CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

MEDICAL REVIEW(S)

SEP - 1 2000

Review and Evaluation of Clinical Data
Safety Team Leader Comments

NDA: 21-120
Sponsor: Immunex Corporation
Drug: Novantrone™ (mitoxantrone)
Material Submitted: Immunex' response to Division comments on Final Protocol for Phase IV Safety Study and Primary Reviewer's Evaluation of sponsor's response
Correspondence Date: 8-10-00
Date Received: 8-10-00, 8-28-00, 8-31-00
Date Review Completed: 9-1-00

I have read Dr. Boehm's review of the Immunex's response to the Division comments on the Novantrone Phase IV safety study and concur with his conclusions.

At this juncture, there are two points that still need to be addressed with the sponsor:

1. On page 7 of the CRF, in the "Infection Table", two additional pieces of information need to be recorded: ANC nadir and duration of neutropenia. Spaces for this information could be included in the column "Associated with severe neutropenia?"

2. The sponsor has amended the protocol to include pregnancy tests prior to each dose for those women of childbearing potential *who are not receiving birth control pills* (my emphasis). Since oral contraceptives do not protect against pregnancy 100% of the time, pregnancy testing prior to Novantrone therapy should not be conditioned on the type of contraception being used. All women should receive pregnancy tests prior to each Novantrone dose.

/S/
Judith A. Racoosin, MD, MPH
Safety Team Leader, DNDP

cc: NDA 21-120/Katz/Racoosin/Rouzer/Boehm

APPEARS THIS WAY
ON ORIGINAL

SEP - 1 200

Submission Review

NDA:	21-120
Drug Name:	Generic: Mitoxantrone Trade name: Novantrone™
Sponsor:	Immunex Corporation
Material Reviewed:	Review of sponsor's response to division comments About the proposed safety study, 8/10/2000, 8/28/2000
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	8/31/2000

Background

The sponsor has agreed to conduct a post marketing study to examine the safety of mitoxantrone when used to treat MS according to proposed labeling. The sponsor provided their proposed protocol for this safety study in a document dated 7/28/2000 and the division faxed our comments regarding the protocol to the sponsor on 8/7/2000. This document reviews the sponsor's response to the division's comments.

Review

A list of the division's comments about the sponsor's proposed protocol are included as an attachment to this document. For points 1, 2 and 3 the sponsor agreed with the division and incorporated the requested changes.

Division point 4 asked the sponsor to capture time since last dose, ANC nadir, and duration of neutropenia for patients with serious infections and neutropenia. The sponsor changed the CRF to capture the date of the onset of infection and now would be able to calculate the interval between infection and last dose. They also stated that it was not standard of care to monitor patients post treatment, that they have carefully studied duration of neutropenia in their phase II study, and that the clinically relevant issue is the incidence of infection associated with ANC which the study addresses. The sponsor commented that they would not collect data regarding ANC nadir and duration of neutropenia. The division was not asking for monitoring of ANCs in all patients following dosing, but instead our intention was to capture relevant descriptive information for those patients who experienced the event of interest. If infection occurs in the setting of neutropenia, we feel that information about the duration and degree of neutropenia is relevant to assessment of the event and is necessary to document outcome. We consider this information pertinent and hope that it would be contained in a narrative of the event, but by requesting the information in the CRF, there would be a greater likelihood of capturing the data.

Division comment 5 asked for a list of investigators participating in the study and the sponsor responded that they would provide the list after NDA approval. They also commented that they had tentative agreement to participate from 31 investigators at this time.

Division point 6 requested that the protocol include pregnancy testing prior to each dose in females. The sponsor has amended the protocol to include pregnancy tests prior to each dose for those women of childbearing potential who are not receiving birth control pills.

Division point 7 asked for clarification about the length of follow up and the sponsor responded that all enrolled patients would be followed for 5 years regardless of time of enrollment.

Division point 8 asked for an update on the proposed retrospective dosing and monitoring study, the educational plan for physicians, and the marketing research assessment. The sponsor responded that they would provide a protocol for the retrospective study of dosing and monitoring 6 months after approval. They provided information to be contained in the physician starter kit but stated that the information won't be finalized until final labeling is agreed upon and DDMAC has reviewed the materials. The sponsor also reaffirmed their commitment to conducting a marketing research assessment to assess compliance with monitoring and safety guidelines but provided no new information.

Comments

The sponsor has incorporated most of the division's suggestions into their safety study protocol. Their refusal to gather information about ANC nadir and duration of neutropenia for patients with neutropenia and infections is somewhat puzzling and may be the result of a misunderstanding about our request.

/S/

Gerard Boehm, MD, MPH

/S/ 1-00

cc: Katz, Racoosin, Rouzer, Boehm

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Attachment- Division comments faxed to the sponsor about their proposed safety protocol.

The sponsor should address the following points.

1. The sponsor should clarify the EF monitoring schedule during visit 36 and the annual post treatment follow up exams (schedule is different on p.51, 53, and 58 of submitted protocol).
2. The sponsor should require investigators to record and report all pertinent information for *all* serious adverse events (not just "drug-related" ones).
3. The Supplemental Cardiac Function form included as part of the CRF should be changed to request results of **all** pertinent cardiac testing performed to evaluate a patient with CHF symptoms. Currently, the submitted Supplemental Cardiac Function form only inquires about treatment for CHF and ECG results.
4. For patients with serious infections and neutropenia, the case report form should request the time interval between the infection and the last Novantrone dose, the nadir for the ANC, and the duration of neutropenia.
5. The sponsor should forward a list of the study sites and investigators that are participating in the trial.
6. The current monitoring plan provides for a pregnancy test only prior to enrolling in the study. Given the intermittent (every 3 months) dosing schedule, and the teratogenic effects of the drug observed in animals, pregancy tests should be administered prior to each dose.
7. Please clarify the length of patient follow-up. In the discussion of study duration (p. 42), the protocol states that "Patients will be enrolled within the first 2 years. Patients will then be followed for up to a total of 5 years, including treatment and follow-up periods." Because the drug-related cardiotoxicity does not develop until a certain exposure has been received, we think it is important to ensure that each patient is followed for the full five years. Thus, if a patient isn't enrolled until year 2, the overall study would exceed 5 years in length because this patient wouldn't complete their 5 year follow-up until year 6.
8. What is the current status of the programs discussed during the March 28, 2000 teleconference, specifically an "Assessment of Novantrone Dosing and Monitoring in MS in a Range of Practice Settings" and an "Educational Plan and Marketing Research Assessment".

REVIEW AND EVALUATION OF EFFICACY DATA

NDA: 21-120

APPLICANT: IMMUNEX

DATE SUBMITTED: June 2, 1999

DATE COMPLETED: September 10, 1999

GENERAL INFORMATION:

1a. Name of Drug

(1) Generic: Mitoxantrone

(2) Trade: Novantrone

(3) Chemical:

1,4-Dihydroxy-5,8-bis [[2-[(2-hydroxyethyl) amino] ethyl] amino]-9,10-anthracenedione di hydrochloride

b. Pharmacologic Category: Antineoplastic

c. Dosage Form: sterile aqueous solution containing mitoxantrone hcl at a concentration equivalent to 2 mg mitoxantrone free base per ml supplied in vials for multidose use as follows:
NDC 58406-640-03- 10 mL/multidose vial (20 mg)
NDC 58406-640-05-12.5 mL/multidose vial (25 mg)
NDC 58406-640-07-15 mL/multidose vial (30 mg)

d. Proposed New Indication

"Novantrone is indicated for the treatment of patients with secondary progressive multiple sclerosis, including progressive relapsing disease.

e. Legacy Information

Immunex is providing extensive legacy information from NDA 19-297 for Novantrone. The initial indication under NDA 19-297 was acute non-lymphocytic leukemia (ANLL), approved on December 23, 1987. Most of the data of Nonclinical Pharmacology and Toxicology and Human Pharmacokinetics and Bioavailability have been extracted from NDA 19-297 and reproduced for inclusion in this NDA. Carcinogenicity and toxicology studies and most of the nonclinical pharmacology studies are from the original NDA 19-297

2. CMC
(under review by Dr. Broadbent)

3. Pharmacology

(under review by Dr.Roney)

Pharmacokinetics
In humans mitoxantrone given I.V. follows first order elimination kinetics with a rapid initial distribution phase and a prolonged second phase. The pharmacokinetics in humans has been described as either biphasic or triphasic. There has been some variability in pharmacokinetic parameters in humans from study to study but the following values are representative: t1/2 alpha 0.2 hours, t1/2 beta 37.4 hours. Mitoxantrone is rapidly and extensively distributed to tissues except the nervous system. The drug is excreted unchanged, primarily through the bile, and 2 metabolites, the mono and dicarboxylic acid derivatives have been identified in the urine. Serum concentrations of several hundred to thousand nanograms/ml are attained in patients treated with 1 to 24 mg/M2. Mitoxantrone is highly bound to plasma protein and blood cells. Mitoxantrone is poorly absorbed when given orally.

b. Pharmacodynamics

Mitoxantrone is a synthetic anthracenedione with cytocidal effect on prolifering and resting cells. Nucleic acid synthesis is inhibited through interaction with DNA and both RNA and DNA synthesis are affected.

The replacement of the amino sugar moiety of doxorubicin by a bis-substituted aminoalkylamino group was thought to reduce the cardiotoxic potential of this agent.

4.0 SAFETY REVIEW

(under review by Dr. Gerry Boehm)

APPEARS THIS WAY
ON ORIGINAL

5.0 STATISTICAL REVIEW

(under review by Sharon Yan)

6.0 Clinical Background

Mitoxantrone has been studied under the sponsor's [redacted] and also under the NCI sponsored [redacted] This drug has undergone extensive Phase II testing in a large number of studies and activity was noted in breast cancer, lymphoma, leukemia, and non-small lung cancer. No significant activity has been noted in small cell lung cancer, melanoma, sarcoma, renal hepatic, pancreatic, colon, head and neck and gastric carcinomas. Conclusions regarding activity in multiple myeloma, ovarian, cervical and prostate carcinoma are not complete. Toxicity has been myelosuppression and gastrointestinal. Conclusions regarding cardiotoxicity are preliminary.

7.0 Clinical Categories of Multiple Sclerosis

Disease Category	Definition
Relapsing Remitting	Episodes of acute worsening (relapses) with recovery and a stable course between relapses
Secondary Progressive	Gradual neurologic deterioration with or without acute relapses in a patient who previously had relapsing-remitting MS
Primary Progressive	Gradual, nearly continuous neurologic deterioration from the onset of symptoms

Progressive relapsing	Gradual neurologic deterioration from the onset of symptoms but with superimposed relapses

8.0 Foreign Marketing History

Mitoxantrone is currently approved in the following countries for one or more of the following indications: 1) in combination with other approved drugs, for the initial therapy of acute non-lymphocytic leukemia in adults 2) for the treatment of advanced breast cancer 3)for the treatment of hepatoma, 4) for the treatment of non-Hodgkin's lymphoma, and 5) for the treatment in combination with corticosteroids as initial chemotherapy for patients with pain related to advanced hormone-refractory prostate cancer:(see attachment E).

9.0 Clinical Studies

The safety and efficacy of Novantrone in multiple sclerosis were assessed in two randomized, multicenter clinical studies. Study 0901 used a protocol –based composite primary endpoint consisting of 5 variables whereas Study 0902 used MRI as the primary endpoint.

Protocol 031.0901 This is a multicenter, observer-blind, randomized, placebo-controlled Phase III study to evaluate mitoxantrone in patients with secondary progressive or progressive-relapsing MS , using a three-group parallel design of 12 mg/M2 or 5 mg/M2 of mitoxantrone or a matched placebo, administered intravenously every three months for 24 months..

Note: After submission of the NDA, a number of errors were discovered in the Final Clinical Study Report for Study 031.0901, Most of the corrections were to the SmarTest output tables. This reviewer has inspected these tables and discovered that none of the errata are significant or change the statistical significance of the test.

Diagnosis and Main Criteria for Inclusion:

- -Definite, clinically or laboratory supported MS as defined by the Poser criteria
- -Progressive relapsing or secondary progressive MS in an active stage with evidence of deterioration
- -EDSS from 3 through 6
- -age 18 to 55
- -standard lab tests within the normal range
- -negative pregnancy test at enrollment, and agreement to practice effective contraception throughout the study

Number of Patients
Patients Planned: 180
Patients Enrolled: 194
Patients included in efficacy analyses:188
Patients included in safety analyses: 191

Study Drug, Dose and Mode of Administration:
Patients received mitoxantrone at a dose of 12mg/m2 or 5mg/m2 administered intravenously at 0, 3, 6, 9, 12, 15, 18, and 21 months.

Reference Therapy, Dose and Mode of Administration:
A placebo consisting of 3 mg methylene blue in 15 mL was administered intravenously at 0, 3, 6, 9, 12, 15, 18, and 21 months

Selection of Doses in the Study
The mitoxantrone dose of 12 mg/M2 was selected because it had the most favorable risk/benefit profile in Phase I-II studies. The treatment arm of 5 mg/M2 was included to determine whether a lower dose of mitoxantrone was also effective in slowing disease progression. Treatment at a

lower dose allows patients a longer interval of treatment before close monitoring of cardiac status is necessary.

Disposition of Patients

There were 194 patients enrolled into the study in four European countries: Germany, Belgium, Hungary, and Poland. (see Table 10.1.A) The first patient was randomized on June 2, 1993 and the last patient finished the study July 10, 1997. Of the 194 patients enrolled in the study, 149 completed the study. Three patients withdrew after randomization and before receiving study drug, three were not evaluated for efficacy after a single dose of study, and 39 withdrew prematurely from the study . (see Table 10.1.B,attached)

Patient Withdrawals

One patient in each study group withdrew after randomization and before receiving any study medication:

-Patient 5309 (PBO) had an EDSS of less than 3 on the day of scheduled Month 0 administration and was withdrawn because of ineligibility.

-Patient 5312 (5 mg/m2 mitoxantrone) disclosed a history of tachycardia on the day of scheduled Month 0 administration and was withdrawn at the physician's request.

-Patient 5701 (12 mg/m2 mitoxantrone) disclosed that she had used corticosteroids intermittently during the preceding weeks and had experienced gi bleeding prior to first scheduled study drug administration.

Three patients discontinued from the study after receiving a single administration of study medication but without having the Month 3 efficacy evaluation:

-Patient 1106 (5 mg/m2 mitoxantrone) refused further treatment

-Patient 5004 (12 mg/m2 mitoxantrone) withdrew due to adverse laboratory event and a worsening of neurologic condition due to MS

-Patient 5311 (12 mg/m2 mitoxantrone) refused further treatment

These six patients were not included in the intent-to-treat efficacy analysis.

Thirty –nine patients withdrew prematurely from the study:17 patients in the PBO group, 10 in the 5 mg/m2 mitoxantrone , and 12 in the 12 mg/m2 mitoxantrone group. The following table 10.I.IA (attached) lists these patients and their reasons for withdrawal from study.

Evaluation Criteria:

Clinical criteria included EDSS, AI, relapses, SNS, and other efficacy and safety parameters. Imaging by MRI was conducted in a predefined subset of patients.

Efficacy Evaluation

Assessment of the efficacy of mitoxantrone compared to PBO was based on the intent-to-treat cohort.(n=188).All patients randomized to the study were included in the intent-to-treat 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..

Disease History

Patients were diagnosed as having MS based on laboratory (54.3%) or clinical (45,2% assessments. Overall, the type of MS was classified as 'remmittent progressive (i.e.-progressive relapsing) or "secondary progressive" for equal numbers of patients

The mean number of relapses during the 12 months before entering the study was 1.34, and was not different between treatment groups. The mean duration of MS was 9.64 years overall, and the differences among treatment groups were not statistically significant

The mean deterioration in EDSS during the 18 months before study enrollment was 1.57 points. Eighty-nine patients (47.3%) had a deterioration of 1 point, 42 patients (22,.3%)of 1.5 points, and 33 patients (17,6%) of 2 points. The remaining 24 patients had deterioration in EDSS of between 2.5 and 5.5 points.

The mean EDSS for all patients before start of treatment was 4.6 (SD=1.01), The difference between treatment groups was not statistically significant..

The mean Ambulatory Index before start of treatment was 2.55 (SD=1.04) for all patients. Differences between treatment groups were not statistically significant.

The mean standard neurological status (SNS) before start of treatment was 19.72 (SD=7.63) for all patients, Differences between treatment groups was not statistically significant.. The table that follows summarizes disease characteristics of the ITT cohort at baseline.

Table 10.1.1.B (attached) summarizes the duration on study by treatment arm for patients who prematurely withdrew from the study.. There was no statistical difference in observation time for patients who did not prematurely discontinue 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 for patients of the 5 mg/m2 mitoxantrone group, and 385 days for patients of the 12 mg/m2 mitoxantrone group.

9.0 EFFICACY EVALUATION

Data Sets Analyzed

Assessment of the efficacy of mitoxantrone compared to placebo was based on the intent-to-treat cohort (n=188). All patients randomized to the study were included in the intent-to-treat 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.

Demographic Data

As shown in Table 11.2.1, no significant differences in baseline characteristics were found among the three treatment groups. Ninety –eight of the patients (52.1%) were female and 90 of the patients (47.9%) were male.There were more males in the placebo and the 12 mg/m2 mitoxantrone groups and more female patients in the 5mg/m2 mitoxantrone group. The mean age was 40 years. No statistically significant differences were found among the three treatment groups. There were no differences among treatment groups concerning height, weight, and body surface area. The mean LVEF was 66.7%, with no difference between treatment groups. The minimal ejection fraction was 50% and the maximal fraction was 87%. ECG were normal for 184 (97.9%) before the first drug administration, with 4 patients in the placebo group having abnormal ECGs. No pathological finding was seen by chest X-ray in any patient.

Concomitant Medication

One hundred twelve (59.6%) patients were receiving medication at baseline: muscle relaxant (20 PBO) 10 Mitox 5, 7 Mitox 12, vitamins, symptomatic urologic drugs, and minerals

Disease History

Overall, the type of MS was classified as "remittent progressive" (i.e. progressive relapsing) or "secondary progressive" for equal numbers of patients. The slightly higher percent of patients in the 5 mg/m2 group with progressive relapsing disease was not statistically different from the other groups. The mean number of relapses during the 12 months before entering the study was 1.34 and was not different between treatment groups. The mean duration of MS was 9.64 years overall, and the differences among treatment groups were not statistically significant.

The mean deterioration in EDSS during the 18 months before study enrollment was 1.57 points. Eighty-nine patients (47.3%) had a deterioration of 1 point, 42 patients (22.3%) of 1.5 points and

33 patients (17.6%) of 2 points. The remaining 24 patients had deterioration in EDSS of between 2.5 and 5.5 points.

The mean EDSS for all patients before start of treatment was 4.6 (SD=1.01). There were slightly more patients (26.7%) in the 12 mg/m2 mitoxantrone group who had a score of 3.0 or 3.5 compared to the 5 mg/m2 mitoxantrone group (17.2%) and the placebo group (15.7%). The difference between treatment groups was not statistically significant..

The mean Ambulatory Index before start of treatment was 2.55 (SD=1.04) for all patients. Differences between treatment groups were not statistically significant.

The mean standard neurological status (SNS) before start of treatment was 19.72 (SD=7.63) for all patients. Differences between treatment groups were not statistically significant.

Sponsor's Table 11.2.3 (attached) Disease Characteristics at baseline summarizes disease characteristics of the ITT cohort at baseline.

EFFICACY RESULTS

Statistical tests cited in this report were conducted for two-sided hypotheses. Since the protocol specified a one-sided analysis of the primary efficacy criterion, the one-sided analysis was also conducted..

The primary efficacy criterion was a multivariate test of 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, measured from the day of first study drug administration until the day of first sign of a relapse requiring corticorsteroid treatment.
-Change in SNS score at 24 months compared to baseline value

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 12 mg/m2 mitoxantrone and placebo groups.

All Mann-Whitney differences are greater than zero, including the lower limits of the 95% confidence intervals. Therefore, the multivariate Mann-Whitney difference is greater than zero and the error probability for rejecting the "null hypothesis" is $p<0.0001$.

The patients treated with 12 mg/m2 mitoxantrone showed significantly better ($p<0.0001$) results after 24 months of treatment than patients receiving placebo.

Because the global test of stochastic ordering showed a significant advantage for the 12 mg/m2 mitoxantrone group, all five primary efficacy variables were tested separately, with alpha = 0.05, according to the closed test procedure.

The sequence of testing (EDSS,AI, number of relapses requiring corticosteroid treatment, time to the first relapse requiring such treatment, and SNS) was a priori ordered and tests were interpreted as "statistically significant" when p values were less than 0.05. After the first test that was found to be not significant, no further testing was to be performed and differences between groups were to be regarded as "not significant" for the remaining variables.

EDSS

Sponsor's Table 11.3.1.2. (attached) gives an overview of the results for the primary efficacy variables and shows that all variables were significantly better (2-sided tests) in the 12 mg/m2 mitoxantrone group. As shown in sponsor's Table 11.3.11.2.1.A (attached), 12 patients in the 12

mg/m2 mitoxantrone group, 18 patients in the 5mg/m2 mitoxantrone group, and 7 patients in the placebo group showed an improvement of at least 1 point in EDSS. Deterioration of at least one point in the EDSS was seen in sixteen patients in the placebo group compared to 10 patients in the 5 mg/m2 mitoxantrone group and five patients in the 12mg/m2 mitoxantrone group. 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.

AI

Four patients in the placebo group showed an improvement in AI, compared to 12 patients in the 5 mg/m2 mitoxantrone group and 12 patients in the 12 mg/m2 group. Deterioration in AI was most frequently seen in the placebo group (n=28, 43.8%) compared to patients in the 5 mg/m2 mitoxantrone group (n=20,31.3%) and patients in the 12 mg/m2 mitoxantrone group (n=20, 33.3%). See sponsor's Table 11.3.1.2.2.C Test Results for AI. This revised Table corrects SmarTest output for PBO vs.Mitox 5" comparison.

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 (Patient No. 5806; adjustment=1.071). The total adjusted number of treated relapses is summarized in sponsor's Table 11.3.1.2.3.A; the difference between the placebo and 12mg/m2 mitoxantrone groups was significant (p=0.0002). The mean adjusted number of treated relapses per patient during the 24-month study period was higher in the placebo group (mean=1.20) than in the 5 mg/m2 mitoxantrone group (mean 0.73) and the 12 mg/m2 mitoxantrone group (mean=0.40).

Patients receiving placebo had significantly more treated relapses than did patients receiving 12 mg/m2 mitoxantrone (p=0.0002) and patients receiving 5 mg/M2 mitoxantrone (p=0.0293). The difference between the two mitoxantrone groups was not significant.

Time to First Treated Relapse

There was a significant difference in time to first treated relapse between the placebo and 12 mg/m2 mitoxantrone groups (p=0.0004; log rank test). 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 groups. Therefore, the 25th percentile is given as a descriptive measure. The 25th percentile for time to first treated relapse was 6.7 months for the placebo group and 20.4 months for the 12 mg/m2 mitoxantrone group, a difference of 13.7 months. The difference in 25th percentiles for patients receiving 5mg/m2 vs 12 mg/m2 was 13.5 months. The difference between the two mitoxantrone groups was not statistically significant.

Overall Rating of Observer

The blinded observer rated the efficacy of the study treatment at the 24-month assessment as "none", "fair", "good" or "very good"... For 26 patients (43%) in the 12 mg/m2 mitoxantrone group the rating was "good" or very good" compared to 11 patients (17%) in the placebo group (p=0.001). For patients in the 5 mg/m2 mitoxantrone group, the ratings were also significantly better than for patients in the placebo group (5mg/m2 mitoxantrone:n=37, 42%) (p=0.002).

MRI

MRI was performed for a subgroup of 110 patients at predefined centers.

Patient Discontinuations or Missing Data

Except for 6 patients who did not receive study drug (n=3) or had no follow-up evaluation (n=3), all patients who discontinued prematurely were included in the intent-to-treat analysis. If data were not available for assessment at 24 months because a patient left the study prematurely or had

no measurement at the Month 24 visit, the last available result before that time was used to calculate the intra-individual differences (last value carry forward).

The number of relapses was adjusted for an observation period of 24 months as follows:

> The mean number of relapses was calculated for patients in the placebo group at six month intervals, i.e. up to Month 6, Month 6 up to Month 12, Month 12 up to Month 18, and Month 18 up to Month 24. The calculated means were 0.56, 0.59, 0.54, and 0.32. From these six- month rates, a daily rate of relapse was calculated.
>
> For each patient, the missing number of days up to the period of 24 months was multiplied by the relapse rates for the placebo group during the corresponding 6-month interval and added to the number of relapses actually observed for the patient.

The sponsor's approach is based on the hypothesis that placebo has no effect on the rate of relapses. Assignment of the rate from the placebo group to the missing days in the mitoxantrone Group is expected to reduce the potential difference in treatment effect for the comparison of the 12 mg/m2 mitoxantrone and placebo groups

The sponsor suggests there is a possibility for bias favoring the mitoxantrone group if discontinuation in the groups is not independent of success and is unequally distributed among groups. If all patients in the placebo group with unsuccessful treatment discontinued early, only those patients without relapses will remain in the study. This would result in a biased low estimate for the relapse rate in the placebo group and therefore adjustment would favor the mitoxantrone group. When the time of onset of a relapse was unknown, it was assumed that the relapse had happened one day after the last visit of the patient to the treating physician. This assumption was made for 24 relapses.

Interim Analyses and Data Monitoring
No interim analysis was done. A statistical steering committee developed an analysis plan for statistical evaluation. Monitoring was performed by the sponsor at 6 to 8 week intervals.

Effect of Center Pooling on Analyses
To assess the effects of multiple centers on the study, an analysis of covariance on the efficacy variable "Change in EDSS" was performed. For this analysis, all centers that had enrolled at least 12 patients were assessed individually. Centers that had enrolled 8 to 11 patients (Center Nos. 34.5, 13, and 53) were combined as a single center, as were centers with 1 to 7 patients (Center Nos. 10,11, 12, 50, 54, and 56). The mean changes in EDSS at Month 24 compared to baseline are tabulated by the sponsor for the pooled center groups.. Although there is some heterogeneity among centers , the analysis of variance showed no significant influence of the centers (F-value=1.23, df=8, p=0.2832). The differences between the placebo group and the mitoxantrone groups remain statistically significant after this adjustment (F-value =3.22, df=2, p=0.0421. Since the protocol-specified primary response criterion is a multivariate test of stochastic ordered alternatives based on the five primary efficacy variables, no adjustment of alpha levels is needed.

Use of an "Efficacy Subset" of Patients
In order to analyze the true efficacy of the treatment with 12 mg/M2 mitoxantrone for 24 months and to evaluate possible bias introduced by the 'last –value-carried-forward" principle that was applied to those patients who either had no assessment at Month 24 or for whom there were severe violations of the study protocol, two different efficacy subsets were created:

Per Protocol Cohort I: included all patients from the ITT cohort except those who had severe protocol violations or were prematurely withdrawn from the study because of reasons not related to the disease (lost to follow-up and compliance)

Per Protocol Cohort II: included all patients from Per Protocol Cohort I except those who were prematurely withdrawn from the study because of lack of efficacy or adverse events.

Per Protocol Cohort I consisted of 54 patients in the placebo group, 56 patients in the 5 mg/m2 mitoxantrone group, and 52 patients in the 12 mg/m2 mitoxantrone treatment group.

Statistical estimates of the differences between the placebo group and the 12 mg/m2 mitoxantrone group in primary efficacy variables were nearly unchanged from those of the ITT cohort. Differences between the 12 mg/m2 mitoxantrone and placebo groups (except for AI) remained statistically significant, although there was a loss in power because of the smaller sample size. The number of relapses was reduced due to exclusion of patients, but differences between the treatment groups remained of the same magnitude as those of the ITT cohort.

Per Protocol Cohort II
Per Protocol Cohort II consisted of 44 patients in the placebo group, 53 patients in the 5 mg/m2 mitotoxantrone group, and 43 patients in the 12 mg/m2 mitoxantrone group. Thus, the sample size was reduced by about 30% from the ITT cohort.

Because patients who had an adverse event or showed lack of efficacy were excluded, the changes in EDSS, AI, and SNS are smaller for the placebo group and more pronounced in patients treated with 12 mg/m2 mitoxantrone. Nevertheless, the trend of the differences between the treatment groups remained unchanged. The number of relapses was reduced to about 50% that of the ITT cohort, but the differences between the treatment groups was still statistically significant.

The analyses of efficacy subsets show an improvement in variables related to neurological signs of MS and in the number of relapses patients had during the 24-month study period. This is the consequence of excluding patients who showed progession, especially in PerProtocol II.

The absolute difference between the group receiving placebo and those receiving 12 mg/m2 mitoxantrone remains stable, and the advantage of the 12 mg/m2 treatment is still demonstrated. Although the power of the statistical tests is reduced by the smaller sample sizes of the groups, most of the differences remained statistically significant.

10.0 Evaluation of MRI

Magnetic resonance imaging (MRI) was performed for a subgroup of 110 patients at predefined centers. Non-enhanced (T2 weighted) and gadolinium (Gd)-enhanced, T1 weighted MRIs were performed at baseline, Month 12, and Month 24. The centers were selected based on their ability to perform the MRI scans according to protocol requirements. MRI results were not available for all patients at all time points. All MRI images were analyzed at a central facility by two experienced readers who were blinded to the patient's clinical status and randomized treatment. The two reviewers evaluated the MRI scans independently, then together arrived at a consensus.The prognostic significance of the MRI findings in this study has not been evaluated.

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. Numbers of patients enrolled in the MRI subgroup are summarized by treatment arm in the sponsor's following table.

Tabulation of Individual. Response Data
The following table lists (11.3.3 attached) data for the principal response variable for individual patients in each treatment group.

The efficacy variables defined in the protocol are reasonable choices and have been used for other studies in MS. However, they do not cover all aspects of the disease and might therefore give a biased result for recommendation of treatment. To determine whether the choice of other

aspects of these variables would have given different results, the applicant performed sensitivity analyses on two of the five primary efficacy variables (EDSS and number of relapses)

Sensitivity of EDSS
Change in EDSS was defined as the intra-individual difference between the baseline and Month 24 assessments. Thus change in EDSS is a summary of effect over the entire study period and does not take into account changes noted in individual patient visits during the study.:

-absolute change in EDSS from baseline
-deterioration of at least 1-point at the end of the study
-deterioration of at least one point during the study
-deterioration of at least 0.5 confirmed after 3 months during the study
-deterioration of at least 1 point confirmed after three months during the study
-deterioration of at least 1 point confirmed after 6 months during the study

The analysis (attached) shows that except for the modest change in EDSS (0.5 points for at least 3 months), approximately two to three times more patients in the placebo group showed deterioration compared to the 12 mg/m2 mitoxantrone.

All differences between the placebo and 12 mg/m2 mitoxantrone groups, except deterioration of at least 0.5 confirmed after 3 months, were statistically significant. An overview of the results is summarized in the following table: 11.3.5.1. (attached)

There were about three times as many relapses among patients receiving placebo as there were in patients treated with 12 mg/m2 mitoxantrone (113/39=2.89 ratio). This ratio relationship remained similar for the number of relapses (66/18=3.66 ratio), severe relapses (60/17=3.53 ratio) and relapse reported by the treating physician (63/21=3.0 ratio).

SUMMARY of EFFICACY
In this three arm, placebo-controlled, randomized Phase III study, mitoxantrone was administered as a 5-minute intravenous infusion at a dose of 5mg/m2 and12 mg/m2 every 3 months for 2 years to patients with secondary progressive or progressive relapsing MS.. Compared to PBO, Mitoxantrone significantly slowed the progression of neurologic impairment over the two-year period. Slowed progression resulting from mitoxantrone treatment was demonstrated by effects on EDSS, AI, SNS, the proportion of patients with confirmed 1-point EDSS deterioration, and the time to confirmed 1-point EDSS deterioration. Mitoxantrone also had a significant effect on the number of relapses requiring corticosteroid treatment, the time to the first relapse requiring such treatment, the total number of relapses, the number of patients free of relapses, and the time to first relapse regardless of treatment.

A clinical dose-response effect was evident: mitoxantrone given a 5 mg/m2 resulted in an effect that was generally intermediate between placebo and mitoxantrone given at 12 mg/m2..

This study provided efficacy of mitoxantrone at the dose 12 mg/m2. administered every three months for two years in patients with secondary progressive or progressive relapsing MS

.1 CLINICAL STUDY REPORT-031.0902. Multicenter, Randomized, Open –Label Study Evaluating the Efficacy of Mitoxantrone plus Methylprednisolone Vs.Methylprednisolone Alone for the Treatment of Multiple Sclerosis Using Magnetic Resonance Imaging (MRI)
Study Period: April 1992 to March 1995 (Phase of Development- Phase 2)

Objective: The objective of the study was to evaluate the efficacy of mitoxantrone in patients with MS by assessing the development of CNS inflammatory brain lesions using MRI with gadolinium (Gd) injections. The primary outcome criterion was the percentage of patients who developed new brain-lesions as seen on serial Gd-enhanced MRI scans performed each month.

Study Design

This was a multicenter, open label, randomized study in two parts: a two month triage period (Month –2 to Month 0) to screen patients for eligibility for randomized treatment Month –2 to Month 0: all patients received 2 monthly courses of methylprednisolone (1g/month IV) and had monthly MRIs. Month 0: Inclusion based on MRI criteria. Followed by a six month treatment period (Month 0 to 6). Patients who were eligible for the treatment period were to be randomlized into two parallel groups of at least 20 patients each and randomized to recieive 6 monthly courses of mitoxantrone (20 mg/month IV) plus methylprednisolone (1 g/month IV) or methylprednisolone (1 g/month IV) alone. Initially , patients were recruited in four French medical centers: Lyon, Paris, Toulouse and Rennes. Later, to expedite enrollment in the study, a fifth center was added in Bordeaux.

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 methylprednisolone ; and month 0, 30 days after the second course of methylprednisolone). 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 part 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. .

In order to demonstrate a 50% decrease in the incidence of new MRI lesions (chi-square test: alpha=0.05, beta =0.10), approximately 21 patients per group were determined to be necessary in the treatment part of the study.. Patients selected for enrollment in this study were expected to have more aggressive disease than patients evalulated by the published data of (Miller 1991) whose 88% of patient with untreated MS would be expected to develop new brain lesions on MRI lesions. A population of 40 patients was required to compare the efficacy of mitoxantrone plus methylprednisolone with methylpredisolone alone. The rationale for administering high dose methylprednisolone in both arms of the study was an ethical decision based on the fact that corticsteroids may provide a therapeutic benefit to patients with MS. At the same time, corticosteroids do not have a significant impact on MRI scans performed 4 weeks following administration. Methylprednisolone was administered intravenously as a single dose of 1 g per month following each scan.

In order to meet these criteria, 85 patients were clinically selected for enrollment in the triage period . Forty-two patients met MRI criteria and were randomized to receive study drug in the treatment period at the five centers: Bordeaux (n=4), Lyon (n=7), Paris (n=7), Toulouse(n=7, and Rennes (n=17).

Amendments

Three amendments were made to the protocol and approved by the Ethical Review Committee:
Amendment 1(03/16/92):
-Mandated that the maximum allowable cumulative doses of mitoxantrane were 160 mg/m2 for patients without risk factors and 120 mg/m2 for patients with risk factors.
-Mandated that a minimum granulocyte count (>1500 cells/mm3 and platelet count (>100,000/mm3) were required before another cycle of mitoxantrone could be initiated.
-Excluded patients who had received prior cardiotoxic drugs, such as cyclophosphamide and lithium
Added as an inclusion criterion a baseline left ventricular ejection fraction >50% by radioisotopic study or >40% by echocardiogram.

Amendment 2 (04/15/92):
-patients who discontinued from the study will not be replaced
-Change the "intent-to-treat" population to include all patients who had been randomized

Amendment 3 (11/30/92):
-changed the age of patients to be screened to 18 to 45 years (instead of 18 to 40 years in the original protocol)
-Changed the exclusion criteria to permit immunosuppressant therapy in the preceding year as long as it was less than 3 months in duration and was discontinued at least 3 months prior to entry in triage period.

Percentage of patients with New Gd-Enhanced MRI Lesions
The primary outcome criterion was the percentage of patients who developed new brain lesions as seen on serial Gd-enhanced MRI scans performed each month.. MRIs were performed locally at each neurology center. The MRI imaging protocol followed the criteria proposed by the European Concerted Action guidelines (Miller 1991). Axial 5 mm-thick slices were obtained through the brain with proton density and T2 weighted spin-echo (SE) images before contrast, as well as a T1-weighted SE sequence after injection of 0.1 mmol/kg Gd DTPA.. A central treatment –blinded analysis of MRI scans was performed by two experienced investigators from the [redacted] who were blinded to the clinical data.

Clinical assessments were made by EDSS at Months –2,-1,0,1,2,3,4,5, and 6. Secondary criteria were the mean numbers of new and total Gd-enhanced brain lesions per month and per patient..

Assessment of Exacerbation
Exacerbations, documented by neurology examination, were defined as the occurrence of neurologic dysfunction symptoms. The symptoms must have appeared after a 30-day period of stability or improvement and lasted for more than 2 days. An MRI scan was routinely performed during each exacerbation. . Additional methylprednisolone treatment at 1 g per day IV for 3 days was allowed to treat exacerbations. Only patients who developed at least one enhanced MRI brain lesion during the two month triage period were randomized to the treatment period.

Mitoxantrone and methylprednisolone were administered once a month from Month 0 through Month 5, for a total of six courses. All assessments for safety and efficacy (including the MRI) 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/m2 per cycle)

Patients were enrolled in five centers in France. Eighty-five patients fulfilled the clinical criteria for inclusion in the triage phage of the study. Forty-one of these patients were excluded after the two-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 numbers of patients enrolled in the triage phase (Month-2) compared to the treatment phase (Month 0) were consistent across the five sites. Thirty-seven patients completed the treatment phase of the study per the protocol and five were prematurely withdrawn due to marked deterioration due to disease. The five patients withdrawn from the study were all in the methylprednisolone-alone arm.

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. Patient No. 304 was randomized to the mitoxantrone-plus-methylprednisolone group, received one dose of study drug, and was withdrawn by the treating physician on Day 1 due to an increase in liver enzymes (ALT and AST). These biochemical abnormalities were considered by the investigator to be due to fluoxetine and were unrelated to study drug. Patient No. 205 was randomized to the methylprednisolone –alone group, received one dose of methylprednisolone, and was withdrawn by the investigator on Day 21 due to rapid disease progression.

Protocol Violations
A major protocol violation occurred at Center 2 with Patient No.204. The patient was randomized and a treatment group was assigned before the results of the MRI scan at Month 0 were available. It was subsequently discovered that there were no new lesions on MRI. As a result, the patient was never treated with study drug and was not included in the intent-to-treat analysis.

Minor Protocol Violations
Four patients were randomized in the treatment phase of the study with minor protocol violations and were included in the analyses for efficacy and safety. Three minor protocol violations occurred at randomization in Center 1 regarding a mix-up of drug sets. At Center 3, one patient had a non-interpretable MRI scan at Month-2. Therefore, the MRI scan at Month 0 was actually the second and not the third of the triage series. However, at Month 0, this patient was erroneously randomized to drug set No.306 in the mitoxantrone-plus-methylprednisone group, and assumed that identification for the remainder of the study. Therefore, no patient was actually identified for drug set No. 305 in this study.

Several other additional patients were enrolled in the study despite minor exclusion or inclusion deviations .

Of the 85 patients fulfilling the clinical inclusion criteria for the triage phase, 41 were subsequently excluded before randomization to the treatment phase. Two other patients were randomized, received one course of therapy, and then were withdrawn from study at the request of the Study Chair. The reasons for exclusion of the 43 patients are as follows:

-36 had no new brain lesions on MRI
-three had borderline abnormalities on echocardiography
-three had clinical adverse events during triage precluding entry or continuation on study
-one had a severe exacerbation at entry and was too ill to be continued on study

A summary of patient flow in the study is shown in the applicant's diagram that is attached (figure 5.1.3)

Withdrawal from Study
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 withdrawal were a marked deterioration in MS and lack of therapy effectiveness. Withdrawals were not due to adverse advents. Patients had to stop treatment when any MRI scan was more than 15 days beyond the scheduled time required by the protocol. For all the patients who withdrew, effectiveness was judged "null" and safety "good" by the applicant.

All five patients who withdrew prematurely from study had highly active disease by both clinical and MRI criteria. The data in Sponsor's Table 5.1.4. document the severity of disease progression in these five patients. Three of these five patients were subsequently treated with immunosuppressive agents, a common practice in France for severe active MS. Two patients received mitoxantrone and one received total lymphoid irradiation.

There were no differences between the groups in age, duration of disease, and total number of exacerbations since onset of MS. The average numbers of exacerbations within the previous 12 months were 2.4 and 3.1 in the methylprednisolone –alone group and the mitoxantrone-plus-methylprednisolone group, respectively (no statistically signiificant difference). Six patients in the methylprednisolone-alone group had secondary progressie 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 statistical difference). The EDSS at clinical inclusion was moderate to severe in both groups, indicating

relatively severe handicaps with respect to disease duration (no statistically difference). In addition there was no difference between the two groups with respect to the Ambulation Index.

Eleven patients in the methylprednisolone-alone group and six in the methylprednisolone-plus-mitoxantrone group received methylprednisolone or prednisolone to treat exacerbations during the study. Three of the patients listed in the methyprednisolone –alone group (Nos. 201,401, and 403) subsequently withdrew from the study, due to an apparent lack of effectiveness of the treatment Applicant's (Table 5.3)attached summarizes the number of courses received by the 42 patients who were included in all efficacy and safety analyses. The dose of mitoxantrone administered in this study was 20 mg IV once per month. For purposes of comparison with other studies of mitoxanthrone in patients with MS, the mean dose per square meter of body surface area was calculated, resulting in an overall mean (for all patients and courses) of 11.9 mg/m2 (range 10.1 to 14.8 mg/m2). The cumulative mean dose over patients was 81.2 mg/m2 (range 61.6 to101.0 mg/m2.

MRI Findings

To qualify for randomization in the treatment phase of the study, patients must have had at least one new Gd enhanced brain lesion during the 2-month triage phase At randomization for treatment (Month 0), the percentage of patients without new Gd-enhanced brain lesions 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 new 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 patient without new lesions increased to 31.3% (n=5/16) during the same time period. As shown in applicant's Table 6.1.1 and figure 6.1.1 (attached) patients in the mitoxantrone-plus-methylprednisolone had consistently better MRI results than those in the methylpredisolone-alone group and differences between the groups were significant at Month 2 (p=0.009, Months 3 and 5 (p=0.030 and p=0.033, respectively). The conclusions in Table 6.1.1. are not altered if the two patients who were randomized and then withdrawn after receiving one course each of study drug are 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).

Mean Number of Gd-Enhanced Lesions

During the triage period, the mean monthly number of new Gd-enhanced brain lesions was 6.8 (Month-1) and 4.6 (Month 0) in the mitoxantrone-plus-methylprednisolone group and 9.1 (Month-1) and 5.1 (Month 0) in the methylprednisolone-alone group. During the six-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. As shown in Table 6.1.2.A, the number of new Gd-enhanced lesions was significantly lower in the mitoxantrone-plus-methylprednisolone group every month from Month 1 through Month 6.

Sponsor's Table 6.1.3.A(attached) displays the monthly mean total number of Gd-enhanced brain lesions (i.e., new lesions plus persisting lesions) in the two treatment arms. The total numbers were significantly lower from Month 1 to Month 6 in the mitoxantrone-plus-methylprednisolone group compared to the methylprednisolone-alone group.

Table 6.1.3.C (attached) displays the number of new and total Gd-enhanced lesions per scan over time. In the mitoxantrone –plus-methylprednisolone, new and total Gd-enhanced lesions were significantly lower in the treatment period compared to the triage period. In contrast, there were no statistically significant differences between triage and the treatment period in the methylprednisolone-alone group.

The number of new brain lesions on T2-weighted scans between Month 0 and at Month 6 were compared. New T2-weighted lesions at end of study were recorded and categorized as small,

moderate, or large. As shown in Table 6.1.4(attached), the mean number of new T2-weighted lesions were consistently lower in the mitoxantrone-plus-methlprednisolone group, and was statistically significant for all new lesions as well as the moderate and large lesion categories.

There were significant differences in EDSS between the two groups during the treatment period. As shown in Table 6.2.1.A (attached), mean monthly EDSS values were consistently lower in the mitoxantrone –plus –methylprednisolone group for all six months of treatment but not statistically lower except for Month 4. . Decreasing EDSS values indicate improvement in disability.

Also shown in Table 6.2.1.A, mean changes in EDSS from baseline at month 1 (i.e.delta EDSS) were consistently better in the mitoxantrone-plus-methylprednisolone group, with a mean change of –0.3 at month1 and –1.1 at month 6. Thus mean EDSS improvement in the mitoxantrone-plus-methylprednisolone was 1.1 +1.1 (+SD) after 6 months of treatment. In contrast, mean EDSS in the methylprednisolone-alone group deteriorated progressively from Month 1 to Month 4. At six months, the methylprednisolone-alone group had a mean EDSS improvement of only 0.1 +1.1. The detected improvement in the methyprednisolone –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 neurologic deterioration. Overall, mean EDSS changes were significantly better in the mitoxantrone-plus-methylprednisolone group compared to the methylprednisolone-alone group each month from Month 2 to Month 6.

The number of patients with a 1-point EDSS improvement between Month 0 and the last month on treatment was also significantly higher in the mitoxantrone –plus-methyprednisolone group (14%vs 57% p=0.004). As shown in Table 6.2.1B(attached) 12of 21 patients in the mitoxantrone-plus-methylprednisolone group improved by one point or more on the EDSS and only one deteriorated... In contrast, in the methylprednisolone –alone group, six patients deteriorated by one point and only three patients improved by one point (overall p=0.008).

As shown in sponsor's Figure 6.2.1, an intent-to-treat analysis using the value obtained in the preceding month (last observation carried forward analysis) for the five patients who withdrew due to disease progressive also showed significant differences between the two treatment groups from Month 2 to Month 6.

Exacerbations

During the 2-months triage period, the mitoxantrone-plus-methylprednisolone group and the methylprednisolone groups had a total of 11 and 10 exacerbations, respectively. The calculated annual rate of exacerbations were 3.1 and 2.9, respectively, which were similar to the 12 preceding months (Table 6.2.2 ,attached). During the 6 –month treatment period, there were fewer exacerbations in the mitoxantrone-plus-methylprednisolone (7 vs.31) in the methylprednisolone-alone group). This effect was even more pronounced during the last four months of treatment (1 vs. 19 exacerbations). The calculated annual exacerbation rate by patient during the study was 0.7 in the mitoxantrone-plus-methylprednisolone group, significantly lower than the rate of 3 in the methylprednisolone-alone group (p=0.003). During the 6-month treatment period, seven courses of high-dose corticosteroid treatment were prescribed for exacerbation in the mitoxantrone-plus-methylprednisolone group compared to 21 courses of corticosteroid treatments in the methylprednisolone-alone group.

During the 6-month treatment period, the number of patients free of exacerbations was 14 out of 21 (67%) in the mitoxantrone-plus-methylprednisolone group compared to 7 out of 21 (33%) in the methylprednisolone-alone group (p=0.031).Figure 6.22 shows the number of new exacerbation each month in the two treatment groups.

There were no significant differences observed between the two groups in the Ambulation Index from Month 0 to Month 6

EFFICACY SUMMARY

The applicant's intent was to enroll a subset of MS patients with very active disease. The combination of clinical and MRI criteria used to qualify patients for this study was successful: during the 2-month triage period, patients enrolled in the treatment phase had an annualized rate of about three exacerbations, whereas patients who were excluded from treatment based on MRI criteria had fewer exacerbations. The three monthly MRI assessments generated sufficient baseline data to provide a reasonably accurate assessment of lesion frequency.

The randomization achieved comparable patient characteristics between the two groups at baseline with respect to demographics (age, gender, race) and disease status (neurological signs, EDSS, age at onset of MS, duration of MS, number of exacerbations). Eighty-five patients were clinically assessed for the 2-month triage period: 42 of those 85 patients qualified by MRI assessment to be randomized for the 6 month treatment period, 21 in the mitoxantrone-plus-methylprednisolone group and 21 in the methylpredisolone-alone group.The numbers of patients enrolled in the triage phase compared to the treatmen; phase were proportionate at each site.

Blinding of the patients in this trial was not possible due to side effects from mitoxantrone .would be likely to unblind the study drug. Blinding of the treating physician was also impractical due to the expected neutropenia. associated with mitoxantrone . To provide an unbiased analysis of the primary endpoint, MRIs were reviewed centrally by observers who were blinded to study drug and to clinical data.

Since corticosteroid treatment has been shown to shorten the duration of exacerbations of MS (Rose 1970, Beck 1992), it has been considered unethical to withhold such treatment from these patients with very active MS. In this study, patients on the control arm received 1 gm of methylprednisolone each month: 11 of these 21 patients also received one to four additional courses of high dose corticosteroids to treat severe exacerbations while on study. Despite treatment with high dose corticosteroids, the number of patients with new Gd-enhanced MRI brain lesions decreased only slightly in the control arm, with a slight increase in mid-study in the mean total number of MRI lesions. These findings were comparable with the premise that about 80% of patients with MS will have progression of disease as shown on MRI without treatment. In the methylprednisolone –alone group, the moderate MRI improvements at end of study were not associated with meaningful clinical benefit since the exacerbation rate and EDSS did not improve in the control arm, and five patients in this group withdrew from the trial because of severe deterioration.

The recommended dosage of mitoxantrone is 12 mg/m2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.

The methodology of this trial did not address the question of whether the addition of corticosteroids to Mitoxantrone had an effect additive to that of mitoxantrone alone. In this trial, efficacy data beyond the 6-month study period were not collected.

The inclusion criteria used in this study were specifically aimed at selecting patients with severe MS. The number of patients enrolled was sufficient to show significant improvement in radiological and clinical parameters with mitoxantrone. The study had shown that in MS patients with very active disease, mitoxantrone was effective in improving both clinical and MRI indicators of disease activity over a 6-month period .

OVERALL EFFICACY SUMMARY

The sponsor has submitted data from two European trials, 0901 and 0902 to support efficacy.of mitoxantrone in severe MS, that is, secondary progressive and progressive relapsing disease..Study 0901 uses a composite primary endpoint consisting of 5 variables and Study 0902 uses MRI as the primary measure of efficacy which is read by two blinded readers. Except for some minor protocol violations, the conduct of the two studies appears to be satisfactory. The design of the two studies is quite different however they tend to support each other. The dose

selected is 12 mg/m2 although the 5 mg/m2 was examined in study 0901 and 20 mg/m2 was the dose employed in the study 0902.

/S/

Janeth Rouzer-Kammeyer

cc.
orig. NDA 21-120
HFD-120/ Div. File
HFD-120/Rkatz/J Rouzer-Kammeyer
Novotrone doc
Sept 10,1999

E. Foreign Marketing History

Mitoxantrone is currently approved in the following countries for one or more of the following indications: 1) in combination with other approved drugs, for the initial therapy of acute non-lymphocytic leukemia in adults, 2) for the treatment of advanced breast cancer, 3) for the treatment of hepatoma, 4) for the treatment of non-Hodgkin's lymphoma, and 5) for the treatment in combination with corticosteroids as initial chemotherapy for patients with pain related to advanced hormone-refractory prostate cancer:

Argentina	Ecuador	Indonesia	Mexico	Saudi Arabia
Aruba	Finland	Iraq	Netherlands	Singapore
Australia	France	Ireland	New Zealand	South Africa
Austria	Germany	Israel	Nicaragua	Spain
Bahrain	Greece	Italy	Norway	Sweden
Belgium	Guatemala	Japan	Pakistan	Taiwan
Brazil	Honduras	Jamaica	Panama	Thailand
Chile	Hong Kong	Korea	Paraguay	United Kingdom
Columbia	Iceland	Luxembourg	Philippines	Uruguay
Cyprus	India	Malaysia	Portugal	Venezuela

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Argentina	Ecuador	Indonesia	Mexico	Saudi Arabia
Aruba	Finland	Iraq	Netherlands	Singapore
Australia	France	Ireland	New Zealand	South Africa
Austria	Germany	Israel	Nicaragua	Spain
Bahrain	Greece	Italy	Norway	Sweden
Belgium	Guatemala	Japan	Pakistan	Taiwan
Brazil	Honduras	Jamaica	Panama	Thailand
Chile	Hong Kong	Korea	Paraguay	United Kingdom
Columbia	Iceland	Luxembourg	Philippines	Uruguay
Cyprus	India	Malaysia	Portugal	Venezuela

ERRATA

The following revisions to the original 031.0901 study report dated May 25, 1999 were made on August 23, 1999.

Page	Table Number	Table Title	Comments
55	11.3.1.1	Primary Efficacy Criterion	Corrected SmarTest output for "time to first treated relapse" and "global difference" variables
58	11.3.1.2.1.C.	Test Results for Change in EDSS	Corrected SmarTest output for "Placebo vs. Mitox 5" and "Mitox 5 vs. Mitox 12" comparisons
59	11.3.1.2.2.C.	Test Results for Change in AI	Corrected SmarTest output for "Placebo vs. Mitox 5" comparison
61	11.3.1.2.3.D.	Test Results for the Adjusted Number of Treated Relapses	Corrected SmarTest output for "Placebo vs. Mitox 5" and "Mitox 5 vs. Mitox 12" comparisons
62	11.3.1.2.4.B.	Test Results for Time to First Treated Relapse	Corrected SmarTest output for all 3 group comparisons
63	11.3.1.2.5.C	Test Results for Change in SNS	Corrected SmarTest output for "Placebo vs. Mitox 5" comparison
78	11.3.2.4	Effect of Center Pooling on Mean EDSS	Original table of the mean change in EDSS showed baseline minus last value. This was corrected to last value minus baseline, thus reversing the sign of all the mean change values.
118	12.4.1.1	Summary of LVEF Changes	Added footnotes to clarify table

In addition to these changes in the in-text tables, the supporting Statistical Table A 11.3.1-1 in Appendix VII was also corrected.

Efficacy Results at Month 24
Phase III Study

	Treatment Groups			p value
		Novantrone		Placebo vs
Primary Endpoints	Placebo (N = 64)	5 mg/m² (N = 64)	12 mg/m² (N = 60)	12 mg/m² Novantrone
EDSS change* (mean)	0.23	−0.23	−0.13	0.0194
Ambulatory Index change* (mean)	0.77	0.41	0.30	0.0306
Mean number of relapses per patient requiring corticosteroid treatment (adjusted for discontinuation)	1.20	0.73	0.40	0.0002
Months to first relapse requiring corticosteroid treatment (median [1st quartile])	14.2 [6.7]	NR [6.9]	NR [20.4]	0.0004
Standard Neurological Status change* (mean)	0.77	−0.38	−1.07	0.0269
Clinically Relevant Secondary Endpoints				
Related to EDSS				
Patients (%) with at least 1 point deterioration in EDSS (Month 24 vs baseline)	16 (25%)	10 (16%)	5 (8%)	0.030
Patients with 6-month confirmed EDSS deterioration of at least 1 point	12 (19%)	6 (9%)	4 (7%)	0.045
Related to Relapses				
Months to first relapse (median [1st quartile])	8.3 [3.2]	15.0 [3.4]	NR [7.1]	0.009
Months to first severe relapse (median [1st quartile])	15.0 [7.2]	NR [9.2]	NR [22.8]	0.0009
Total number of relapses (adjusted for discontinuation)	129.38	77.44	48.18	0.0002
Patients (%) without relapses	23 (36%)	25 (39%)	34 (57%)	0.021
Related to Quality of Life				
Patients (%) with deterioration in HAQ	41 (66%)	25 (40%)	25 (42%)	0.012
Patients (%) with overall clinical rating of good or very good	11 (17%)	27 (42%)	26 (43%)	0.001
Patients (%) hospitalized for reasons other than treatment administration	43 (67%)	36 (56%)	24 (40%)	0.002
MRI‡	(n = 36)	(n = 40)	(n = 34)	
Mean change in number of Gd-enhancing lesions*	−0.19	−3.27	−2.03	0.0038
Mean change in number of T2-weighted lesions*	1.94	0.68	0.29	0.027

NR = not reached within 24 months; HAQ = Stanford Health Assessment Questionnaire; MRI = magnetic resonance imaging.

* Month 24 value minus baseline.

‡ A subset of 110 patients was selected for MRI analysis. MRI results were not available for all patients at all time points. The prognostic significance of the MRI findings in this study has not been evaluated.

The first patient was randomized on 2 June 1993 and the last patient finished the study on 10 July 1997.

Table 10.1.A. Patient Enrollment by Study Center and by Treatment Arm

Country	Center Location (Center Number)	Treatment Group			Total Number of Patients
		Placebo	Mitox 5	Mitox 12	
Germany	Berg (1)	10	10	10	30
	Würzburg (7)	4	5	5	14
	Mainz (4)	3	4	3	10
	Westerstede (13)	3	3	3	9
	Nürnberg (5)	3	3	2	8
	München (11)	2	2	2	6
	Magdeburg (12)	1	1	1	3
	Lübeck (10)	1	0	0	1
Belgium	Overpelt (58)	5	5	5	15
	Fraiture (59)	5	5	4	14
	Bruxelles (53)	4	4	4	12
	Melsbroek (50)	2	1	2	5
	Liege (56)	1	1	1	3
	Edegern (54)	0	1	0	1
Poland	Warsaw (14)	8	8	8	24
	Katowice (16)	6	6	7	19
Hungary	Szekesfehervar (15)	7	7	6	20
Total		65	66	63	194

Ref. Table 10.1-1

Of the 194 patients enrolled in the study, 149 completed the study. Three patients withdrew after randomization and before receiving study drug, three were not evaluated for efficacy after a single dose of study drug, and 39 withdrew prematurely from the study.

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

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10.1.1 Patient Withdrawals

One patient in each study group withdrew after randomization and before receiving any study medication:

- Patient 5309 (placebo) had an EDSS of less than 3 on the day of scheduled Month 0 administration and was withdrawn because of ineligibility.
- Patient 5312 (5 mg/m^2 mitoxantrone) disclosed a history of tachycardia on the day of scheduled Month 0 administration and was withdrawn at the physician's request.
- Patient 5701 (12 mg/m^2 mitoxantrone) disclosed that she had used corticosteroids intermittently during the preceding weeks and had experienced gastrointestinal bleeding prior to first scheduled study drug administration.

Three patients discontinued from the study after receiving a single administration of study medication but without having the Month 3 efficacy evaluation:

- Patient 1106 (5 mg/m^2 mitoxantrone) refused further treatment.
- Patient 5004 (12 mg/m^2 mitoxantrone) withdrew due to adverse laboratory events and a worsening of neurologic condition due to MS.
- Patient 5311 (12 mg/m^2 mitoxantrone): refused further treatment.

These six patients were not included in the intent-to-treat efficacy analysis.

Thirty-nine patients withdrew prematurely from the study: 17 patients in the placebo group, 10 in the 5 mg/m^2 mitoxantrone group, and 12 in the 12 mg/m^2 mitoxantrone group. The following table lists these patients and their reasons for withdrawal from study.

Table 10.1.1.A. Reason for Withdrawal by Treatment Arm

Reason for Premature Withdrawal	Treatment Arm		
	Placebo	Mitox 5	Mitox 12
Lack of efficacy (n = 15)	101 407 504 1309 5301 5814 5901 5904	123 1202 5914	1101 1203 1416 5303
Patient refusal (n = 11)	107 121 5801[a] 5804 5812 5913	109 1511 5302[a]	108 1302
Lost to follow-up (n = 4)	5809	409[a] 5802 5806	
Adverse event (n = 7)	404 5310		125 1105 1308 1411 5803
Other reasons (n = 2)		5601[b]	5905[c]

[a] Patient Nos. 409, 5302, and 5801 received all 8 planned doses of study drug but did not undergo the Month 24 evaluation.
[b] Patient No. 5601 received lithium after study initiation.
[c] Patient No. 5905 became pregnant on study.
Ref. Table 10.1-4

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Narratives for patients 125, 404, 1105, 1106, 1308, 1411, 5004, 5310, 5311, 5312, 5701, 5803, and 5905 are presented in Appendix I.

The following table summarizes the duration on study by treatment arm for patients who prematurely withdrew from the study.

Table 10.1.1.B. Time of Withdrawal from Study

Time of Last Visit	Treatment Group			Total No. of Patients
	Placebo	Mitox 5	Mitox 12	
Patients in the ITT cohort	64	64	60	188
Month 3	3	1	1	5
Month 6	5	2	3	10
Month 9	3	2	4	9
Month 12	3	0	1	4
Month 15	2	0	1	3
Month 18	1	5	2	8
Month 21	0	0	0	0
Patients completing the study	47	54	48	149

There was no statistical difference in observation time for patients who did not prematurely discontinue 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 for patients of the 5 mg/m^2 mitoxantrone group, and 385 days for patients of the 12 mg/m^2 mitoxantrone group (Ref. Table A 10.1-3).

Table 10.1.1.C. Duration of Observation (ITT Cohort)

Duration of observation (days)	Treatment Group		
	Placebo	Mitox 5	Mitox 12
Patients who completed study	(n = 47)	(n = 54)	(n = 48)
Mean	729.4	736.4	735.7
SD	17.0	22.5	23.1
Median	730	730	730
Maximum	756	822	834
Minimum	657	677	672
Patients who withdrew prematurely	(n = 17)	(n = 10)	(n = 12)
Mean	349.1	442.9	420.8
SD	141.5	224.0	160.6
Median	342	501	385
Maximum	617	654	735
Minimum	175	85	162

See Ref. Table A 10.1-3 for details on time of withdrawal and number of valid assessments.

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10.1.2 Protocol Violations

The Steering Committee identified the following violations as major protocol violations:

- Overdosage or underdosage by more than 10% of the protocol dosage (n = 2)

Visual evoked potentials were comparable among treatment groups, although the mean amplitude was lower for both eyes in the 12 mg/m^2 mitoxantrone group (Ref. Table A 11.2.1-11 – A 11.2.1-12).

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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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

11.2.4 Quality of Life

The mean score derived from the Health Assessment Questionnaire (HAQ) for all patients with available data was 0.92 (SD = 0.6), and the scores for the individual treatment groups did not show a statistically significant difference.

The mean Self-rating Depression Score (SDS) before start of treatment was 48.9 (SD = 11.03) for all patients with available data, and scores were not different between treatment groups. Thirteen patients (21%) in the placebo group showed marked to severe

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 12 mg/m^2 mitoxantrone and placebo groups.

The Mann-Whitney differences between the groups are given in the detailed description of the variables (Ref. Table A 11.3.1.1). The global Mann-Whitney difference was 0.2941 (95%-CI: 0.1644 – 0.4234).

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	0.4431	(0.1974, 0.6888)	
Change in SNS	0.2302	(0.0299, 0.4305)	
Global difference	0.3016	(0.1667, 0.4366)	<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.

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All Mann-Whitney differences are greater than zero, including the lower limits of the 95% confidence intervals. Consequently, the multivariate Mann-Whitney difference is greater than zero and the error probability for rejecting the "null hypothesis" is $p < 0.0001$.

The patients treated with 12 mg/m^2 mitoxantrone showed significantly better ($p < 0.0001$) results after 24 months of treatment than patients receiving placebo.

11.3.1.2 Univariate Analysis of Primary Efficacy Variables

Because the global test of stochastic ordering showed a significant advantage for the 12 mg/m^2 mitoxantrone group, all five primary efficacy variables were tested separately, with alpha = 0.05, according to the closed test procedure.

The sequence of testing (EDSS, AI, number of relapses requiring corticosteroid treatme time to the first relapse requiring such treatment, and SNS) was a priori ordered and test were interpreted as "statistically significant" when p values were less than 0.05. After tl first test that was found to be not significant, no further testing was to be performed and differences between groups were to be regarded as "not significant" for the remaining variables (principle of a priori ordered hypotheses).

The following table gives an overview of the results for the primary efficacy variables and shows that all variables were significantly better (2-sided tests) in the 12 mg/m^2 mitoxantrone group.

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

11.3.1.2.1 Change in EDSS

As shown in the table that follows, 12 patients in the 12 mg/m^2 mitoxantrone group, 18 patients in the 5 mg/m^2 mitoxantrone 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 sixteen patients in the placebo group compared to ten patients in the 5 mg/m^2 mitoxantrone group and five patients in the 12 mg/m^2 mitoxantrone group (Ref. Table A 11.3.1-3).

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

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As shown in the following table, the median change in EDSS was 0.5 (range: -3.0 to 2.0) in the placebo group and 0.0 in both treatment groups (5 mg/m^2 mitoxantrone: range: -2.5 to 2.5; 12 mg/m^2 mitoxantrone: range: -2.5 to 2.5).

Table 11.3.1.2.1.B. Descriptive Statistics for Change in EDSS

Change in EDSS	Treatment Group Placebo	Mitox 5	Mitox 12
Mean	0.23	-0.23	-0.13
SD	1.01	1.10	0.90
Median	0.5	0.0	0.0
Max	2.0	2.5	2.5
75th percentile	0.75	0.25	0.5
25th percentile	-0.5	-1.0	-0.5
Min	-3.0	-2.5	-2.5

Ref. Table A 11.3.1-5

The table that follows indicates 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. Test Results for Change in EDSS* Corrected Table.

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.

11.3.1.2.2 Change in AI

Four patients in the placebo group showed an improvement in AI, compared to 12 patients in the 5 mg/m^2 mitoxantrone group and 12 patients in the 12 mg/m^2 mitoxantrone group. Deterioration in AI was most frequently seen in placebo group patients (n = 28, 43.8%) compared to patients in the 5 mg/m^2 mitoxantrone group (n = 20, 31.3%) and patients in the 12 mg/m^2 mitoxantrone group (n = 20, 33.3%).

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

The median change in AI was 0.0 for all groups. The mean deterioration was 0.77 for patients in the placebo group, 0.41 for patients treated with 5 mg/m^2 mitoxantrone, and 0.30 for patients treated with 12 mg/m^2 mitoxantrone (Ref. Table A 11.3.1.9).

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Table 11.3.1.2.2.B. Descriptive Statistics for Change in AI

	Treatment Group		
Change in AI	Placebo	Mitox 5	Mitox 12
Mean	0.77	0.41	0.30
SD	1.26	1.40	1.24
Median	0.0	0.0	0.0
Max	5.0	5.0	5.0
75th percentile	1.0	1.0	1.0
25th percentile	0.0	0.0	0.0
Min	-1.0	-2.0	-2.0

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

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Table 11.3.1.2.2.C. Test Results for AI*

	Mann-Whitney Difference	
Group Comparisons	95% CI	p value
Placebo vs. Mitox 12	0.2107 (0.0240, 0.3974)	0.0270
Placebo vs. Mitox 5	0.1745 (-0.0134, 0.3624)	0.0688
Mitox 5 vs. Mitox 12	0.0159 (-0.1728, 0.2046)	0.8689

*Results from SmarTest software

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11.3.1.2.3 Adjusted Number of Treated Relapses

The total number of treated relapses is given as an adjusted number. The adjustment procedure is described in Section 11.3.2.2. 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 (Patient No. 5806; adjustment = 1.071) (Ref. Table A.11.3-3). The total adjusted number of treated relapses is summarized in the table below; the difference between the placebo and 12 mg/m^2 mitoxantrone groups was significant ($p = 0.0002$).

Table 11.3.1.2.3.A. Total Adjusted Number of Treated Relapses by Treatment Arm

Treatment Group		
Placebo	Mitox 5	Mitox 12
76.8	46.9	24.1

The number of patients categorized by the adjusted number of treated relapses is presented in the table below.

Table 11.3.1.2.3.B. Adjusted Number of Treated Relapses

	Treatment Group (No. of Patients)		
Range of Treated Relapses	Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
0-0.99	28	37	43
1-1.99	19	17	16
2-2.99	8	5	1
3-3.99	6	4	0
4-4.99	2	1	0
≥ 5	1	0	0

The mean adjusted number of treated relapses per patient during the 24-month study period was higher in the placebo group (mean = 1.20) than in the 5 mg/m^2 mitoxantrone group (mean = 0.73) and the 12 mg/m^2 mitoxantrone group (mean = 0.40).

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

Patients receiving placebo had significantly more treated relapses than did patients receiving 12 mg/m^2 mitoxantrone ($p = 0.0002$) and patients receiving 5 mg/m^2 mitoxantrone ($p = 0.0293$). The difference between the two mitoxantrone groups was not significant.

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	0.2229 (0.0242, 0.4216)	0.0279
Mitox 5 vs. Mitox 12	0.1542 (-0.0477, 0.3560)	0.1344

*Results from SmarTest software

11.3.1.2.4 Time to First Treated Relapse

There was a significant difference in time to first treated relapse between the placebo and 12 mg/m^2 mitoxantrone groups (p = 0.0004; log-rank test). 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. Therefore, the 25th percentile is given as a descriptive measure. The 25th percentile for time to first treated relapse was 6.7 months for the placebo group and 20.4 months for the 12 mg/m^2 mitoxantrone group, a difference of 13.7 months.

The difference in the 25th percentile between the 5 mg/m^2 mitoxantrone and placebo groups in time to first treated relapse was very small (6.9 vs. 6.7 months). Time-to-event curves for the two groups overlap just after 7 months and therefore the validity of the log-rank test is questionable. Patients in the placebo group continued to have relapses after that time, whereas there were only a few later events in the 5 mg/m^2 mitoxantrone group.

The difference in 25th percentiles for patients receiving 5 mg/m^2 vs 12 mg/m^2 mitoxantrone was 13.5 months. The difference between the two mitoxantrone groups was not statistically significant.

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Table 11.3.1.2.4.A. Time to First Treated Relapse (Months)

	Treatment Group		
	Placebo	Mitox 5	Mitox 12
Median	14.2	NR	NR
25th percentile	6.7	6.9	20.4

NR = median not reached within 24 months.

Kaplan-Meier curves representing the time to first treated relapse are located in Section 14.0. The table that follows summarizes test results for the time to first treated relapse.

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.

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11.3.1.2.5 Change in SNS

The number of patients categorized by change in SNS over 24 months is presented in the table below.

Table 11.3.1.2.5.A. Change in SNS Distribution

Change in SNS (Last Value – Baseline)	Treatment Group Placebo (N = 64)	Mitox 5 (N = 64)	Mitox 12 (N = 60)
≥ 21	1	1	2
16 to 20	1	1	0
11 to 15	1	3	3
6 to 10	9	5	2
1 to 5	16	15	9
0	10	4	7
-5 to -1	18	23	24
-10 to -6	4	7	8
-15 to -11	4	3	4
< -15	0	2	1

Ref. Table A 11.3.1-14

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Patients in the placebo group showed a mean deterioration in SNS of -0.77 compared to improvements in the 5 mg/m^2 mitoxantrone group (mean 0.38) and the 12 mg/m^2 mitoxantrone group (mean 1.07).

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Table 11.3.1.2.5.B. Descriptive Statistics for Change in SNS

Change in SNS	Treatment Group		
	Placebo	Mitox 5	Mitox 12
Mean	0.77	-0.38	-1.07
SD	6.79	7.27	8.61
Median	0.0	-1.0	-1.5
Max	25	23	35
75th percentile	5	2.5	1
25th percentile	-4	-3	-5
Min	-13	-17	-19

Ref. Table A 11.3.1-17

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

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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	0.1082 (-0.0884, 0.3047)	0.2809
Mitox 5 vs. Mitox 12	0.1310 (-0.0703, 0.3323)	0.2022

*Results from SmarTest software

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11.3.1.3 Analysis of Secondary Efficacy Variables

11.3.1.3.1 Overview

Secondary efficacy variables were classified as variables related to EDSS, variables related to relapses, variables related to quality of life, and other variables. MRI results collected for a subgroup of patients are described in Section 11.3.2.7.

Table 11.3.2.4. Effect of Center Pooling on Mean EDSS Change (SD)

Center (Pooled)	Original Center (Center No.)	N	Treatment Group		
			Placebo	Mitox 5	Mitox 12
1	Berg (1)	30	0.15 (1.38)	-0.30 (0.86)	-0.25 (0.95)
2	Warsaw (14)	24	-0.31 (1.34)	-0.44 (1.24)	-0.13 (1.28)
3	Szekesfehervar (15)	20	0.0 (0.82)	-0.50 (0.91)	-0.17 (0.68)
4	Katowice (16)	19	0.25 (0.94)	0.0 (1.14)	-0.36 (0.38)
5	Overpelt (58)	15	0.30 (1.35)	1.10 (0.96)	-0.80 (1.20)
6	Würzburg (7)	14	0.20 (0.45)	0.40 (0.74)	0.25 (0.96)
7	Fraiture (59)	14	0.0 (0.71)	-0.80 (0.67)	-0.30 (0.91)
8	Bruxelles (53) Mainz (4) Westerstede (13) Nürnberg (5)	36	0.86 (0.69)	0.0 (1.62)	0.38 (0.48)
9	München (11) Melsbroek (50) Magdeburg (12) Liege (56) Lübeck (10) Edegem (54)	16	0.46 (0.84)	-0.62 (1.04)	0.18 (0.85)

Although there is some heterogeneity among centers, the analysis of variance showed no significant influence of the centers (F-value = 1.23, $df = 8$, p = 0.2832). The differences between the placebo group and the mitoxantrone groups remained statistically significant after this adjustment (F-value = 3.22, $df = 2$, p = 0.0421).

11.3.2.5 Multiple Comparisons/Multiplicity

Since the protocol-specified primary response criterion is a multivariate test of stochastic ordered alternatives based on the five primary efficacy variables, no adjustment of alpha levels is needed.

11.3.2.6 Use of an "Efficacy Subset" of Patients

In order to analyze the true efficacy of the treatment with 12 mg/m^2 mitoxantrone for 24 months and to evaluate possible bias introduced by the "last-value-carried-forward" principle that was applied to those patients who either had no assessment at Month 24 or for whom there were severe violations of the study protocol, two different efficacy subsets were created:

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Table 11.3.5.1. Overview of Sensitivity of EDSS

EDSS Deterioration	Treatment			p value Placebo vs.
	Placebo	Mitox 5	Mitox 12	Mitox 12
Mean change in EDSS (baseline – last value [SD])	0.23 (1.01)	-0.23 (1.1)	-0.13 (0.90)	0.0194*
Deterioration ≥ 1 point from baseline No. of patients (%)	16 (25.0%)	10 (15.6%)	5 (8.3%)	0.030**
Deterioration ≥ 1 point during study No. of patients (%)	24 (37.5%)	12 (18.75%)	9 (15.0%)	0.005**
Confirmed deterioration ≥ 0.5 (3 months) No. of patients (%)	26 (40.6%)	22 (34.4%)	24 (40.0%)	0.943**
Confirmed deterioration ≥ 1 (3 months) No. of patients (%)	14 (21.9%)	9 (14.1%)	5 (8.3%)	0.0364**
Confirmed deterioration ≥ 1 (6 months) No. of patients (%)	12 (18.8%)	6 (9.4%)	4 (6.7%)	0.045**

* Wilcoxon-Mann-Whitney test
** Pearson's chi-square test

11.3.5.2 Sensitivity of Relapses

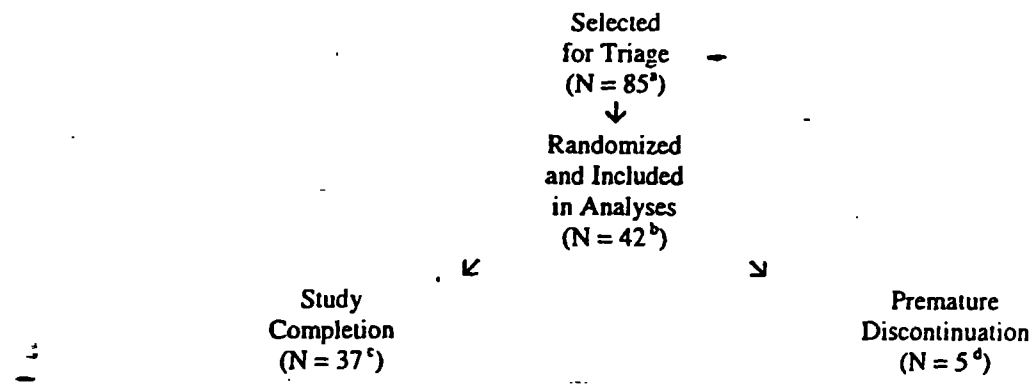
The relapses that patients experienced during the study may have varied in severity, may have required treatment with methylprednisolone, may have been confirmed by the treating physician's assessment, or may have been diagnosed by another physician who was not involved in the study.

For the primary efficacy analysis, the number of relapses reported in a group was adjusted for premature dropout, using the relapse rate of the placebo group.

In order to evaluate reporting bias and the effect of adjustment on the interpretation of results, we analyzed the following:

- all relapses reported
- all treated relapses, regardless of severity
- all severe relapses, regardless of treatment required
- all relapses observed by the treating physician
- the number of relapses adjusted for 24 months

Figure 5.1.3. Summary of Patient Flow in Study



[a] Two patients (Nos. 205, 304) were randomized for treatment but withdrawn from the study after one course of study drug; they are not included with the 42 patients analyzed in the treatment period.
[b] Intent-to-treat population
[c] Standard population
[d] All discontinued due to lack of effectiveness (Patient Nos. 105, 109, 201, 401, 403)

5.1.4 Withdrawal from Study

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. Withdrawals were not due to adverse events, as illustrated in the final Clinical Global Impression (CGI). For all the patients who withdrew, effectiveness was judged "null" and safety "good" (CGI evaluation).

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	mP alone	3	Lack of effectiveness	6.0	7.5	2	51	6/6
109		5		4.5	8.0	3	86	7/7
201		4		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

Three of these five patients were subsequently treated with immunosuppressive agents, a common practice in France for severe active MS: two patients received mitoxantrone and one received total lymphoid irradiation.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

For the 42 patients randomized and included in these analyses, the mean age was 31.8 ± 8.1 years and the sex ratio was 16/26 (male/female). In this population, the average weight was 61.6 ± 12.0 kg and the average height was 169.2 ± 9.3 cm.

All randomized patients were Caucasian except one patient in the methylprednisolone-alone group who was Black.

Table 5.2.1 summarizes demographic data according to treatment (see Appendix Section B1.1). There were no significant differences between the two groups.

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Table 5.3. Study Drug Dosing Summary

No. of Courses	Number of Patients	
	mP	MITOX + mP
7	16	17
6	1	4
5	3	0
4	1	0
Total	21	21

mP = methylprednisolone; MITOX = mitoxantrone

A total of 143 courses of mitoxantrone were administered in this trial. The average number of days between courses (per patient) ranged from 27 to 37, with a mean of 30 days. Six patients had ≥ 42 days between some courses.

The dose of mitoxantrone administered in this study was 20 mg IV once per month. For purposes of comparison with other studies of mitoxantrone in patients with MS, the mean dose per square meter of body surface area was calculated, resulting in an overall mean (for all patients and courses) of 11.9 mg/m^2 (range 10.1 to 14.8 mg/m^2). The cumulative (total) mean dose over patients was 81.2 mg/m^2 (range 61.6 to 101.0 mg/m^2).

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)

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The conclusions in the above table are not altered if the two patients who were randomized and then withdrawn after receiving one course each of study drug are 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).

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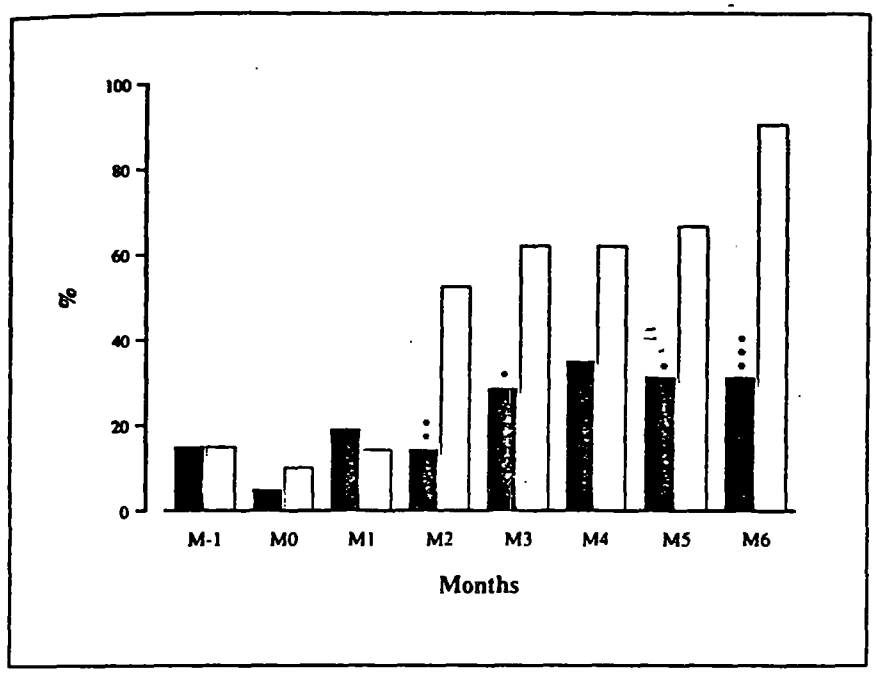
Figure 6.1.1. Percentage of Patients Without New MRI Gd-Enhanced Lesions During the 6-Month Treatment Period



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

6.1.2 Mean Number of Gd-Enhanced Lesions

During the triage period, the mean monthly number of new Gd-enhanced brain lesions was 6.8 (Month -1) and 4.6 (Month 0) in the mitoxantrone-plus-methylprednisolone group and 9.1 (Month -1) and 5.1 (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. As shown in Table 6.1.2.A, the number of new Gd-enhanced lesions was significantly lower in the mitoxantrone-plus-methylprednisolone group every month from Month 1 through Month 6.

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

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

When analyses were performed using the mean new lesion frequency from the previous months to calculate the missing values at Months 4, 5, and 6 for the five patients who withdrew, the results were similar, as shown in Table 6.1.2.B.

Table 6.1.2.B. Mean Number of New Gd-Enhanced Lesions Including Missing Values of Five Patients Who Withdrew

	mP			MITOX + mP			
Month	N	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	p value *
M-2	--	--	--	--	--	--	--
M-1	20†	9.1 ± 17.9	2.5 (—)	20†	6.8 ± 8.3	3 (—)	NS
M0	21	5.1 ± 5.7	3 (—)	20†	4.6 ± 4.6	3 (—)	NS
M1	21	12 ± 28.8	5 (—)	21	1.9 ± 1.5	2 —	0.036
M2	21	6 ± 7.5	2 (—)	21	2.6 ± 5.8	0 (—)	0.017
M3	21	9 ± 25.8	2 (—)	21	1.1 ± 2.7	0 (—)	0.011
M4	21‡	9 ± 16.3	1 (—)	21	0.9 ± 1.6	0 —	0.021
M5	21‡	5 ± 5.8	2 (—)	21	0.6 ± 1.5	0 —	< 0.001
M6	21‡	4 ± 4.7	3 (—)	21	0.1 ± 0.5	0 —	< 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
‡ Includes the five patients who withdrew; the mean new lesion frequency from the previous months was used to calculate the missing values at Months 4, 5, and 6

Table 6.1.3.A. Mean Total Number of Gd-Enhanced Lesions (New and Persisting)

	mP			MITOX + mP			
Month	N	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	p value *
M-2	20†	8.2 ± 8.6	6 (—)	20†	7.1 ± 8.3	5 (—)	NS
M-1	20†	10.2 ± 18.6	4 (—)	20†	9.5 ± 12.2	3.5 (—)	NS
M0	21	6.3 ± 6.7	4 (—)	21	5.7 ± 6.3	3 (—)	NS
M1	21	13.1 ± 28.6	6 (—)	21	3.3 ± 4.0	2 (—)	0.049
M2	21	6.2 ± 7.8	3 (—)	21	3.6 ± 7.6	1 (—)	0.024
M3	21	9.8 ± 25.7	3 (—)	21	2.5 ± 6.6	0 (—)	0.004
M4	20‡	9.7 ± 17.3	2 (—)	21	2.3 ± 6.6	0 (—)	0.012
M5	16‡	4.2 ± 5.7	2 (—)	21	1.9 ± 6.0	0 (—)	0.006
M6	16‡	3.1 ± 3.2	2.5 (—)	21	1.4 ± 5.7	0 (—)	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)

When analyses were performed using the mean total lesion frequency from the previous months to calculate the missing values at Months 4, 5, and 6 for the five patients who withdrew, the results were again similar, as shown in Table 6.1.3.B.

Table 6.1.3.B. Mean Total Number of Gd-Enhanced Lesions Including Missing Values of Five Patients Who Withdrew (New and Persisting)

	mP			MITOX + mP			
Month	N	Mean ± SD	Median (range)	N	Mean ± SD	Median (range)	p value *
M-2	20†	8.2 ± 8.6	6 (—)	20†	7.1 ± 8.3	5 (—)	NS
M-1	20†	10.2 ± 18.6	4 (—)	20†	9.5 ± 12.2	3.5 (—)	NS
M0	21	6.3 ± 6.7	4 (—)	21	5.7 ± 6.3	3 (—)	NS
M1	21	13.1 ± 28.6	6 (—)	21	3.3 ± 4.0	2 (—)	0.049
M2	21	6.2 ± 7.8	3 (—)	21	3.6 ± 7.6	1 (—)	0.024
M3	21	9.8 ± 25.7	3 (—)	21	2.5 ± 6.6	0 (—)	0.004
M4	21‡	9.7 ± 16.9	2 (—)	21	2.3 ± 6.6	0 (—)	0.008
M5	21‡	5.6 ± 6.1	2 (—)	21	1.9 ± 6.0	0 (—)	< 0.001
M6	21‡	4.7 ± 4.9	2.5 (—)	21	1.4 ± 5.7	0 (—)	< 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
‡ Includes the five patients who withdrew; the mean total lesion frequency from the previous months was used to calculate the missing values at Months 4, 5, and 6

Table 6.1.3.C displays the number of new and total Gd-enhanced lesions per scan over time. In the mitoxantrone-plus-methylprednisolone group, new and total Gd-enhanced lesions were significantly lower in the treatment period compared to the triage period. In contrast, there were no statistically significant differences between triage and the treatment period in the methylprednisolone-alone group.

Table 6.1.3.C. Number of New and Total Gd-Enhanced Lesions Per Scan (Triage vs. Treatment Period)

Variable		Triage (M-2 - M0)	Treatment (M1 - M6)	p value*
Number of new Gd-enhanced lesions per scan				
mP	Mean ± SD	7.0 ± 13.0	7.5 ± 18.3	NS
	Median (range)	3 —	2 —	
MITOX + mP	Mean ± SD	5.6 ± 6.7	1.2 ± 2.9	0.0001
	Median (range)	3 —	0 —	
Total number of Gd-enhanced lesions per scan				
mP	Mean ± SD	8.3 ± 12.5	8.1 ± 18.4	NS
	Median (range)	5 —	3 —	
MITOX + mP	Mean ± SD	7.5 ± 9.2	2.5 ± 6.1	0.0001
	Median (range)	4 —	0 —	

mP = methylprednisolone; MITOX = mitoxantrone
SD = standard deviation; NS = no statistical difference
* p values determined by Wilcoxon test

Results were similar when predicted values were used for the five patients who withdrew to calculate mean number of new and total Gd-enhanced lesions per scan over time. Results are provided in Appendix B6.

6.1.4 Lesion Load on T2-Weighted Scans

The number of new brain lesions on T2-weighted scans between Month 0 and at Month 6 were compared. New T2-weighted lesions at end of study were recorded and categorized as small, moderate, or large. As shown in Table 6.1.4, the mean number of new T2-weighted lesions was consistently lower in the mitoxantrone-plus-methylprednisolone group, and was statistically significant for all new lesions as well as the moderate and large lesion categories.

Table 6.1.4. Number of New Lesions on T2-Weighted Scans

Variable		mP (N=20)*	MITOX + mP (N=20)*	p value†
No. of new small lesions	Mean ± SD	1.7 ± 2.8	0.6 ± 1.1	NS
	Median (range)	1	0	
No. of new moderate lesions	Mean ± SD	2.3 ± 4.0	0.5 ± 0.8	0.036
	Median (range)	1	0	
No. of new large lesions	Mean ± SD	1.6 ± 3.2	0.1 ± 0.2	0.001
	Median (range)	0.5	0	
No. of total new lesions	Mean ± SD	5.5 ± 9.0	1.1 ± 1.4	0.024
	Median (range)	3	1	

mP = methylprednisolone; MITOX = mitoxantrone
SD = standard deviation; NS = no statistical difference
Small < 5 mm; moderate 5 – 10 mm; large > 10 mm
* One MRI was not interpretable
† p values determined by Wilcoxon test

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6.2 Clinical Findings

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6.2.1 Change in Expanded Disability Status Scale

There were significant differences in EDSS between the two groups during the treatment period. As shown in Table 6.2.1.A, mean monthly EDSS values were consistently lower in the mitoxantrone-plus-methylprednisolone group for all six months of treatment. Decreasing EDSS values indicate improvement in disability.

Also shown in Table 6.2.1.A, mean changes in EDSS from baseline at Month 0 (i.e., delta EDSS) were consistently better in the mitoxantrone-plus-methylprednisolone group, with a mean change of -0.3 at Month 1 and -1.1 at Month 6. Thus, mean EDSS improvement

in the mitoxantrone-plus-methylprednisolone group was 1.1 ± 1.1 (± SD) after six months of treatment. In contrast, mean EDSS in the methylprednisolone-alone group deteriorated progressively from Month 0 to Month 4. At 6 months, the methylprednisolone-alone group had a mean EDSS improvement of only 0.1 ± 1.1. 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 neurologic deterioration. Overall, mean EDSS changes were significantly better in the mitoxantrone-plus-methylprednisolone group compared to the methylprednisolone-alone group each month from Month 2 to Month 6.

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)

The number of patients with a 1-point EDSS improvement between Month 0 and the last month on treatment was also significantly higher in the mitoxantrone-plus-methylprednisolone group (14% vs. 57%, p = 0.004). As shown in Table 6.2.1.B, 12 of 21 patients in the mitoxantrone-plus-methylprednisolone group improved by one point or more on the EDSS and only one deteriorated. In contrast, in the methylprednisolone-alone group, six patients deteriorated by one point and only three patients improved by one point (overall p = 0.008).