CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	21-120
DRUG COMPANY:	Immunex Corp.
NAME OF DRUG:	Novantrone
INDICATION:	Multiple Sclerosis
STUDIES REVIEWED:	P310901, P310902
DOCUMENTS REVIEWED:	Sponsor's original NDA submission, Vol. 1, 104-125

I. Introduction

Novantrone is currently approved for the treatment, in combination with other approved drugs, of acute non-lymphocytic leukemia in adults and for the treatment of pain, in combination with corticosteroids in advanced hormone refractory prostate cancer patients. In the current NDA submission the sponsor, Immunex Corp., is requesting approval of a new indication for the product, Novantrone, for the treatment of patients with secondarily progressive multiple sclerosis, including progressive relapsing disease.

This submission is comprised of two clinical studies for efficacy evaluation: a blinded placebo controlled phase III study and an open labeled add-on phase II study. Another retrospective data analysis of a large cohort of patients treated with mitoxantrone was also included in the submission for safety information. The design features of the three studies are summarized in the following table.

Table B.2.3.A. Clinical Trials of Mitoxantrone in MS: Study Design and Methods

	Study 031.0901	Study 031.0902	Study 031.0903
Trial type	Phase III, multicenter	Phase II, multicenter	Single center
Type of MS	Secondary progressive Progressive-relapsing	Relapsing remitting Secondary progressive	Any type of MS
Entry criteria	1-point EDSS increase in 18 months	2-point EDSS increase or 2 relapses in prior 12 months, Gd+ lesions	Any patient given at least one dose of mitoxantrone
Number of groups	3 arms	2 arms	1 arm
Mitoxantrone dose	12 mg/m^2 or 5 mg/m^2	20 mg fixed dose	12 mg/m^2 then adjusted
Control arm	Placebo	Methylprednisolone	Not applicable
Therapy schedule	Every 3 months	Every month	Every 3 months
Therapy duration	24 months	6 months	Not predefined
Safety evaluations	Every 3 months	Every month	Before each course
Long-term follow-up	1 year after last course	None	Over 10 years

Gd+ = gadolinium-enhanced lesions by MRI

Information on patient enrollment in the three studies is summarized in sponsor's Table B.2.3.B and information on baseline demographics is summarized in sponsor's Table B.2.3.C.

Table B.2.3.B. Clinical Trials of Mitoxantrone in MS: Enrollment Data

	Study 031.0901	Study 031.0902	Study 031.0903
Enrollment dates	6/93 – 7/97	4/92 – 3/95	1/89-12/97
Number of sites	17	5	1
Countries	Germany, Belgium, Poland, Hungary	France	Germany
No. patients:			
randomized	194	44	454
received drug	191	44	454
evaluable for efficacy	188	42	454
evaluable at most effective dose	60	21	454

Table B.2.3.C. Clinical Trials of Mitoxantrone in Multiple Sclerosis: Characteristics of Patients Treated with Mitoxantrone

	Study 031.0901	Study 031.0902	Study 031.0903
No. of patients given mitoxantrone	124*	21†	454
Mean age	40.0 years	31.4 years	37.0 years
No. of female/male (ratio)	98/90 (1.1)	15/6 (2.5)	276/178 (1.6)
Mean MS duration	9.6 years	6.9 years	9.1 years
Type MS: No. of patients (%)			
relapsing-remitting	0 (0%)	17 (81%)	287 (63%)
secondary progressive	59 (48%)	4 (19%)	102 (22%)
progressive-relapsing	65 (52%)	0 (0%)	0 (0%)
primary progressive/unknown	0 (0%)	0 (0%)	65 (14%)
Mean EDSS score at baseline	4.6	4.4	5.11
Mean no. of relapses in prior year	1.3	3.1	1.02

* Three additional patients withdrew after one mitoxantrone dose

† One additional patient withdrew after one mitoxantrone dose

In the following Section II Clinical Studies, details of the two controlled studies and their efficacy evaluations are described. The reviewer's comments are given for each of the two studies. Section III gives the overall summary and the conclusions of the efficacy results of the two studies.

II. Clinical Studies

1. Protocol 031.0901

1.1 Objectives

The main objectives of the study were to determine the efficacy, safety, and tolerability of two different dose levels of mitoxantrone to placebo. Efficacy variables were various

parameters related to disability and relapses. In a subgroup of patients, the effect of mitoxantrone on cranial MRI scans was also measured.

1.2 Study Design

The study was an observer-blind, randomized, placebo-controlled, Phase III study using a three-group parallel design of 12 mg/m^2 or 5 mg/m^2 of mitoxantrone or a matched placebo, administered intravenously every 3 months for a total of 8 courses to patients with an active stage of multiple sclerosis. The study was conducted at 17 centers in four Europe countries.

Sample size was determined based on the difference of EDSS from baseline. It was calculated that 60 patients per group for a total of 180 patients should be sufficient to detect an 1.0 point deterioration in EDSS with 90% of power.

In this study the primary investigator was not blinded. The primary investigator administered each treatment cycle and did tolerability and safety evaluation. An additional physician was designated for each center, who was responsible for the routine evaluation of study patients and was blinded.

A separate randomization was done for each center.

Study dates: 6/2/93 – 7/10/97

1.3 Diagnosis and Main Criteria for Inclusion

- Definite, clinical or laboratory supported MS as defined by the Poser criteria
- Remittent-progressive (progressive relapsing) or secondary progressive MS in an active stage with evidence or deterioration
- EDSS from 3 through 6
- Age 18 to 55 years
- Standard laboratory test results within the normal range
- Negative pregnancy test at enrollment, if female and of child-bearing potential
- Agreement to practice effective contraception throughout the study and for 6 months following the last dose of mitoxantrone, if of reproductive age
- Written informed consent

1.4 Dose Selection and Dose Adjustments

The sponsor stated that the mitoxantrone dose of 12 mg/m^2 was selected because it had most favorable benefit and risk profile in Phase I-II studies. The treatment arm of 5 mg/m^2 was included to determine whether a lower dose of mitoxantrone was also effective in slowing disease progression.

A differential blood count was performed within 7 days preceding the next dosage administration. In addition, the non-hematological toxicity was assessed using the WHO toxicity grading. If significant toxicity was observed, the dose was adjusted.

In the mitoxantrone 12 mg/m^2 group, low leukocyte and/or platelet counts in the hematology test within 7 days preceding the next dose could result the next dose decrease to 10 mg/m^2 to 6 mg/m^2 or the patient be removed from the study. In the mitoxantrone 5 mg/m^2 group, if non-hematologic toxicity of WHO Grade 2 or 3 occurred, the next dose was to be reduced to 4 mg/ m^2. If WHO Grade 4 non-hematologic toxicity was observed, the patient was to be removed from the study.

1.5 Prior and Concomitant Therapy

Patients who experienced severe relapses during the study treatment could be treated with courses of short-term (5 days) high dose (500 mg) methylprednisolone. The treating physician was responsible for making the decision to administer such treatment. Administration of all other immunosuppressive and chemotherapeutic agents or any other investigational drug were prohibited throughout the study.

1.6 Efficacy Variables

1.6.1 Primary Efficacy Variables

The primary efficacy criteria was a multivariate test for the five primary efficacy variables:

- Change in EDSS at 24 months compared to baseline value
- Change in AI at 24 months compared to baseline value
- Number of relapses requiring corticosteroid treatment, regardless of severity
- Time to first relapse requiring corticosteroid treatment
- Change in SNS score at 24 months compared to baseline value

1.6.2 Secondary Efficacy Variables

The following variables were defined as secondary efficacy variables. Analyses based on secondary efficacy variables are for descriptive purpose only and not confirmatory.

Variables Related to EDSS:

- Number of patients with improvement, no change, or deterioration of EDSS>=1 point after 24 months of treatment compared to baseline
- Number of patients with confirmed (3 months) EDSS deterioration >=1 point during the study
- Time to first confirmed (3 months) EDSS deterioration >=1 point
- Number of patients with confirmed (6 months) EDSS deterioration >=1 point during the study

- Time to first confirmed (6 months) EDSS deterioration >=1 point
- Number of patients requiring wheelchair
- Time to requiring a wheelchair

Variables Related to Relapse:

- Time to first relapse (regardless of treatment or severity)
- Time to first severe relapse
- Number of relapses (regardless of treatment or severity)
- Number of patients without a relapse
- Rate of relapse

MRI (subgroup of patients)

- Gadolinium-enhanced scans
- T2-weighted scans

MRI evaluation was performed in a subgroup of patients at predetermined centers before treatment, at Month 12, and at Month 24.

1.7 Statistical Methods

The five primary efficacy variables, EDSS, SNS, AI, number of attacks requiring corticosteroid treatment, and time to the first attack requiring such treatment, were to be tested in one combined hypothesis of "stochastic ordered alternatives" by the generalized Wilcoxon-Mann_Whitney (Wei-Lachin) (Lachin 1992, Wei and Lachin 1984) procedure. Evaluated were to be the changes from baseline to the end of two-year treatment comparing mitoxantrone 12 mg/m^2 and placebo. If the test was significant, all five single criteria were to be tested in the sequence of EDSS, AI, number of attacks requiring corticosteroid treatment, time to the first attack requiring such treatment and SNS according to the principle of priori ordered hypotheses.

If the first test was significant, the dose response relationship among the three treatment groups was to be analyzed by applying the Jonckheere test to the EDSS criterion, and the effect of the mitoxantrone 5 mg/m^2 as compared to placebo or mitoxantrone 12 mg/m^2 was to be assessed.

All other tests, especially for those for secondary efficacy variables, are for descriptive purpose only and not confirmatory.

The precision of the study is specified by means of confidence interval. The Mann-Whitney test was used for this purpose. For quasi-normal distributions such as EDSS and the SNS, mean difference was also used.

Time to occurrence of event data was evaluated by means of the log-rank test. The number of patients without an event was analyzed by standard procedures for 2*2 tables (Pearson's chi-square test without continuity adjustment).

As indicated in the protocol, data with only a few ordered categories, such as number of attacks and improvement, are evaluated by means of the exact permutational Wilcoxon-Mann-Whitney test.)

Finally, an analysis of responsiveness (sensitivity to change) was performed for all criteria to qualify the ability of each criterion to discriminate therapeutic regimens. The main responsiveness measure is the Mann-Whitney statistic.

Data analysis was performed using SAS and SmarTest, a program of idv, Gauting/Munchen, Germany, for the Wei-Lachin procedure.

1.8 Results (Sponsor's Findings)

1.8.1 Patients Disposition

There were 194 patients enrolled into the study at 17 centers in four European countries – Germany, Belgium, Hungary, and Poland. Of the 194 patients enrolled in the study, 149 completed the study. Three patients withdrew after randomization and before receiving the study drug, three were not evaluated for efficacy after a single dose of the study drug, and 39 withdrew prematurely from the study. See Table 10.1.B for a summary of patient disposition by treatment group.

Table 10.1.B. Disposition of Patients

	Treatment Group			
Disposition of Patients	Placebo	Mitox 5	Mitox 12	Total no. of patients
Patients randomized	65	66	63	194
No treatment[a]	1	1	1	3
No follow-up	0	1	2	3
Intent to treat (ITT) cohort	64	64	60	188
Patients prematurely withdrawn	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 reasons	0	1	1	2
Patients completing the study	47	54	48	149

a. Ref. Table A 10.1-2

The sponsor stated that there was no statistical difference in observation time for patients who did not prematurely discontinue the study. The median duration of participation (defined as the time from first study drug administration to the time of last visit) in the study for patients who withdrew prematurely was 342 days in the placebo group, 501 days in the mitoxantrone 5 mg/m^2 group, and 385 days in the mitoxantrone 12 mg/m^2 group.

1.8.2. Data Sets Analyzed

Assessment of efficacy of mitoxantrone compared to placebo was based on the ITT cohort (n=188). All patients randomized to the study were included in the ITT cohort except six, three who never received any study medication and three for whom no assessment of the efficacy variables could be made because they had no follow-up visit after the first dose of study drug.

1.8.3 Demographic and Baseline Characteristics of the ITT Cohort

The sponsor stated that there were no differences among treatment groups concerning physical characteristics of height and weight. No statistically significant differences in age were found among the three treatment groups. There were more male patients in the placebo and the mitoxantrone 12 mg/m^2 groups and more female patients in the mitoxantrone 5 mg/m^2 group. No significant differences in baseline characteristics were found among the three treatment groups. A summary of demographic and baseline characteristics of patients by treatment groups is displayed in the sponsor's Table 11.2.1.

Table 11.2.1. Patient Characteristics at Baseline

		Treatment Group		
		Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
Gender[a]				
	Male	33 (51.6%)	25 (39.1%)	32 (53.3%)
	Female	31 (48.4%)	39 (60.9%)	28 (46.7%)
Age (years)[b]				
	Mean	40.02	39.92	39.94
	SD	7.88	8.06	6.85
Height (cm)[c]				
	Mean	170.0	168.7	170.2
	SD	9.6	8.36	8.94
Weight (kg)[c]				
	Mean	67.5	66.2	68.4
	SD	10.9	13.4	12.4
Body surface area (m^2)[c]				
	Mean	1.78	1.75	1.78
	SD	0.18	0.19	0.21
Status of female pts[d]				
	Premenopausal	21	27	25
	Perimenopausal	1	4	1
	Postmenopausal	6	7	1
	Other	3	1	1
LVEF[e]				
	Mean	66.0	67.1	66.9
	SD	7.45	7.32	8.41
ECG[f]				
	Normal	60	64	60
	Abnormal	4	0	0
Residual urine[g]				
	0-50 mL	25	25	24
	51-100 mL	3	5	1
	>100 mL	4	3	3
	not determined	32	31	32

a. Gender: Ref. Table A 11.2.1-1
b. Age: Ref. Table A 11.2.1-2
c. Height, weight, and body surface area: Ref. Table A 11.2.1-3 – A 11.2.1-5
d. Status of female patients: Ref. Table A 11.2.1-6
e. LVEF: Ref. Table A 11.2.1-7
f. ECG: Ref. Table A 11.2.1-8
g. Residual urine: Ref. Table A 11.2.1-12

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1.8.4 Concomitant Medication

One hundred twelve (59.6%) patients were receiving medication at baseline. Of these, 76 patients (40.4%) took medication for symptoms of MS: 22 patients (36.7%) in the

mitoxantrone 12 mg/m^2 group, 21 (32.8%) in the mitoxantrone 5 mg/m^2 group, and 33 patients (51.6%) in the placebo group.

1.8.5 Disease History

The sponsor stated that patients were diagnosed as having MS based on laboratory (54.3%) or clinical (45.2%) assessment.

Overall, the type of MS was classified as "remittent progressive" (i.e., progressive relapsing) or "secondary progressive" for equal number of patients. The sponsor stated that the slightly higher percent of patients in the mitoxantrone 5 mg/m^2 group with progressive relapsing disease was not statistically different from the other groups. The sponsor's Table 11.2.3 summarizes disease characteristics of the ITT cohort at baseline.

Table 11.2.3. Disease Characteristics at Baseline

		Treatment Group		
		(N = 64)	(N = 64)	(N = 60)
		Placebo	Mitox 5	Mitox 12
Type of MS[a]				
Progressive relapsing	N (%)	29 (45.3%)	37 (57.8%)	28 (46.7%)
Secondary progressive	N (%)	35 (54.7%)	27 (42.2%)	32 (53.3%)
Number of relapses (preceding 12 months)[b]				
	Mean	1.31	1.42	1.27
	SD	1.14	1.26	1.12
Duration of MS (years)[c]				
	Mean	10.27	9.03	9.63
	SD	6.86	6.18	6.94
EDSS deterioration (preceding 18 months)[d]				
	Mean	1.58	1.62	1.50
	SD	0.85	0.71	0.77
EDSS[e]				
	Mean	4.69	4.64	4.45
	SD	0.97	1.01	1.05
Ambulatory Index[f]				
	Mean	2.63	2.52	2.52
	SD	1.02	0.98	1.14
SNS[g]				
	Mean	20.94	18.88	19.33
	SD	7.67	6.66	8.46

a. Type of MS: Ref. Table A 11.2.3-2
b. Mean number of relapses: Ref. Table A 11.2.3-4
c. Duration of MS: Ref. Table A 11.2.3-3
d. EDSS deterioration: Ref. Table A 11.2.3-5
e. Mean EDSS: Ref. Tables A 11.2.3-7
f. Mean AI: Ref. Table A 11.2.3-9
g. Mean SNS: Ref. Table A 11.2.3-11

1.8.6 Efficacy Results (Sponsor's Analysis)

1.8.6.1 Primary Efficacy Criterion

The primary efficacy criteria was a composite test of the five primary efficacy variables of EDSS, AI, number of relapses requiring corticosteroid treatment, time to the first relapse requiring such treatment, and SNS. The five primary efficacy variables were tested in a combined hypothesis of stochastic ordered alternatives using the generalized Wilcoxon-Mann-Whitney test. The test was performed to assess changes during the 2 years after onset of treatment and to identify differences between the mitoxantrone 12 mg/m^2 and placebo group. The sponsor reported the Mann-Whitney differences between the groups in Table 11.3.1.1. The global Mann-Whitney difference was reported as 0.3094 (95% CI: .1721 - .4468), and the p-value of the multivariate composite test was reported as .0001 in favor of mitoxantrone 12 mg/m^2 group vs. placebo.

Table 11.3.1.1. Primary Efficacy Criterion*

Variable	Mann-Whitney Difference (95% CI)	p value of Global Test
Change in EDSS	0.2393 (0.0414, 0.4373)	
Change in AI	0.2107 (0.0240, 0.3974)	
Number of treated relapses	0.3849 (0.1801, 0.5897)	
Time to first treated relapse	0.4821 (0.2077, 0.7565)	
Change in SNS	0.2302 (0.0299, 0.4305)	
Global difference	0.3094 (0.1721, 0.4468)	<0.0001*

*Two-sided global test result is given (SmarTest software).
p < 0.0001 for one-sided test as specified in protocol
Ref. Table A 11.3.1-1.

1.8.6.2 Univariate Analysis of Primary Efficacy Variables

Since the global test of the five combined efficacy variables was significant in favor of mitoxantrone 12 mg/m^2 group, all five primary efficacy variables were tested separately with alpha=0.05. The results of the separate test of the five primary efficacy variables are reported in Table 11.3.1.2. The order of the sequential test was revised in Amendment 3, which changed the order of SNS to the last one. The differences of the changes from baseline of the five separate tests are all significant in favor of mitoxantrone 12 mg/m^2 with p-values below .05.

Table 11.3.1.2. Overview of Primary Efficacy Variables

Variable	Treatment	Value	p value Placebo vs. Mitox 12
EDSS change (last value - baseline) Mean (SD)	Placebo	0.23 (1.01)	0.0194[a]
	Mitox 5	-0.23 (1.1)	
	Mitox 12	-0.13 (0.90)	
AI change (last value - baseline) Mean (SD)	Placebo	0.77 (1.26)	0.0306[a]
	Mitox 5	0.41 (1.40)	
	Mitox 12	0.30 (1.24)	
Adjusted total no. of relapses requiring treatment	Placebo	76.77	0.0002[a]
	Mitox 5	46.88	
	Mitox 12	24.08	
Time to 1st relapse requiring treatment median (months)	Placebo	14.19	0.0004[b]
	Mitox 5	NR	
	Mitox 12	NR	
SNS change (last value - baseline) Mean (SD)	Placebo	0.77 (6.79)	0.0269[a]
	Mitox 5	-0.38 (7.27)	
	Mitox 12	-1.07 (8.61)	

NR = not reached within 24 months.
a. Wilcoxon-Mann-Whitney test
b. Log-rank test

Additional analyses for each of the individual efficacy variables were performed by the sponsor and were reported below.

Change in EDSS

The sponsor reported that 12 patients in the mitoxantrone 12 mg/m^2 group, 18 patients in the mitoxantrone 5 mg/m^2 group, and 7 patients in the placebo group showed an improvement of at least 1 point in EDSS. Deterioration of at least 1 point in the EDSS was seen in 16 patients in the placebo group compared to 10 in the mitoxantrone 5 mg/m^2 group and 5 patients in the mitoxantrone 12 mg/m^2 group (Table 11.3.1.2.1.A).

Table 11.3.1.2.1.A. Change in EDSS

Change in EDSS (last value - baseline)		Treatment Group (N) Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
Deterioration	2.5	0	1	1
	2.0	5	2	1
	1.5	5	3	1
	1.0	6	4	2
No change	0.5	17	6	15
	0	13	23	15
	-0.5	11	7	13
Improvement	-1.0	2	5	6
	-1.5	2	6	4
	-2.0	2	5	0
	-2.5	0	2	2
	-3.0	1	0	0

The sponsor stated that patients receiving placebo had significantly more deterioration than patients receiving either dose of mitoxantrone. No statistically significant difference was seen between the two mitoxantrone groups (Table 11.3.1.2.1.C.).

Table 11.3.1.2.1.C. Test Results for Change in EDSS*

Change in EDSS	Mann-Whitney Difference (95% CI)	P value
Placebo vs. Mitox 12	0.2393 (0.0414, 0.4373)	0.0178
Placebo vs. Mitox 5	0.2605 (0.0664, 0.4546)	0.0085
Mitox 5 vs. Mitox 12	-0.0542 (-0.2503, 0.1420)	0.5883

*Results from SmarTest software.

Change in AI

The sponsor reported that four patients in the placebo group showed an improvement in AI, compared to 12 patients in the mitoxantrone 5 mg/m^2 group and 12 patients in the mitoxantrone 12 mg/m^2 group. Deterioration in AI was most frequently seen in placebo-treated patients (n=28, 43.8%) compared to patients in the mitoxantrone 5 mg/m^2 group (n=20, 31.3%) and patients in the mitoxantrone 12 mg/m^2 group (n=20, 33.3%) (Table 11.3.1.2.2.A).

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Table 11.3.1.2.2.A. Change in AI

Change in AI[a] (last value – baseline)		Treatment Group Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
Deterioration	5	1	1	1
	4	2	2	1
	3	3	3	2
	2	9	5	1
	1	13	9	15
No change	0	32	32	28
Improvement	-1	4	9	10
	-2	0	3	2

a. AI: Ref. Table A 11.3.1-6 - A 11.3.1-7

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The sponsor reported that patients receiving mitoxantrone 12 mg/m^2 showed significantly less deterioration than patients receiving placebo (p=0.0306). Patients receiving mitoxantrone 5 mg/m^2 showed a trend toward better results than patients receiving placebo. The difference between the two mitoxantrone groups was not significant (Table 11.3.1.2.2.C).

Table 11.3.1.2.2.C. Test Results for Change in AI*

Group Comparisons	Mann-Whitney Difference 95% CI	p value
Placebo vs. Mitox 12	0.2107 (0.0240, 0.3974)	0.0270
Placebo vs. Mitox 5	0.1826 (-0.0018, 0.3671)	0.0523
Mitox 5 vs. Mitox 12	0.0159 (-0.1728, 0.2046)	0.8689

*Results from SmarTest software

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Adjusted Number of Treated Relapses

The total number of treated relapses is given as an adjusted number. Adjustment was performed for patients who discontinued before receiving all 8 courses of therapy (n=39) as well as for patients who completed all 8 courses but had their last evaluation prior to

the end of Month 24. Only one patient had an adjustment greater than 1.0 (Adjustment =1.071). The mean adjusted number of treated relapses is summarized in Table 11.3.1.2.3.C. The sponsor reported that the difference between the placebo and mitoxantrone 12 mg/m^2 groups was significant with a p-value of .0002.

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Table 11.3.1.2.3.C. Descriptive Statistics for Adjusted Number of Treated Relapses

	Treatment Group		
	Placebo	Mitox 5	Mitox 12
Mean[a]	1.20	0.73	0.40
SD	1.25	0.99	0.57
Median	1.00	0.00	0.00
Max.	5.00	4.00	2.00
75th Percentile	2.00	1.01	1.00
25th Percentile	0	0	0
Min.	0	0	0

a. Mean adjusted number of treated relapses: Ref. Table A 11.3.1-13

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The sponsor reported that patients receiving placebo had significantly more treated relapses that did patients receiving mitoxantrone 12 mg/m^2 (p=.0002) and patients receiving mitoxantrone 5 mg/m^2 (p=.0293). The difference between the two mitoxantrone groups was reported not significant (Table 11.3.1.2.3.D).

Table 11.3.1.2.3.D. Test Results for the Adjusted Number of Treated Relapses*

Adjusted Number of Relapses	Mann-Whitney Difference (95% CI)	p value
Placebo vs. Mitox 12	0.3849 (0.1801, 0.5897)	0.0002
Placebo vs. Mitox 5	0.2299 (0.0432, 0.4167)	0.0158
Mitox 5 vs. Mitox 12	0.1427 (-0.0334, 0.3189)	0.1123

*Results from SmarTest software

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Time to First Treated Relapse

The sponsor reported that there was significant difference in time to first treated relapse between the placebo and 12 mg/m^2 mitoxantrone groups (p=.0006; log-rank test, Table 11.3.1.2.4.B). The difference between the two mitoxantrone groups was not statistically significant.

Table 11.3.1.2.4.B. Test Results for Time to First Treated Relapse*

Group Comparisons	Mann-Whitney Difference (95% CI)	p value
Placebo vs. Mitox 12	0.4821 (0.2077, 0.7565)	<0.0006
Placebo vs. Mitox 5	0.1930 (-0.0620, 0.4480)	0.1380
Mitox 5 vs. Mitox 12	0.2374 (-0.0661, 0.5408)	0.1253

*Results from SmarTest software.

Change in SNS

The sponsor reported that patients receiving placebo showed a significant deterioration compared to patients receiving mitoxantrone 12 mg/m^2 (p=0.0269) but could not be distinguished from patients receiving mitoxantrone 5 mg/m^2. No difference was seen between the two mitoxantrone groups, as shown in Table 11.3.1.2.5.C.

Table 11.3.1.2.5.C. Test Results for Change in SNS*

Group Comparison	Mann-Whitney Difference (95% CI)	p value
Placebo vs. Mitox 12	0.2302 (0.0299, 0.4305)	0.0243
Placebo vs. Mitox 5	0.1096 (-0.0910, 0.3103)	0.2842
Mitox 5 vs. Mitox 12	0.1310 (-0.0703, 0.3323)	0.2022

*Results from SmarTest software

1.8.6.3 Analysis of Secondary Efficacy Variables

Secondary efficacy variables were classified as variables related to EDSS, vatriables related to relapses, variables related to quality of life, and other variables. MRI results collected for a subgroup of patients are also described. As specified in the protocol, analyses based on secondary efficacy variables are for descriptive purpose only and not confirmatory. In this review, only results from MRI evaluation are presented.

Evaluation of MRI

MRI was performed for a subgroup of 110 patients at predefined centers. Non-enhanced (T2-weighted) and gadolinium (Gd)-enhanced, T1 weighted MRIs were carried out at

baseline, Month 12, and Month 24. The centers were selected based on their ability to perform the MRI scans according to protocol requirements. All MRI images were analyzed at a central facility by two experienced readers who were blinded to the patients' clinical status and randomized treatment. The two reviewers evaluated the MRI scan independently, then together arrived at consensus.

Fifty-nine percent of patients overall were included in the MRI subgroup. Demographics of the MRI subgroup were similar to those of the ITT population. In addition, demographics were similar among the placebo, mitoxantrone 5 mg/m^2 and mitoxantrone 12 mg/m^2 groups. Numbers of patients enrolled in the MRI subgroup are summarized by treatment in the following table.

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Table 11.3.2.7.1.A. MRI Subgroup Population

	Treatment Group		
Member of MRI Subgroup	Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
Yes	36 (56%)	40 (63%)	34 (57%)
No	28 (44%)	24 (27%)	26 (43%)

Ref. Table 11.3.2.7-2

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Number of patients with new Gd-enhanced lesions

The sponsor reported that 4 patients (11.8%) in the mitoxantrone 12 mg/m^2 group, 6 patients (15%) of the mitoxantrone 5 mg/m^2 group, and 7 patients (19.4%) in the placebo group had new lesions after 12 months of treatment. None of the patients of the mitoxantrone 12 mg/m^2 group had new lesions in the assessment at Month 24 compared to baseline. Four patients in the mitoxantrone 5 mg/m^2 group and 5 patients in the placebo group had new lesions at Month 24 compared to baseline. The sponsor reported that the difference between the mitoxantrone 12 mg/m^2 and placebo groups at Month 24 was significant (p=0.022).

Mean number of Gd-enhanced lesions per patient

The sponsor reported that there was no difference between the mitoxantrone 12 mg/m^2 group and the placebo group in terms of the mean number of Gd-enhanced lesions per patient at baseline and Month 12. There were more lesions per patient at Month 24 in the placebo group compared to mitoxantrone 12 mg/m^2 group (p=0.092). There was no difference at Month 12 and 24 between the mean number of lesions per patient in the mitoxantrone 5 mg/m^2 group and the placebo group. The results are summarized in the following table.

Table 11.3.2.7.1.D. Gd-enhancing (Gd+) Lesions

Evaluated Criteria		Treatment Group		
		Placebo	Mitox 5	Mitox 12
No. of patients (%) with Gd^+ lesions[a]	Baseline	8 (22.2%)	19 (47.5%)	10 (29.4%)
	Month 12	7 (19.4%)	6 (15.0%)	5 (14.7%)
	Month 24	5 (15.6%)	4 (10.8%)	1 (3.2%)
No. of patients (%) with new Gd^+ lesions	Month 12	7 (19.4%)	6 (15.0%)	4 (11.8%)
	Month 24	5 (15.6%)	4 (10.8%)	0 (0%)
Mean no. (SD) of Gd^+ lesions[b] per patient	Baseline	0.44 (0.97)	3.23 (8.91)	1.88 (5.29)
	Month 12	0.31 (0.71)	0.30 (0.91)	0.15 (0.36)
	Month 24	0.28 (0.73)	0.11 (0.31)	0.03 (0.18)
Mean change from baseline (SD) in no. of Gd^+ lesions[c]	Month 12	-0.14 (0.93)	-2.93 (9.01)	-1.74 (5.25)
	Month 24	-0.19 (1.20)	-3.27 (9.26)	-2.03 (5.52)

[a] Ref. Tables A 11.3.2.7-24 – A 11.3.2.7-26
[b] Ref. Table A 11.3.2.7-29
[c] Ref. Table A 11.3.2.7-30

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1.9 Reviewer's Analysis

1.9.1 Composite Analysis

The primary efficacy analysis is based on a German developed software SmarTest. A laptop was delivered by the sponsor to the agency with the software installed together with the requested validation and the manual of the software. A short training was provided to the statistical reviewer to use the software. The result from the composite analysis was confirmed by running the software at the training. However, neither the sponsor nor the agency has any knowledge about how the software was implemented.

Based on the composite test the treatment effect of mitoxantrone 12 mg/m^2 is highly significant with a p-value of 0.0001. However, the global difference of 0.3094 from combined five variables is difficult to be interpreted.

1.9.2 Analysis of Individual Efficacy Variables

Mitoxantrone 12 mg/m^2 versus placebo

Since the difference between mitoxantrone 12 mg/m^2 and placebo from the composite analysis was significant, the analysis of each individual efficacy variable was performed based on the pre-specified order. The EDSS was first analyzed followed by AI, adjusted number of treated relapse, time to first treated relapse, and SNS. The following table presents the test results from five individual efficacy variables. These results agree with the corresponding results obtained by the sponsor.

Table 1. Test of individual efficacy variables comparing 12mg/ m^2 and placebo

	Mitox 12 mg / m^2	Placebo	Test/ p-value
EDSS			Wilcoxon rank sum/
Mean change from baseline	- 0.13	0.23	p=0.0194
AI			Wilcoxon rank sum/
Mean change from baseline	0.30	0.77	p=0.0306
Adjusted # of treated relapse			Wilcoxon rank sum/
Mean of total per person	0.40	1.20	p=0.0002
Time to 1st treated relapse			Log-rank /
Median time (days)	Not reached	432.0	p=0.0004
Mean time (days)	604.5	425.5	
SNS			Wilcoxon rank sum/
Mean change from baseline	- 1.07	0.77	p=0.0269

Mitoxantrone 5 mg/m^2 versus placebo

The global test of the five primary efficacy variables comparing mitoxantrone 5 mg/m^2 and placebo was significant at a p-value of 0.0053 from the composite analysis, reported by the sponsor. The following paragraphs present the results from analysis of individual efficacy variables.

The difference in the change of EDSS from baseline between mitoxantrone 5 mg/m^2 and placebo was also significant (p=0.0098). The decrease in EDSS showed in mitoxantrone 5 mg/m^2 group was 0.23, which was larger than the decrease showed in mitoxantrone 12 mg/m^2 group.

For the ambulatory index (AI) the effect of mitoxantrone 5 mg/m^2 vs. placebo was found to be marginally unsignificant at p=0.0560. The mean deterioration in AI score for the mitoxantrone 5 mg/ m^2 group was 0.41 compared to deterioration of 0.76 for the placebo group and 0.30 for the mitoxantrone 12 mg/m^2 group.

The adjusted number of treated relapses in patients receiving placebo is significantly larger compared to patients receiving mitoxantrone 5 mg/m^2 with a p-value of 0.0293. The mean adjusted number of treated relapses for the mitoxantrone 5 mg/m^2 group and placebo group were 0.73 and 1.20, respectively.

The difference in time to the first treated relapse for the mitoxantrone 5 mg/m^2 group and the placebo group was marginally unsignificant with a p-value of 0.0549. The median time to the first treated relapse was 770 days for the mitoxantrone 5 mg/m^2 group and 432 days for the placebo group. The result of time to first relapse from this reviewer's analysis is different from the result obtained by the sponsor.

Finally, patients in the placebo group showed a mean deterioration in SNS of –0.77 compared to a mean improvement of 0.38 in SNS score in the mitoxantrone 5 mg/m^2 group. The difference between the two groups in the SNS scores was not statistically significant (p=0.2912).

In summary, among the five primary efficacy variables the difference between mitoxantrone 5 mg/m^2 group and placebo group was found to be statistically significant in EDSS and the adjusted number of treated relapses, marginally insignificant in AI and time to first treated relapse, and not statistically significant SNS. The test results of the five primary efficacy variables in comparing mitoxantrone 5 mg/m^2 and placebo are summarized in the following table.

Table 2. Test of individual efficacy variables comparing 5mg/ m^2 and placebo

	Mitox 5 mg / m^2	Placebo	Test/ p-value
EDSS			Wilcoxon rank sum/
Mean change from baseline	- 0.23	0.23	p=0.0098
AI			Wilcoxon rank sum/
Mean change from baseline	0.41	0.77	p=0.0560
Adjusted # of treated relapse			Wilcoxon rank sum/
	0.73	1.20	p=0.0293
Time to 1st treated relapse			Log-rank /
Median time (days)	770.0	432.0	p=0.0549
Mean time (days)	554.0	425.5	
SNS			Wilcoxon rank sum/
Mean change	- 0.38	0.77	p=0.2912

1.9.3 Analysis of MRI Data

Analysis of MRI data is considered exploratory. At baseline, the mean number of lesions were 2.86 for the mitoxantrone 12 mg/m^2 group, 3.17 for the mitoxantrone 5 mg/m^2 group, and 0.43 for the placebo group. In addition to the reported mean number of Gd-enhanced lesions at Month 12 and Month 24, the change from baseline in the mean number of Gd-enhanced lesions was analyzed. During the 24 months of treatment the mean number of Gd-enhanced lesions reduced by 2.03 in the mitoxantrone 12 mg/m^2 group, 3.27 in the mitoxantrone 5 mg/m^2 group, and 0.18 in the placebo group. The p value obtained from the Wilcoxon rank sum test for the difference between mitoxantrone 12 mg/m^2 group and placebo group is 0.095. The difference between mitoxantrone 5 mg/m^2 group and placebo group is significant with a p value of 0.0031.

1.9.4 Descriptive Statistics of the Efficacy Variables by Demographic Characteristics

The effects of demographic differences and disease characteristics on the efficacy results have been examined and no such effect was found. The center effect was also not found.

The following table presents the descriptive statistics of the efficacy variables by subjects' demographic characteristics.

Table 3. Descriptive statistics of the efficacy variables by demographic characteristics

	Treatment		
	Mitox 12 mg/m^2	Mitox 5 mg/m^2	Placebo
Mean Change in EDSS			
Gender: Male/Female	0.16 / -0.46	-0.30 / -0.18	0.36 / 0.08
Age[1]: <=39.8 / > 39.8	-0.37 / 0.10	-0.56 / 0.15	-0.03 / 0.48
Mean Change in AI			
Gender: Male/Female	0.56 / 0.00	0.20 / 0.54	0.91 / 0.61
Age: <=39.8 / > 39.8	0.13 / 0.47	0.09 / 0.77	0.72 / 0.81
# of relapses			
Gender: Male/Female	0.56 / 0.22	0.68 / 0.76	1.01 / 1.41
Age: <39.8 / > 39.8	0.44 / 0.37	0.95 / 0.49	1.21 / 1.19
Median time to 1st relapse			
Gender: Male / Female	NR[2] / NR	NR / 770.0	NR / 338.0
Age: <=39.8 / > 39.8	NR / NR	614.5 / 770.0	457.0 / 432.0
Mean Change in SNS			
Gender: Male / Female	0.19 / -2.50	-0.32 / -0.41	0.27 / 1.29
Age: <=39.8 / > 39.8	-1.50 / -0.63	-1.06 / 0.40	-0.13 / 1.66

1. The median age is used as cut point for age group.
2. NR: Not reached

1.10 Reviewer' Conclusion

Base on the results reported by the sponsor and this reviewer's independent analysis, I would conclude that there was sufficient evidence that mitoxantrone 12 mg/ m^2 is effective in treating patients with progressive relapsing MS or secondary progressive MS. The effect of mitoxantrone is shown in improving EDSS and SNS scores, slowing the deterioration of AI score, and delaying the time to relapses requiring corticosteroid treatment.

2. Study 031.0902

2.1 Study Objective

The objective of the study was to evaluate the efficacy of mitoxantrone in patients with MS by assessing the development of central nervous system (CNS) inflammatory brain lesions using MRI with gadolinium (Gd) injections.

2.2 Study Design

This was a multicenter, open-label (reader blinded), randomized study in two periods: a 2-month triage period (Month –2 to Month 0) to screen patients for eligibility for randomized treatment, followed by a 6-month treatment period (Month 0 to Month 6). Patients who were eligible for the treatment period were to be randomly allocated into two parallel groups of at least 20 patients each. Patients were recruited in five French medical centers.

2.3 Study Outline

During the 2-month triage period (from Month –2 to Month 0), Gd-enhanced MRI scans were performed once monthly (e.g., Month –2 as baseline; Month –1, 30 days after one course of mythylprednisolone; and Month 0, 30 days after the second course of mythylprednisolone). Methylprednisolone was administered intravenously as a single dose of 1 g per month following each scan. At Month 0, patients who met MRI criteria for progression of disease (i.e., who developed at least one new Gd-enhanced brain lesion) were randomized to one of the two study arms in the treatment period of the study, based on a central allocation list. Treatment was assigned by a third party who was blinded to the clinical data. Randomized treatment in the two study arms was to begin at Month 0 and continue for six courses.

2.4 Efficacy Assessments

Primary efficacy variable

The primary parameter of effectiveness is the percentage of change in patients without active lesions on the MRIs repeated each month. An active lesion is defined as either the appearance of a new lesion or the increase in volume of a preexisting lesion, or the appearance of a contrast picked up after an injection of Gd.

Secondary criteria

- Clinical development of the two groups (patients both treated and untreated with mitoxnantrone) compared using the Kurtzke handicap scale in months M-2, M-1, M0, M1, M2, M3, M4, M5, and M6.
- Change in the number of active lesions in the MRIs.

A central treatment-blinded analysis of MRI scans was performed by two experienced investigators from the Nuclear Magnetic Resonance Research Group In London who were blinded to the clinical data.

2.5 Treatments

Mitoxantrone and methylprednisolone were administered once a month from Month 0 through Month 5, for a total of six courses. In some patients, an additional (seventh)

course was administered at Month 6. All assessments for safety and efficacy (including the MRI scan) were conducted after each of the first six courses.

Patients received mitoxantrone at a fixed dose of 20 mg (the equivalent of 12 to 14 mg/m^2 per cycle).

Methylprednisolone was supplied as 500 mg vial of powder reconstituted in 50 mL of distilled water.

2.6 Efficacy Analysis

Differences between the two groups were evaluated at each time point using Wilcoxon test or the chi-square test (chi-square test was specified in the protocol). The analysis of variance with factors for treatment and time originally proposed in Amendment 2 was not performed because the normality assumptions were not met.

2.7 Results (Sponsor's Findings)

2.7.1 Patients Disposition

Patients were enrolled in five centers in France. 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. Two additional patients were withdrawn from the study following randomization. Forty-two patients were randomized and continued in the treatment phase: 21 to receive mitoxantrone plus methylprednisolone and 21 to continue with methylprednisolone alone.

The sponsor stated that at the request of the Study Chair, two patients randomized at Month 0 were withdrawn from study after randomization. These two patients are not included in the analyses because they did not undergo MRI evaluations after Month 0.

During treatment, five patients, all in the methylprednisolone-alone group, withdrew: one at Month 3, three at Month 4, and one at Month 5. The reasons for withdrawals were a marked deterioration in MS and lack of therapy effectiveness. For all the patients who withdrew, effectiveness was judged "null" and safety "good" (CGI evaluation).

The sponsor reported that all five patients who withdrew prematurely from study had highly active disease by both clinical and MRI criteria. The EDSS at inclusion in the triage phase (Month –2) and at withdrawal, as well as the number of exacerbations and of new enhanced lesions, are shown in Table 5.1.4. The data in this Table document the severity of disease progression in these five patients.

Table 5.1.4. Patients With Premature Withdrawal

Patient No.	Treatment Arm	Mo. of With-drawal	Reason for Withdrawal	EDSS at M-2	EDSS at With-drawal	No. of Exacerba-tions after M-2	No. of New Enhanced Lesions after M-2	No. of Scans with New Enhanced Lesions
105		3		6.0	7.5	2	51	6/6
109		5	Lack of	4.5	8.0	3	86	7/7
201	mP alone	4	effectiveness	5.5	6.5	4	35	6/7
401		4		4.5	5.0	4	8	7/7
403		4		6.0	8.5	4	90	7/7

mP = methylprednisolone; MITOX = mitoxantrone
EDSS = Expanded Disability Status Scale
M-2 = Month -2, beginning of triage period

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2.7.2 Demographics and Baseline Characteristics

Demographics

For the 42 patients randomized and included in these analyses, the mean age was 31.8 years and the sex ratio was 16/26 (male/female). In this population, the average weight was 61.6 kg and average height was 169.2 cm. All randomized patients were Caucasian except on patient in the methlprednisolone-alone group who was Black. Table 5.2.1 summarizes demographic data according to treatment. The sponsor stated that there were no significant differences between the two groups.

Table 5.2.1. Demographic Characteristics

(Mean ± Standard Deviation)

Parameter	mP (N = 21)	MITOX + mP (N= 21)
Age (years)	32.2 ± 8.1	31.4 ± 8.3
Male/female	10/11	6/15
Weight (kg)	62.2 ± 13.4 (n=20)	61 ± 10.8
Height (cm)	169.1 ± 9.9 (n=19)	169.2 ± 8.9

mP = methylprednisolone; MITOX = mitoxantrone

Disease Characteristics

All patients satisfied the Poster criteria for diagnosis of MS. The sponsor stated that there was no statistically significant difference between the two groups, either in neurological function status or in the neurological signs, except for visual signs.

The sponsor also stated that there were no differences between the groups in duration of disease and total number of exacerbations since onset of MS. Six patients in the

methylprednisolone-alone group had secondary progressive MS while the remaining patients had relapsing-remitting MS. In the mitoxantrone-plus-methylprednisolone group, four patients had secondary progressive MS and the remaining patients had relapsing-remitting MS (no statistically significant difference). The EDSS at clinical inclusion was moderate to severe in both groups, indicating relatively severe handicaps with respect to disease duration (no statistical difference). In addition, there was no difference between the two groups with respect to the walking scale and Hauser's ambulation index. These results are summarized in Table 5.2.2.

Table 5.2.2. Disease Characteristics

(Mean ± Standard Deviation)

VARIABLE	mP (N=21)	MITOX + mP (N=21)
Age at onset of MS (years)	26.6 ± 6.5	25.1 ± 7.0
Duration of MS (years)	5.7 ± 4.0	6.9 ± 3.6
No. of exacerbations since MS onset	6.1 ± 3.7	7.4 ± 4.5
No. of exacerbations in the preceding 12 months	2.4 ± 1.7	3.1 ± 1.8
RRMS/SPMS ratio*	15/6	17/4
EDSS rating	4.7 ± 1.5	4.4 ± 1.8
Walking scale	2.9 ± 1.5	2.9 ± 1.6

mP = methylprednisolone; MITOX = mitoxantrone
RRMS = relapsing-remitting multiple sclerosis
SPMS = secondary progressive multiple sclerosis
* SPMS patients were Nos. 301, 307, 309, 407, 409, and 509 in the mP group; and Nos. 108, 306, 410, and 512 in the MITOX + mP group

2.7.3 Concomitant Medications

Nineteen patients in each group were receiving concomitant treatment at randomization for the treatment phase (Month 0). At Month 0, treatment with corticosteroids for MS exacerbations was reported in three patients in the methylprednisolone alone group and in four patients in the mitoxantrone-plus-methylprednisolone group.

Eleven patients in the methylprednisolone-alone group and six in the methylprednisolone-plus-mitoxantrone group received methylprednisolone or prednisolone to treat exacerbatins (including fatigue or aggreavation) during the study. Three of the patients listed in the methylprednisolone-alone group subsequently withdrew from the study, due to an apparent lack of effectiveness of the treatment.

2.7.4 Efficacy Assessment (Sponsor's Analysis)

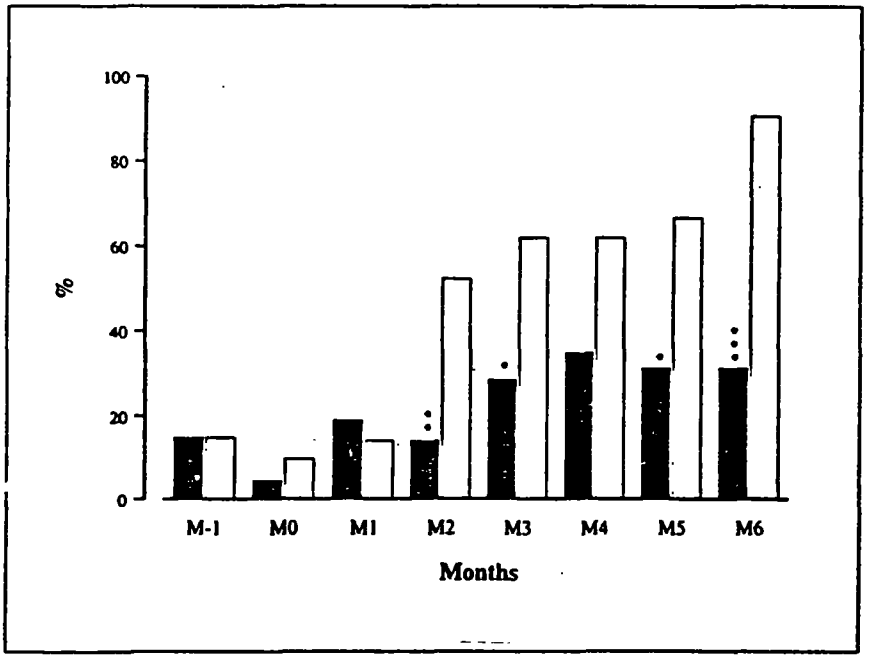
MRI Findings

1). Percentage of Patients without New Gd-Enhanced Lesions

To qualify for randomization in the treatment phase of the study, patients must have had at least one new Gd-enhanced lesion during the 2-month triage phase. At randomization

for treatment (Month 0), the percentage of patients without new Gd-enhanced lesion was 4.8% (n=1) in the methylprednisolone-alone group and 10% (n=2) in the mitoxantrone-plus-methylprednisolone group. During the treatment period, the percentage of patients without Gd-enhanced lesions in the mitoxantrone-plus-methylprednisolone group increased progressively to reach 90.5% (n=19/21) at Month 6. In the methylprednisolone-alone group, the percentage of patients without new lesions increased to 31.3% (n=5/16) during the same time period. The sponsor stated that patients in the mitoxantrone-plus-methylprednisolone group had consistently better MRI results than those in the methylprednisolone-alone group, and difference between the groups were statistically significant at Month 2 (p=0.009), Month 3 and 5 (p=0.030 and 0.033, respectively), and Month 6 (p=0.001). Results are shown in Table 6.1.1 and Figure 6.1.1.

Figure 6.1.1. Percentage of Patients Without New MRI Gd-Enhanced Lesions During the 6-Month Treatment Period



methylprednisolone (■) or methylprednisolone + mitoxantrone (□)
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
* p value = 0.030 at M3 and 0.033 at M5; ** p value = 0.009; *** p value = 0.001

Table 6.1.1. Number (%) of Patients Without Active Gd-Enhanced Lesions on MRIs, by Month

Month	mP		MITOX + mP		p value *
	N	n (%)	N	n (%)	
M-1	20†	3 (15)	20†	3 (15)	1.000
M0	21	1 (5)	20†	2 (10)	0.606
M1	21	4 (19)	21	3 (14)	1.000
M2	21	3 (14)	21	11 (52)	0.009
M3	21	6 (29)	21	13 (62)	0.030
M4	20‡	7 (35)	21	13 (62)	0.085
M5	16‡	5 (31)	21	14 (67)	0.033
M6	16‡	5 (31)	21	19 (90)	0.001

mP = methylprednisolone; MITOX = mitoxantrone
N = number of patients analyzed
* p values determined by chi square or Fisher's exact test
† One MRI was not interpretable
‡ Reflects data available; five patients withdrew because of severe deterioration (see Table 5.1.4)

The sponsor stated that the conclusions in the above table were not altered if the two patients who had been randomized and then withdrawn after receiving one course each of study were added to it (assuming the worst case scenario for mitoxantrone, i.e., Patient No. 205 was without active lesions, and No.304 was with active lesions).

2). Number of Gd-Enhanced Lesions

During the triage period, the mean monthly number of new Gd-enhanced brain lesions was 6.8 in Month –1 and 4.6 in Month 0 in the mitoxantrone-plus-methylprednisolone group and 9.1 in Month –1 and 5.1 in Month 0 in the methylprednisolone-alone group. During the 6-month treatment period, the mean monthly number of new Gd-enhanced lesions ranged from 0.1 to 2.6 in the mitoxantrone-plus-methylprednisolone group and from 2.9 to 12.3 in the methylprednisolone-alone group. The sponsor stated that the number of new Gd-enhanced lesions was significantly lower in the mitoxantrone-plus-methylprednisolone group every month from Month 1 through Month 6. Results are shown in Table 6.1.2.A.

Table 6.1.2.A. Mean Number of New Gd-Enhanced Lesions

Month	mP			MITOX + mP			p value *
	N	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	
M-2	--	--	--	--	--	--	--
M-1	20†	9.1 ± 17.9	2.5 (0-78)	20†	6.8 ± 8.3	3 (0-32)	NS
M0	21	5.1 ± 5.7	3 (0-23)	20†	4.6 ± 4.6	3 (0-18)	NS
M1	21	12.3 ± 28.8	5 (0-135)	21	1.9 ± 1.4	2 (0-5)	0.036
M2	21	5.7 ± 7.5	2 (0-26)	21	2.6 ± 5.7	0 (0-21)	0.017
M3	21	9.2 ± 25.8	2 (0-120)	21	1.1 ± 2.7	0 (0-12)	0.011
M4	20‡	8.9 ± 16.7	1 (0-65)	21	0.9 ± 1.6	0 (0-7)	0.035
M5	16‡	3.8 ± 5.3	1 (0-17)	21	0.6 ± 1.5	0 (0-7)	0.009
M6	16‡	2.9 ± 3.2	2 (0-11)	21	0.1 ± 0.5	0 (0-2)	0.001

mP = methylprednisolone; MITOX = mitoxantrone
N = number of patients analyzed; NS = no statistical difference
* p values determined by Wilcoxon test
† One MRI was not interpretable
‡ Reflects data available; five patients withdrew because of severe deterioration (see Table 5.1.4)

The sponsor stated that when analyses were performed using the mean new lesion frequency from the previous months to calculate the missing values at Month 4, 5, and 6 for the five patients who withdrew, the results were similar.

Clinical Findings

The sponsor reported that there were significant differences in EDSS between the two groups during the treatment period. Mean monthly EDSS values were consistently lower in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group for all six months of treatment. Mean EDSS improvement in the mitoxantrone-plus-methylprednisolone group was 1.1 (+-1.1) after six months of treatment. In contrast, mean EDSS in the methylprednisolone-alone group deteriorated progressively from Month 0 to Month 4. At Month 6, the methylprednisolone-alone group had a mean EDSS improvement of 0.1 (+-1.1). The sponsor reported that the detected improvement in the methylprednisolone-alone group at Month 6 (-0.1+-1.1) was due to the withdrawal from study of five patients in that group who experienced severe neurological deterioration. The results are shown in Table 6.2.1.A.

Table 6.2.1.A. EDSS Values During Triage and Treatment Periods

(Mean [M] ± Standard Deviation [SD])

	Mean EDSS Value					Mean Delta EDSS*				
	mP		MITOX + mP			mP		MITOX + mP		
Month	N	M ± SD	N	M ± SD	p value†	N	M ± SD	N	M ± SD	p value†
M-2	21	4.7 ± 1.5	21	4.4 ± 1.9	NS	--	--	--	--	--
M-1	21	4.5 ± 2.0	21	4.5 ± 1.7	NS	--	--	--	--	--
M0	21	4.6 ± 1.7	21	4.5 ± 1.6	NS	--	--	--	--	--
M1	21	4.9 ± 2.1	21	4.2 ± 1.6	NS	21	0.2 ± 1.3	21	-0.3 ± 0.7	NS
M2	21	4.9 ± 1.8	21	4.1 ± 1.7	NS	21	0.3 ± 1.2	21	-0.4 ± 0.8	0.024
M3	21	5.0 ± 1.7	21	3.9 ± 1.8	NS	21	0.3 ± 1.1	21	-0.6 ± 0.8	0.008
M4	20‡	5.1 ± 1.8	21	3.6 ± 2.0	0.014	20‡	0.6 ± 1.3	21	-0.9 ± 0.9	0.001
M5	17‡	4.5 ± 2.1	21	3.4 ± 1.9	NS	17‡	0.1 ± 1.2	21	-1.1 ± 1.0	0.002
M6	16‡	4.3 ± 2.1	21	3.4 ± 1.9	NS	16‡	-0.1 ± 1.1	21	-1.1 ± 1.1	0.013

mP = methylprednisolone; MITOX = mitoxantrone

N = number of patients analyzed; NS = no statistical difference

* Changes in EDSS compared to Month 0

† p values determined by Wilcoxon test

‡ Reflects data available; five patients withdrew because of severe deterioration (see Table 5.1.4)

2.8 Reviewer's Analysis

MRI Results

The efficacy results from analysis of MRI data reported by the sponsor were verified and the results from this reviewer's analysis agree with the results reported by the sponsor.

As stated in the original protocol, the primary parameter of effectiveness was the percentage of change (instead of percentage) in patients without active lesions on the MRIs repeated each month. Therefore, the patients were re-categorized as had a change in status (without active lesions at baseline and had lesions at Month 6, or vise versa) or not. The chi-square test was applied and a significant difference in change of percentage from Month 0 to Month 6 was found in favor of mitoxantrone-plus-methylprednisolone group with a p-value of 0.011.

The following is a summary of results from this reviewer's analyses.

1. At Month 6, the percentage of patients with active lesions was found significantly lower in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group with a p-value of 0.001 from chi-square test.
2. The percentage change from Month 0 to Month 6 in the number of patients without active lesions was significantly different between the two groups with larger improvement shown in the mitoxantrone-plus-methylprednisolone group with a p-value of 0.011 from chi-square test.

3. At Month 6, the mean number of Gd-enhanced lesion was significantly lower in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group with a p-value of 0.001 from Wilcoxon rank sum test.
4. The reduction from Month 0 to Month 6 in the number of new lesions was significantly larger in the mitoxantrone-plus-methylprednisolone group than in the methylprednisolone-alone group with a p-value of 0.0210 from Wilcoxon rank sum test.

EDSS Results

The protocol specified analysis for EDSS was the analysis of variance with factors of treatment and time. It was verified that the normal assumption for the analysis was not satisfied, and therefore, Wilcoxon's rank sum test was used in analyzing EDSS values.

The protocol specified that clinical development of the two groups was to be compared using the Kurtzke handicap scale in months M-2, M-1, M0, M1, M2, M3, M4, M5, and M6. It was not clear whether the change from baseline in EDSS values or the EDSS values at Month 6 were to be analyzed. It was also not clear whether Month –2 or Month 0 served as baseline. Therefore, both EDSS values at Month 6 and change in EDSS values from Month 0 to Month 6 were analyzed, and the two treatment groups were compared. It was found that

1. At Month 6, the difference in mean EDSS value was not significantly different for the two groups (p=.1465) using data from all completers. However, when LOCF was used for the missing values the difference of mean EDSS for the two groups was found to be statistically significant with a p-value of 0.0174 from Wilcoxon rank sum test.
2. The change in EDSS from Month 0 to Month 6 was found significantly different in favor of mitoxantrone-plus-methylprednisolone group with a p-value of 0.0134 from data of all completed patients and a p-value of 0.0011 using LOCF, Wilcoxon rank sum test.

The effect of demographic differentials on the primary and secondary efficacy variables has been examined and no evidence was found that such effect exists. The following table summarizes the descriptive statistics of MRI and EDSS measures by demographic characteristics.

Table 4. Efficacy results by gender and age group[1]

	Treatment	
	Mp	Mitox+Mp
% without active lesions		
Gender: Male/Female	30.00 / 18.18	83.33 / 93.33
Age: <=30.5 / > 30.5	20.00 / 27.27	81.82 / 100.00
Change in mean # of new lesions		
Gender: Male/Female	2.9 / -0.73	-6.2 / -3.8
Age: <=30.5 / > 30.5	1.8 / 0.27	-3.9 / -5.0
Mean change in EDSS		
Gender: Male/Female	0.55 / 0.05	-1.42 / 0.97
Age: <30.5 / > 30.5	-0.10 / 0.64	-1.23 / -0.95

1. Median age is used as cut point for age group.

2.9 Reviewer's Comments

The above efficacy analysis has showed that the patients in the mitoxantrone-plus-methylprednisolone group had better disease condition at Month 6 with respect to MRI results as well as EDSS measures. The question is whether the differences observed are primarily contributed by the effect of mitoxantrone.

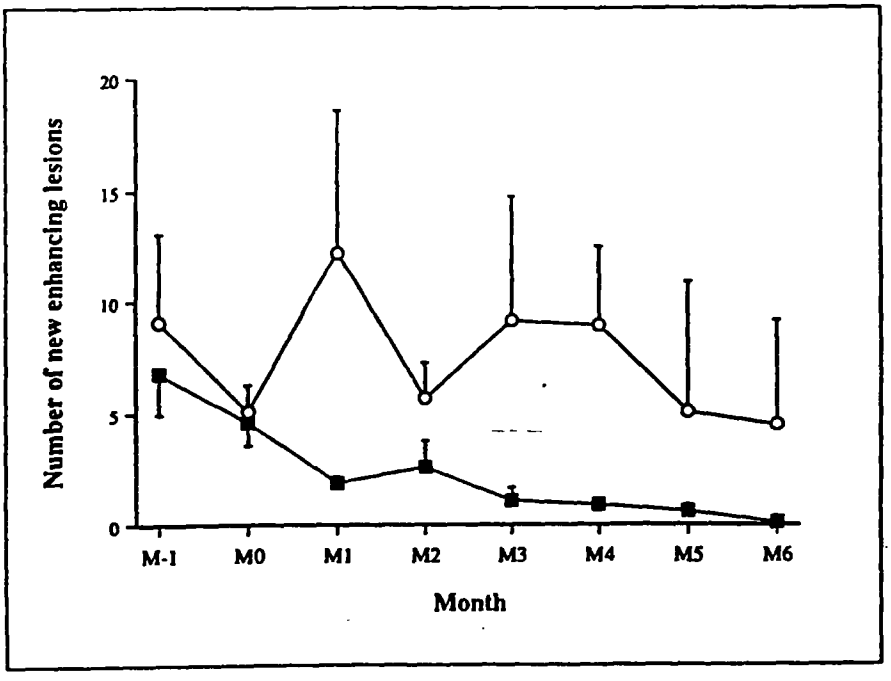
The issue that needs to be raised here is that the comparison was not based on the same ground due to the fact that the treatment was not blinded to patients. If we look at month by month change of the mean number of new lesions or EDSS scores (Table 5 and 6), it can be found that the biggest change occurred at Month 0 to Month 1, which is the first monthly change after randomization. For example, a biggest monthly increase in the number of new lesions in the methylprednisolone-alone group and a biggest monthly decrease in the number of new lesions in the mitoxantrone-plus-methylprednisolone group were all observed from Month 0 to Month 1. The Table 5 shows the mean number of new lesions from Month –1 to Month 6 as well as month by month changes. It is not understood why the biggest drug effect occurred at Month 0 to Month 1 and then seems weakened later, why the control group had largest increase in the mean number of lesions from Month 0 to Month 1, and whether there exits any subject's effect that contributed to the efficacy results.

Table 5. Mean number of new lesions from Months –1 to Month 6 and changes of each month compared to previous month.

Treatment	Mean Number of New Lesions							
	M-1	M 0	M 1	M 2	M 3	M 4	M 5	M 6
MP								
Mean	9.10	5.14	12.33	5.71	9.24	8.90	3.81	2.94
Change from Previous month		-3.96	7.19	-6.62	3.53	-0.34	-5.09	-0.87
Mitox+mP								
Mean	6.75	4.55	1.90	2.62	1.14	.90	.62	.14
Change from previous month		-2.2	-2.65	0.72	-1.48	-0.24	-0.28	-0.48

The data also shows that the mean number of new lesions in the mitoxantrone-plus-methylprednisolone group kept decreasing month by month except from Month 1 to Month 2. Could it be interpreted that the change in the previous month left no room for further improvement, or the effect of mitoxantrone is mainly shown in the first month, or that some effect other than the drug effect started to disappear? The following Figure 6.1.2 provides a picture for the month by month change data.

Figure 6.1.2. Mean Number (±SEM) of New Gd-Enhanced Lesions



methylprednisolone alone (O) or methylprednisolone plus mitoxantrone (■)
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

Such phenomenon was also observed in EDSS, although it was less significant. The following table shows the month by month change in mean EDSS scores.

Table 6. Mean number of EDSS scores from Months –1 to Month 6 by treatment.

Treatment	Mean Number of EDSS Scores							
	M-1	M 0	M 1	M 2	M 3	M 4	M 5	M 6
MP								
Mean	4.50	4.64	4.86	4.93	4.95	5.10	4.47	4.25
Change from previous month		0.14	0.22	0.07	0.02	0.15	-0.63	-0.22
Mitox+mP								
Mean	4.50	4.48	4.17	4.07	3.86	3.57	3.40	3.38
Change from previous month		-0.02	-0.31	-0.10	-0.21	-0.29	-0.17	-0.02

I would still conclude that the evidence of the effect of mitoxantrone in reducing the number of MRI new lesions and EDSS score is established, although the magnitude of the difference between the two treatment groups might not be as large as observed in this study if the trial were blinded.

It should be pointed out that the definition of the new lesion is not clear. Based on the protocol and the report in the NDA submission, a new lesion is defined as opposed to baseline, which means that any lesion not observed at Month –2 is considered as a new lesion. In the submission, three numbers of lesions are recorded for each month and each patient. The three numbers are new, persisting, and total. There are several patients who had number of persisting lesions larger than the number at baseline. From the understanding of this reviewer, the monthly number must be compared to previous month in order for the number to be possible. This reviewer has contacted the statistician of the sponsor to clarify the numbers. The response from the statistician is that the numbers are compared to baseline, not the previous month.

It should be pointed out that for most patients, the lesions observed in each month were mostly disappeared by the next MRI scan. The number of new lesions observed each month ranged from 0 to 135, and mostly represented the total number of lesions observed in that month. Therefore, the effect of mitoxantrone is not in reducing the total number of lesions or in eliminating the existing lesions, but rather in having fewer new lesions appearing in the future.

III. Reviewer's Overall Conclusions and Comments

The statistical review and evaluation of Novantrone for treatment of multiple sclerosis is based on two clinical studies P310901 and P310902. Study P310901 is an observer-blind,

randomized, placebo controlled, phase III study in three parallel groups and study P310902 is an open label (MRI reader-blind), randomized, phase II add-on trial with methylprednisolone as control. Both studies have showed significant treatment effect with respect to their protocol specified primary efficacy variables and main secondary efficacy variables.

Although there are varies issues (described below) associated with the design of the two studies, such as the composite analysis in the study P310901 and the open-label nature and using of MRI as primary endpoint in the study P310902, the two studies have provided sufficient statistical evidence for the efficacy of mitoxantrone. I would therefore conclude that mitoxantrone is effective in treating patients with secondary progressive MS or progressive relapsing MS.

Study P310901 has two dose levels, 12 mg/m^2 and 5 mg/m^2, and study P310902 used a fixed dose of 20 mg, which is equivalent of 12 mg/m^2 to 14 mg/m^2 per cycle. The effectiveness of mitoxantrone 12 mg/m^2 has been established based on study P310901 and is supported by study P310902. There is also evidence of effectiveness of 5 mg/m^2 provided by study P310901. Among the 5 primary efficacy variables, the effectiveness of mitoxantrone 5 was shown in EDSS and adjusted number of treated relapses (p values 0.0098 and 0.0293, respectively, without adjustment).

There are several issues associated with the two studies. For study P310901 the primary analysis is a composite analysis of five primary efficacy variables. The sponsor stated that the method is based on Wei and Lachin's paper titled "Two-Sample Asymptotically Distribution-Free Tests for Incomplete Multivariate Observations" published in Journal of American Statistical Association in 1984. The software, SmarTest, for the composite analysis was developed in Germany. Although the software is provided by Immunex for the review, the source code is unavailable and the validation of the software can not be confirmed. Therefore, the conclusion about the efficacy of study P310901 is heavily weighted on the efficacy results from the five individual efficacy variables.

There are two main issues in study P310902: 1) it is an open-label study; and 2) the primary endpoint is a MRI measurement. The issue of open-label nature of the study has been discussed in Section 2.9. The issue of using a MRI measurement as the primary efficacy endpoint is that MRI has not yet been validated as an indication of multiple sclerosis, and the correlation between clinical outcomes and MRI measures has yet to be established. The efficacy evidence shown in EDSS scores has contributed an important part to the conclusion of the treatment effect for this study.

/S/

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