month 2 to Month 6, as shown below.

**Study 902 - EDSS Changes From Baseline at Month 0**

Month	mP		Mitoxantrone + mP		p-value <sup>†</sup>
	N	Change	N	Change	
1	21	0.2	21	-0.3	NS
2	21	0.3	21	-0.4	0.024
3	21	0.3	21	-0.6	0.008
4	20 <sup>‡</sup>	0.6	21	-0.9	0.001
5	17 <sup>‡</sup>	0.1	21	-1.1	0.002
6	16 <sup>‡</sup>	-0.1	21	-1.1	0.013

mP = methylprednisolone; NS = no statistical difference.

<sup>†</sup> p-values determined by Wilcoxon test.

<sup>‡</sup> Reflects data available; 5 patients withdrew because of severe deterioration.

Categorical Changes in EDSS. A categorical evaluation classifying EDSS changes from Month 0 to Month 6 as deterioration of at least 1 point, no change, or improvement of at least 1 point showed that 20 of 21 patients in the mitoxantrone-plus-methylprednisolone group had either improved or stable EDSS scores. Compared to placebo, significantly more patients in the mitoxantrone-plus-methylprednisolone group had at least 1 point improvement (57% vs 14%, p = 0.004), as shown in the following table.

**Study 902 – Number and Percent of Patients with 1 Point\***

**EDSS Change Between Month 0 and Month 6**

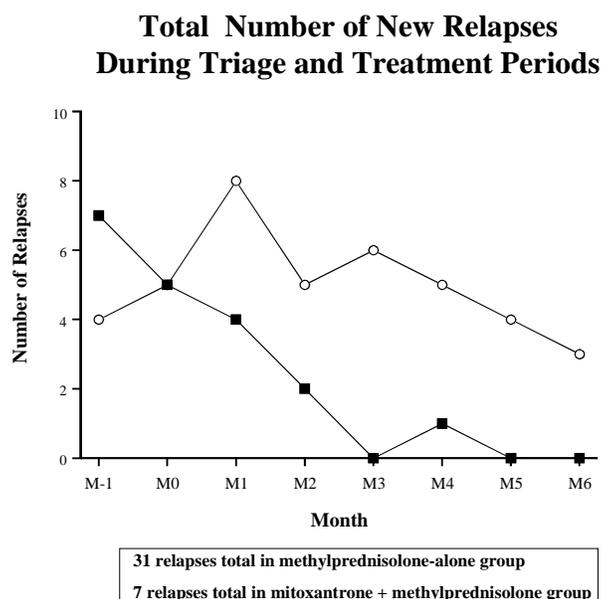
Endpoint	mP	Mitoxantrone + mP	p-value <sup>†</sup>
Deteriorated ≥1 point	6 (28.6%)	1 (4.8%)	0.038
Stable	12 (57.1%)	8 (38.1%)	0.217
Improved ≥1 point	3 (14.3%)	12 (57.1%)	0.004

\* 0.5 point change if baseline EDSS ≥6

<sup>†</sup> p-values determined by Chi-square test

Effect on Relapses. During the 6-month treatment period, there were fewer relapses in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group (annual rates of 0.7 vs. 3.0, respectively, p = 0.003). The figure that follows shows

the number of relapses that occurred each month in the two treatment groups. There were 31 relapses in the methylprednisolone-alone group versus 7 relapses in the mitoxantrone-plus-methylprednisolone group ( $p = 0.003$ ).



Mitoxantrone + methylprednisolone = ■; methylprednisolone alone = O.  
 M-1 = 1 month before starting study drug; M0 = beginning of study drug.  
 M1 to M6 = 1 to 6 month(s) after starting study drug.

Seven courses of high-dose corticosteroids were administered to five patients in the mitoxantrone-plus-methylprednisolone group for relapse, compared to 19 courses administered to 14 patients in the methylprednisolone-alone group ( $p = 0.031$ ).

#### 4.2.5 Efficacy Conclusions for Study 902

Mitoxantrone-plus-methylprednisolone improved both MRI and clinical indicators of disease activity over a 6-month period in patients with highly active MS. All efficacy parameters were significantly improved in the mitoxantrone-plus-methylprednisolone arm compared to the methylprednisolone-alone arm. The strong and rapid reduction in the

inflammatory process suggests a potential role for mitoxantrone administered monthly as rescue or induction therapy in rapidly deteriorating patients with MS.

#### **4.3 Summary of Mitoxantrone Efficacy in the Two Randomized Trials**

Taken together, these two well-designed, randomized studies (Studies 901 and 902) provide compelling evidence for the efficacy of mitoxantrone in patients with active MS.

The two studies had similar design features, including the following:

- Both were randomized, controlled, multicenter studies.
- The control group received an agent unlikely to affect the primary efficacy endpoint.
- The evaluators of the primary efficacy endpoints were masked to study drug.
- The mitoxantrone doses were similar: 12 mg/m<sup>2</sup> and 20 mg fixed dose.
- The cumulative mitoxantrone doses were similar: 96 mg/m<sup>2</sup> and 120 mg fixed dose.
- Both enrolled patients with active MS.
- Both evaluated neurologic disability using the EDSS scale and effect on relapses.
- Both involved efficacy evaluations using MRI scans with Gd enhancement (yearly in Study 901, monthly in Study 902).

There were also differences in study designs, including the following:

- Different eligibility criteria: clinical criteria alone in Study 901 (EDSS deterioration by at least 1.0 point in the previous 18 months) versus both clinical and MRI criteria in Study 902 (two relapses or EDSS deterioration of 2 points in the previous 12 months and at least one new lesion on MRI at study entry).
- Different patient population: evidence of progressive neurologic impairment required in one study (901) but not the other (902).

- Different schedules of mitoxantrone administration, i.e., every 3 months vs. monthly.
- Different study durations, i.e., 24 months vs. 6 months.
- One study used mitoxantrone alone and the other used mitoxantrone plus methylprednisolone.
- The primary efficacy endpoints were clinical in one study and MRI-based in the other.

In spite of the differences in study design and objectives, both studies were complementary in demonstrating the efficacy of mitoxantrone in the treatment of patients with MS. In both studies, mitoxantrone slowed the progression of neurologic disability and decreased the number of relapses. In both studies, MRI findings were consistent with the clinical findings, indicating an effect of mitoxantrone on the inflammatory process in the CNS.

#### **4.4 Applicability of the Efficacy Results to Patients in the U.S.**

The two randomized studies were both conducted in Europe. The results, however, are applicable to U.S. patients.

First, the studies were conducted in five European countries spanning the continent east to west, thus providing a patient population with a diverse ethnic European background.

Second, in the U.S., MS is more prevalent in individuals of European ancestry and is relatively rare in African-Americans or Asian-Americans. It is thus likely that results from studies conducted in Europe should be applicable to Americans as well. For example, the two approved beta interferons and glatiramer acetate were studied in Europe and the U.S. with similar results on the two continents.

Third, mitoxantrone activity in MS is due to its immunosuppressive effects, and the mechanism of its antiproliferative effect is expected to function independently of race.

Fourth, there are no significant differences in the diagnosis and management of patients with MS between the U.S. and Europe except for duration of hospitalizations. Disease

response to therapy is determined using standard measures such as the tabulation of relapses, the Kurtzke Functional Score, the EDSS score, and MRI scans. In addition, concomitant medications used in the two European studies were similar to medications prescribed for patients with MS in the U.S. Also, MS relapses were treated for 3 to 5 days with high-dose corticosteroids, an approach similar to U.S. standard of care.

The major difference between the methods of care in Europe and the U.S. is in the longer duration of hospitalizations in Europe to perform intensive patient rehabilitation, a practice not used in the U.S. This difference should not affect the objective assessments of the clinical efficacy and MRI endpoints in the two studies.

#### **4.5 Types of Multiple Sclerosis in the Two Randomized Trials**

As discussed in Section 1.1, a 1996 consensus classification of patients with MS recognized four disease categories based on the pattern of neurological deficit accumulation. These categories were not well defined in the early 1990s when the two randomized controlled trials were initiated, making it difficult to assign patients to one of the four disease categories based on retrospective chart review. However, based on the inclusion and exclusion criteria defined in the two protocols, it is possible to identify the characteristics of the patients enrolled and to determine what type of patients would benefit from mitoxantrone therapy based on the data from the two trials.

In Study 901, patients were eligible if they had secondary progressive MS or relapsing progressive MS with evidence of EDSS progression by at least 1.0 point in the preceding 18 months. Patients with primary progressive MS and benign MS were excluded. Using the consensus MS classification, eligible patients on Study 901 fit into one of the following three categories: secondary progressive MS, progressive relapsing MS, or relapsing-relapsing MS with accumulated residual deficit after relapse.

In Study 902, patients were eligible if they had active MS as defined by 2-point EDSS progression or the occurrence of two relapses with sequelae in the preceding 12 months, as well as MRI progression during the triage period. For the purpose of patient