Table 6.2.1.B. Number and Percentage of Patients with

1 Point* EDSS Change between Month 0 and Month 6

| Variable	mP (n = 21)	MITOX + mP (n = 21)	p value [t]	Overall p value
Deteriorated	6 (28.6%)	1 (4.8%)	0.038	
Stable	12 (57.1%)	8 (38.1%)	0.217	0.008
Improved	3 (14.3%)	12 (57.1%)	0.004	

mP = methylprednisolone; MITOX = mitoxantrone

*   0.5 point change if baseline EDSS ≥ 6

[t]   p value determined by chi-square test; per the study protocol and standard practice, changes from 6.0 to 6.5 and from 6.5 to 7.0 on EDSS were considered equivalent to one point change

As shown in 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 progression also showed significant differences between the two treatment groups from Month 2 to Month 6.

Figure 6.2.1. Mean EDSS (±SEM) Change from Baseline
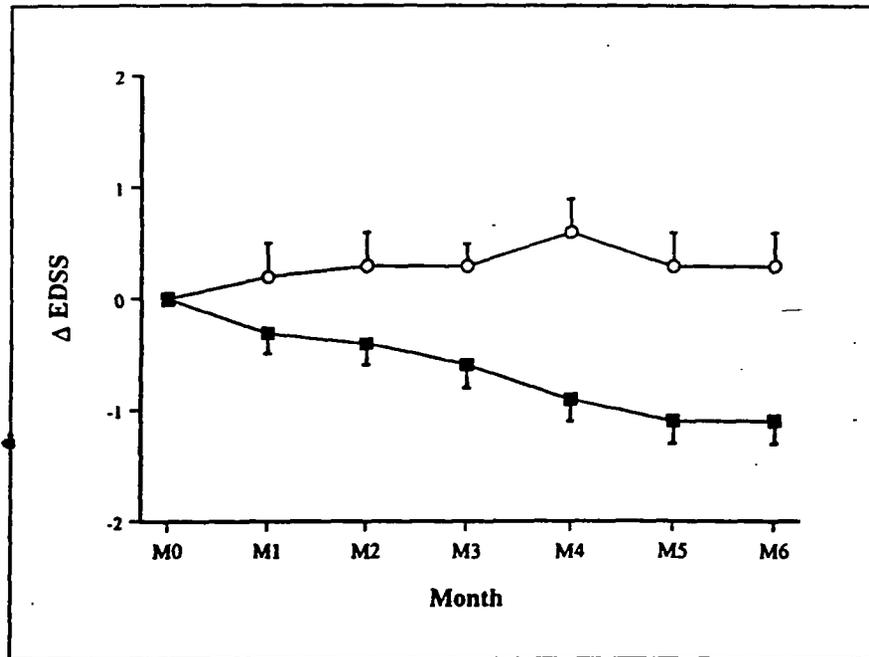
methylprednisolone alone (O) or methyprednisolone plus mitoxantrone (■)
M1 to M6 = 1 to 6 month(s) after starting study drug

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Table 6.2.2. Exacerbations and Patients without Exacerbation

(Triage and Treatment Periods)

Variable	mP	MITOX + mP	p value*
Exacerbations:			
Triage period (M -2 to M -1):			
Number of exacerbations	10	11	
Annual rate/patient (exacerbations)	2.9	3.1	NS
Additional steroid courses (1 g IV for 3 days)	5	6	
Treatment period (M0 to M6):			
Number of exacerbations	31	7	
Annual rate/patient (exacerbations)	3.0	0.7	0.003
Additional steroid courses (1 g IV for 3 days)	19	5	
M0 to M2			
Number of exacerbations	12	6	
Annual rate/patient (exacerbations)	3.4	1.7	
M3 to M6			
Number of exacerbations	19	1	
Annual rate/patient (exacerbations)	2.7	0.1	
Number of patients without exacerbations:			
Triage period	13	10	NS
Treatment period			
M0 to M6	7	14	0.031
M0 to M2	12	15	
M3 to M6	9	20	

mP = methylprednisolone; MITOX = mitoxantrone
NS = no statistical difference; IV = intravenous
M0 = beginning of study drug; M1 to M6 = 1 to 6 month(s) after starting drug
* p value determined by Wilcoxon or chi-square tests

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 6.2.2 shows the number of new exacerbations each month in the two treatment groups.

Table 6.2.2. Exacerbations and Patients without Exacerbation

(Triage and Treatment Periods)

Variable	mP	MITOX + mP.	p value*
Exacerbations:			
Triage period (M -2 to M -1):			
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Annual rate/patient (exacerbations)	2.9	3.1	NS
Additional steroid courses (1 g IV for 3 days)	5	6	
Treatment period (M0 to M6):			
Number of exacerbations	31	7	
Annual rate/patient (exacerbations)	3.0	0.7	0.003
Additional steroid courses (1 g IV for 3 days)	19	5	
M0 to M2			
Number of exacerbations	12	6	———
Annual rate/patient (exacerbations)	3.4	1.7	
M3 to M6			
Number of exacerbations	19	1	
Annual rate/patient (exacerbations)	2.7	0.1	
Number of patients without exacerbations:			
Triage period	13	10	NS
Treatment period			
M0 to M6	7	14	0.031
M0 to M2	12	15	
M3 to M6	9	20	

mP = methylprednisolone; MITOX = mitoxantrone
NS = no statistical difference; IV = intravenous
M0 = beginning of study drug; M1 to M6 = 1 to 6 month(s) after starting drug
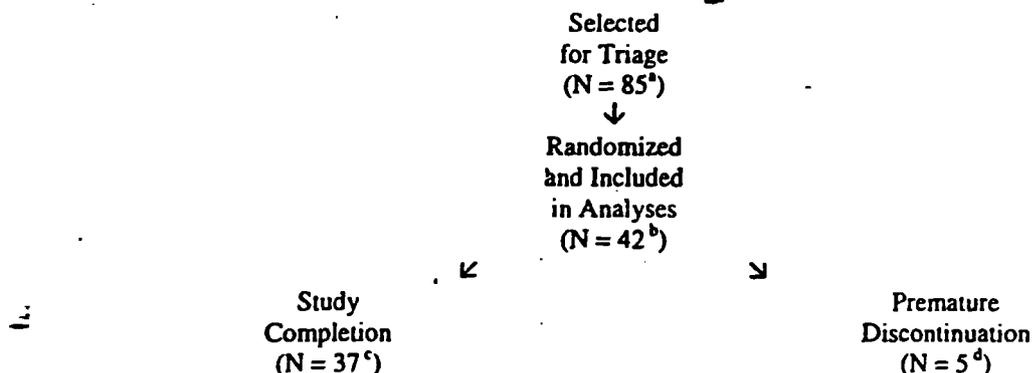*   p value determined by Wilcoxon or chi-square tests

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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 6.2.2 shows the number of new exacerbations each month in the two treatment groups.

Figure 5.1.3. Summary of Patient Flow in Study

Selected
for Triage
(N = 85[a])
↓
Randomized
and Included
in Analyses
(N = 42[b])

Study
Completion
(N = 37[c])

Premature
Discontinuation
(N = 5[d])

[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		3		6.0	7.5	2	51	6/6
109		5	Lack of	4.5	8.0	3	86	7/7
201	mP alone	4	effectiveness	5.5	6.5	4	35	6/7
401		4		4.5	5.0	4	8	7/7
403		4		6.0	8.5	4	90	7/7

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

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).

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NDA: 21-120

Drug Name: Generic: Mitoxantrone
                        Trade name: Novantrone™

Sponsor: Immunex Corporation

Drug Characteristics: Proposed indications: treatment of patients with secondary
                        progressive multiple sclerosis, including relapsing disease.

                        The recommended dosage is 12mg/m^2 given as a short
                        (approximately 5 to 15 minute) intravenous infusion every 3
                        months.

Reviewer: Gerard Boehm, MD, MPH

Completed: 11/5/1999

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1.0 Materials Used in the Review

This review was conducted using Integrated Safety Summary (ISS), data listings, study reports, subject narratives and published studies submitted with the mitoxantrone New Drug Application (NDA) on June 2, 1999. During the course of the review, requests for CRFs, additional narratives, and additional information on specific topics were forwarded to the sponsor. The sponsor responded to a list of requests in a submission dated 9/27/1999 (19 paper volumes). The Four Month Safety Update was submitted on October 1, 1999 (1 paper volume).

2.0 Background

2.1 Description and Prior Approvals

Mitoxantrone is an anthracenedione that intercalates into DNA causing crosslinks and strand breaks. It also interferes with RNA and is a potent inhibitor of topoisomerase II. The FDA has approved the use of mitoxantrone for two treatment indications. In December of 1987, mitoxantrone was approved, in combination with other approved drug(s), for the treatment of Acute Non-Lymphocytic Leukemia (ANLL) in adults. For ANLL, the recommended dose of mitoxantrone is 12mg/m^2 daily given on days 1-3 with cytarabine 100mg/m^2 given as a continuous infusion for 7 days. A second induction course may be given in the event of an incomplete response. For consolidation therapy, doses of 12mg/m^2 daily are given on days 1 and 2 along with cytarabine 100mg/m^2 given as a continuous infusion for 5 days. In November of 1996, mitoxantrone was approved, in combination with corticosteroids, for the treatment of patients with pain related to hormone resistant prostate cancer. For this indication, the recommended dose of mitoxantrone is 12mg/m^2 every 21 days. Although not FDA approved, mitoxantrone has been studied as a treatment for other cancers including breast, colon, lung, and lymphoma. In volume 1, p.87 of the NDA, the sponsor stated that mitoxantrone is approved in 50 countries for one or more of the following indications: acute non-lymphocytic leukemia in adults, advanced breast cancer, hepatoma, non-Hodgkin's lymphoma, and pain related to advanced hormone refractory prostate cancer.

The sponsor noted that pre-clinical trials demonstrated that mitoxantrone had an effect in an animal model of multiple sclerosis (MS) (vol. 82, p.16). They cited evidence from pilot studies in humans that led them to conduct larger trials of mitoxantrone's effectiveness in MS patients. Based on data collected from controlled clinical trials in MS, the sponsor is seeking FDA approval for treatment of secondary progressive MS, including progressive relapsing disease. The safety data comes from 2 controlled trials and a review of the experience of MS patients treated with mitoxantrone at a German clinic. This New Drug Application (NDA) was given accelerated review status since there are currently no approved therapies for this indication.

2.2 Review of Proposed Labeling with Respect to Safety

If approved, the sponsor proposes to update the existing labeling by adding safety and efficacy information from the MS controlled trials. A copy of the proposed labeling was submitted with the NDA. The proposed labeling includes a black box warning which states that mitoxantrone

should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy. It also warns that except for nonlymphocytic leukemia, mitoxantrone should not be given to patients with baseline neutrophil counts less than 1,500 cells/mm^3. Frequent peripheral blood cell counts are recommended to monitor for bone marrow suppression.

Labeling identifies hypersensitivity as the only contraindication to use. In the warning section, the labeling states that when mitoxantrone is used for the treatment of leukemia, severe myelosuppression will occur and that lab and supportive services must be available for hematologic and chemistry monitoring and that blood and blood products must be available to support patients. The labeling mentions that topoisomerase II inhibitors, including mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

The labeling discusses mitoxantrone associated cardiotoxicity. It provides a general discussion of the topic and then summarizes data from clinical trials in separate sections for each treatment indication. It states that functional cardiac changes including decreases in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure (CHF) can occur with mitoxantrone. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease. Labeling recommends that patients with these risk factors should have regular cardiac monitoring of LVEF from the initiation of therapy. Labeling also states that patients treated with mitoxantrone who received up to the cumulative dose of 140mg/m^2 had a cumulative 2.6% probability of clinical congestive heart failure and a cumulative probability rate of moderate or serious decreases in LVEF of 13%.

In a proposed labeling section describing the cardiotoxic effects observed during the MS trials, the sponsor reports that functional cardiac changes may occur in MS patients treated with mitoxantrone. In the Phase III MS trial, the labeling states that no major clinical cardiotoxicity was observed. Five of 62 patients (8%) receiving 12mg/m^2 had decreased LVEF values below the normal range. In addition, the labeling notes that no significant cardiotoxicity was observed in the Phase II study.

In ANLL comparative trials where patients were treated with mitoxantrone + cytarabine or daunorubicin + cytarabine, congestive heart failure occurred in 6.5% of subjects in each treatment arm. In a comparative trial of mitoxantrone and prednisone versus prednisone for prostate cancer, 5.5% (7/128) of patients treated with mitoxantrone had a cardiac event defined as myocardial ischemia, a decrease in LVEF below the normal range, or congestive heart failure (n=3). Among 112 patients treated with mitoxantrone and hydrocortisone for prostate cancer 19% had a reduction in cardiac function, 5% had cardiac ischemia, and 2% developed pulmonary edema.

Under precautions, the sponsor notes that therapy with mitoxantrone should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters as well as frequent patient observation. They recommend that patients be advised of the signs and symptoms of myelosuppression. The label suggests that patients be told that mitoxantrone may impart a blue-green color to urine for 24 hours following administration and that bluish discoloration of the sclera may occur. The sponsor states that serial blood counts and liver function tests are necessary for appropriate dose adjustments.

The adverse event section is presented by treatment indication. In the MS section, the sponsor identifies nausea, alopecia, urinary tract infection, and menstrual disorders including amenorrhea as events occurring significantly more frequently among mitoxantrone treated subjects in the

phase III trial. They also provide a table, which includes AEs occurring in at least 5% of patients in the phase III trial.

The sponsor includes a table of adverse events for subjects treated for ANLL in a US study with mitoxantrone + cytarabine vs. daunorubicin + cytarabine. The table provides, separately, the observed risk for events for patients entering induction and patients entering consolidation. The sponsor comments that it is clear that mitoxantrone plus cytarabine were responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression. Urinary tract infection (UTI) was more than twice as common among mitoxantrone subjects in both the induction (7% v. 2%) and the consolidation (7% v. 2%) groups. Conjunctivitis was seen in 5% of mitoxantrone exposed compared to 1% of daunorubicin exposed in the induction group but was not observed in either treatment group for consolidation. Jaundice was more common in the daunorubicin exposed subjects in the induction group (8% v. 3%) and in the mitoxantrone subjects in the consolidation group (7% v. 0). The entire AE table is included as an appendix to this review.

The labeling includes a table summarizing the risks for the observed adverse events occurring in at least 5% of subjects during the prostate cancer trial CCI-NOV22 (mitoxantrone and prednisone v. prednisone). Fatigue, alopecia, anorexia, dyspnea, nail bed changes, edema, mucositis, UTI, fever, bruise, anemia, cough, and decreased LVEF were observed at least twice as commonly among mitoxantrone + prednisone exposed subjects compared control (prednisone) subjects. The sponsor also includes a table, which compares the risk between treatment groups (mitoxantrone + hydrocortisone v. hydrocortisone) for events occurring in at least 5% of subjects treated for prostate cancer in study CALGB 9182. I have identified the events occurring at least twice as frequently among mitoxantrone exposed subjects and included them in the following table.

Adverse Events Occurring in ≥5% of Patients and at Least Twice As
Frequently among Mitoxantrone Exposed Subjects, Trial CALGB 9182

Event	Mitoxantrone and Hydrocortisone (n=112) % (n)	Hydrocortisone (n=113) % (n)
Decreased WBC	87% (96)	4% (4)
Granulocytes/bands	79% (88)	3% (3)
Lymphocytes	72% (78)	25% (27)
Platelets	39% (43)	7% (8)
Malaise/Fatigue	34% (37)	14% (16)
Edema	30% (31)	14% (15)
Nausea	26% (28)	8% (9)
Alopecia	20% (20)	1% (1)
Cardiac function	18% (19)	0
Infection	17% (18)	4% (4)
Diarrhea	14% (16)	4% (4)
Fever in absence of infection	14% (15)	6% (7)
Vomiting	11% (12)	5% (6)
Other neurologic	11% (11)	5% (5)
Hypocalcemia	10% (10)	5% (5)
Hyponatremia	9% (9)	3% (3)
Sweats	9% (9)	2% (2)
Stomatitis	8% (8)	1% (1)
Cardiac dysrhythmia	7% (7)	3% (3)
Neuro/constipation	7% (7)	2% (2)
Neuro/motor	7% (7)	3% (3)
Neuro/mood	7% (7)	3% (3)

Cardiac ischemia	5% (5)	1% (1)
Chills	5% (5)	0

In addition to the adverse event tables, the sponsor commented that allergic reactions (including hypotension, urticaria, dyspnea, and rashes) and cutaneous reactions (phlebitis, and rare reports of tissue necrosis) have occurred.

The sponsor reports on specific adverse events by body system and by indication. For hematologic events in MS patients, they note that 32% of those receiving 12mg/m^2 in the phase III study had leukopenia, and 10% had thrombocytopenia at some point during the study. In the phase II study, 43% of patients developed grade 4 neutropenia at some point but platelet counts <100,000/mm^3 were not observed. For treatment of leukemia, the sponsor reports that myelopsuppression is rapid in onset. For the 2 prostate cancer trials, the sponsor notes that grade 4 neutropenia was observed in 23% and 54% of mitoxantrone exposed subjects and that neutropenic fever occurred in 10% and 11% of subjects. Platelets less than 50,000/mm^3 were noted in 4% and 3% of mitoxantrone subjects in these trials.

The labeling mentions that interstitial pneumonitis has been reported rarely in cancer patients receiving combination chemotherapy that included mitoxantrone.

2.3 Human Pharmacokinetic Considerations
According to the PK/PD information contained in the product labeling, following a single intravenous dose, the mean terminal or elimination half-life of mitoxantrone is 23 to 215 hours (median approximately 75 hours). Distribution is extensive and the volume of distribution exceeds 1,000L/m^2. In patients administered 15-90mg/m^2 there is a linear relationship between dose and area under the concentration-time curve. Mitoxantrone is 78% protein bound. Protein binding is independent of concentration, and is not affected by phenytoin, methotrexate, doxorubicin, prednisone, prednisolone, heparin or aspirin.

The metabolism and elimination of mitoxantrone has not been well characterized. Mitoxantrone appears to be eliminated primarily through metabolism by the liver and excretion in the bile.

The effect of gender, age, race, and renal impairment on the pharmacokinetics of mitoxantrone is not known. Mitoxantrone clearance is reduced in patients with hepatic impairment, and there is no laboratory measurement that allows for dose adjustment recommendations. Studies of the interaction of mitoxantrone with concomitantly administered medications have not been performed and the interaction with the human P450 system has not been investigated.

3.0 Approach to Safety Review/Methods
As described above, mitoxantrone is currently approved for 2 treatment indications and therefore we have access to safety data from sources other than this NDA. In reviewing the safety of this drug, my approach will be to first review the safety data for the MS trials/patients submitted in this NDA and safety update. That will be followed by a focused review of selected adverse events identified from the AERS spontaneous report database. I will use the Review of Systems section of this review to summarize the NDA safety findings by body system, and to review additional information from the published scientific literature discussing the safety of mitoxantrone in MS patients and in other populations.

Using the submitted volumes, I reviewed the treatment emergent events identified from the mitoxantrone multiple sclerosis studies. For a sample of adverse events (serious events, events leading to discontinuation) I compared preferred terms from the listings to the description in the

CRFs and narratives to determine if the preferred term accurately described the event reported by the investigator. To further investigate events identified from listings, I requested Case Report Forms (CRFs) and narrative summaries from the sponsor that were not provided with the NDA submission. Using a convenience sample (all SAEs, events leading to discontinuation) I compared the data in the listings with the data in the CRFs and narratives to assess the agreement across the different sources. The sponsor's lab summary tables and analyses were reviewed. To further explore and described selected findings, I performed additional analyses, for white blood cell (WBC) counts, neutrophil counts, transaminases, and bilirubin using data included in the patient listings.

The sponsor's approach in the NDA was to provide safety summaries for the controlled trials and the cohort review separately in the Integrated Safety Summary (ISS). In this document, I follow the same format. I review the reported deaths, serious adverse events, discontinuations, lab data, vital signs, and additional studies (echo, ECG). I included information reported in the Four Month Safety Update in the appropriate study section.

Since Mitoxantrone is an approved drug, postmarketing adverse event reports are available in the AERS database. At my request, Mary Mease from the Office of Post Marketing Drug Review and Assessment queried the FDA AERS database and identified the adverse event reports for mitoxantrone. I selected several groupings of events and reviewed the available reports. Since the drug is approved for treatment of leukemia and is known to cause marrow suppression, I chose not to review hematologic adverse event reports. Instead, I focused on reports suggestive of cardiac toxicity, liver toxicity, renal toxicity, and rhabdomyolysis.

The sponsor provided reprints of published articles addressing a variety of adverse event topics including CHF, treatment related leukemia, and amenorrhea. I reviewed the articles provided by the sponsor as well as additional articles that I identified through searches of PubMed. Information from these sources is summarized and referenced under the appropriate body system in the Review of Systems section.

4.0 Review Findings
4.1 Description of Data Sources

4.1.1 MS NDA Data Sources
The safety information for the mitoxantrone NDA consists of data from a Phase III trial (31.0901), a Phase II trial (31.0902) and data from 454 MS patients treated with mitoxantrone at a single center in Germany (31.0903). The Four Month Safety Update provided adverse event, lab and cardiac monitoring data captured 1 year after last dose for subjects who completed study 31.0901. The update also contained additional safety information for the German cohort.

4.1.1.1 Demographics for the NDA MS Subjects
The sponsor summarized the demographic characteristics of the exposed patients included in the NDA in table F.3.B. on p. 86 of vol. 82. That table is reproduced below.

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Table F.3.B. Characteristics of Patients Treated with Mitoxantrone

	Study 31.0901*	Study 31.0902	31.0903
No. of patients given mitoxantrone	124[†]	21[‡]	454
Mean age	40.0 years	31.4 years	37.0 years
No. of female/male (ratio)	98/90 (1.1)	15/6 (2.5)	276/178 (1.6)
Mean MS duration	9.6 years	6.9 years	9 1 years
Type MS: No. of patients (%)			
Relapsing-remitting	0 (0%)	17 (81%)	287 (63%)
Secondary progressive	59 (48%)	4 (19%)	102 (22%)
Relapsing progressive	65 (52%)	0 (0%)	0 (0%)
Primary progressive/unknown	0 (0%)	0 (0%)	65 (14%)
Mean EDSS score at baseline	4.6	4.4	5.11
Mean no. of relapses in prior year	1.3	3.1	1.02

*Based on n=188, total patients evaluable for efficacy
[†] Three additional patients withdrew after 1 mitoxantrone dose
[‡] An additional patient withdrew after one mitoxantrone dose and had no data for safety evaluation

4.1.1.2 Extent of Exposure for the NDA MS Subjects

The sponsor reports safety information for 599 MS patients who were exposed to at least 1 dose of mitoxantrone. One hundred and twenty four individuals were exposed in study 31.0901, 21 in study 31.0902, and 454 patients were treated in the German MS clinic (vol. 82, p. 86). In separate locations in the ISS, the sponsor provided summary data for mean cumulative dose for each of the trials. I summarized that information as well as the dose administered per treatment in the table below.

Mean Cumulative Exposure (mg/m^2) in the NDA Studies

	31.0901*		31.0902[†]	31.0903[‡]
Dose per treatment	5mg/m^2	12mg/m^2	20mg	12mg/m^2
Mean cumulative dose (mg/m^2)	37.2	82.6	81.2	43.5

* vol. 82, p.88; [†] vol. 82, p.101; [‡] vol. 82, p.108

The highest cumulative dose administered in study 31.0901 was 96mg/m^2 (vol. 84, p.102) and in 31.0902 was 101mg/m^2 (vol.93, p.44). In the German cohort, 30 patients received a dose ≥ 100mg/m^2 and 6 patients received a dose ≥140mg/m^2 (vol. 97, p.44).

On page 163 of vol. 82, the sponsor summarized the duration of exposure in the MS trials submitted with this NDA. That table is reproduced below.

Table G.5.B. Duration of Exposure to Mitoxantrone in Clinical Trials in Multiple Sclerosis

	Duration of Exposure	
Study Number	6 Months	12 Months
031.0901	122	111
031.0902	21	0
031.0903	325	238
Total Patients	468	349

4.1.2 Other Data Sources

The FDA spontaneous report database was queried. As of 8/17/99, there were 598 spontaneous adverse event reports for mitoxantrone and 184 of these had death as an outcome. I reviewed a listing of adverse events and identified specific events to review in greater detail. The reports suggestive of cardiac toxicity, hepatic failure, renal failure and rhabdomyolysis were reviewed and summarized.

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As noted above, since this is an approved drug, additional information from sources other than the NDA trials was available for review. The sponsor provided reprints of publications discussing mitoxantrone in both cancer patients and MS patients. Additional articles discussing mitoxantrone safety topics were identified through searches of PubMed and were reviewed. A list of references is included in the appendix.

4.2 Review of the Sponsor's AE Surveillance, Coding Process, and Approach to the Evaluation of the Safety of Mitoxantrone

4.2.1 Audit Findings and Review of Coding
The definition of a serious adverse event was not uniform across studies/sources and these definitions will be provided in the appropriate sections for each study/source.

·The CRF for study 031.0901 included a checklist for the following events: *alopecia, nausea/vomiting, diarrhea, stomatitis, cardiac function rhythm, and cardiac function conduction.* The CRF did not capture the actual event that led to the diagnoses of *cardiac function rhythm* and *cardiac function conduction.* In the adverse event table (vol. 86, p.64) *cardiac function rhythm* was subsumed under the term arrhythmia and *cardiac function conduction* was subsumed under the term ECG abnormal. The preferred term nausea subsumes both nausea and vomiting (the term "vomiting" does not appear in the AE tables). Alopecia, diarrhea and stomatitis appeared as preferred terms.

Adverse events other than those in the checklist were captured on a separate page under the heading *Other non-laboratory adverse events* in the CRF. This study was conducted in several European countries and translations to English were not evaluated. The grouping of adverse event terms into body systems for these events appeared appropriate.

The CRF for study 031.0902 did not use a checklist for adverse events. Instead, any adverse events reported by patients were captured on an AE sheet along with descriptive information about frequency, intensity, severity and duration. This study was conducted in France and translations to English were not evaluated.

The data included in 031.0903 were abstracted from the charts of patients treated with mitoxantrone in a clinic in Germany. The abstraction process specifically identified events of cardiac toxicity, hematologic toxicity, infection, malignancies, pregnancy and menstrual abnormalities. The chart reviewers did not capture information about severity of adverse events. The sponsor did not have access to the clinic charts. The investigators' used CRFs to capture data from clinic charts and these CRFs were forwarded to the sponsor for analysis (vol. 97 pp. 14-18).

After comparing data entries (specifically demographic data, dates, lab values, adverse events) I concluded that there was agreement between sources (CRFs, narrative summaries, and data listings) for the captured data from studies 31.0901 and 31.0902. Assessment of the accuracy of the German cohort safety data was not possible since neither the sponsor nor the agency had access to the patient charts, which were the primary data source.

I identified a potential data quality concern during the review of lab data summary tables for study 31.0901. The summary tables (including mean change and outlier) suggested that there were subjects who experienced extremely abnormal test results, particularly for bilirubin (ex. 25.5 mg/dL) and creatinine (ex. 10mg/dL). The lab data listings also contained these markedly abnormal results. I asked the sponsor to look into this issue to determine if this finding resulted from use of different units, from data entry errors, or if the results were the true values for the

subjects. If these results were due to data entry errors or the use of different units, analyses based on these data would be flawed. If these were the subjects' true test results then additional information discussing these abnormalities would be required. The sponsor responded that these abnormalities arose because some sites reported different units and that this was corrected prior to the analyses but was not corrected in the lab data listings. I sent additional questions about this matter since I detected the problem initially in the summary tables suggesting to me that the analyses were flawed. I am currently awaiting a reply.

4.3 Safety in Study 31.0901

The sponsor provided the safety data from study 31.0901 in section F.4 of the ISS (vol. 82, p. 87). The study report for this trial was in vol. 84. The protocol and amendments were provided as appendices to vol. 84.

4.3.1 Study Description

Study 31.0901 was a European multi-center controlled trial with subjects randomized to placebo (methylene blue) or one of two doses of mitoxantrone ($5mg/m^2$, $12mg/m^2$). The treatment was administered every 3 months over 24 months for a total of 8 courses of therapy (cumulative mitoxantrone doses of $40mg/m^2$ and $96mg/m^2$ respectively). Subjects randomized to mitoxantrone were treated with ondansetron before treatment and then 6-8 hours following infusion, if required. Treatment with short term (5 days) high dose (500mg) methylprednisolone was allowed for patients experiencing severe disabling MS attacks during the trial (vol. 84, p. 172). The neurological and MRI evaluators were blinded to study drug assignment but the investigators reporting the adverse events were not blinded (vol. 82, p.26).

Inclusion criteria required remittent progressive and secondary progressive MS subjects to be 18-55 years old, with baseline leukocytes $> 4 \times 10^9/L$, granulocytes $> 2 \times 10^9/L$, platelets $> 100 \times 10^9/L$, and female subjects to have negative pregnancy tests. Potential subjects were to be excluded from the trial if they had a neurological attack within the preceding 8 weeks, received corticosteroids in the preceding 8 weeks, had previous treatment with mitoxantrone, other anthracendiones, or anthracyclines, were treated with chemotherapeutic agents in the preceding 9 months, or had prior mediastinal radiation. In addition, potential subjects were excluded if they were receiving cardiotoxic drugs, had a history of congestive heart failure, had a history of myocardial infarction, clinically significant rhythm disturbances, clinically relevant conduction disturbances, uncontrolled hypertension or had an LVEF <50% or below the local lower limit or fractional shortening ≤25%. Subjects with major illnesses such as hepatic disease, renal disease, bone marrow disease, autoimmune diseases requiring treatment with corticosteroids, malignancies, severe infections, decubitus ulcers, substance abuse, tuberculosis, or other neurological disturbances were also excluded.

Blood counts were performed at baseline and then 7 days prior to administration of each dose. Since doses were administered every 3 months, the lab testing took place approximately 3 months after infusion of the drug. The protocol included instructions about adjustment of mitoxantrone dose for toxicity based on these hematologic results. The following table provides the required dose adjustments for hematologic toxicity detected 7 days prior to the next dose for subjects in the $12mg/m^2$ treatment arm.

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Dose Adjustments for Hematologic Toxicity for Subjects in the 12mg/m^2 group, Study 31.0901

Dosage	100%	75%	50%	Stop Treatment
Leukocytes (x 10^9/L)	≥ 4.0	3.0-3.99	2.0-2.99	<2.0
Platelets (x 10^9/L)	≥100	75-99	50-74	<50
Granulocytes (x 10^9/L)	≥2.0	1.5-1.99	1.0-1.49	<1.0

Control and documentation of granulocytes was required only in Belgium.

The protocol did not require investigators to monitor blood counts following dose administration to document decline and recovery of marrow function. Subjects were instructed to consult their personal physician if they developed signs or symptoms of infection following treatment. The personal physician would then evaluate the subject and perform a blood count. Hematologic values meeting WHO grade 4 toxicity criteria (see appendix) were to be reported to the investigator.

Subjects were asked about any infections occurring between evaluations. If a patient presented to their personal physician during the three week period following the last dose with signs and symptoms of infection and a blood count demonstrating WHO grade 3 or 4 toxicity, then the mitoxantrone dosage for the next cycle was to be decreased by 2 or 4mg/m^2 respectively. The protocol also required dose reduction for non-hematological WHO grade 2-3 toxicity and withdrawal for WHO grade 4 non-hematologic toxicity (WHO toxicity criteria are provided as an appendix to this review).

Subjects receiving 5mg/m^2 who had hematologic toxicity ≥ WHO grade 3 were to be discontinued from the study. Subjects with WHO grade 2-3 non-hematologic toxicity were to have their dose reduced by 1mg/m^2 and those with grade 4 toxicity were to be discontinued.

The monitored hematology parameters were red blood cells, white blood cells, white blood cell differential, and platelets. The monitored chemistry parameters were gamma-GT, SGOT, alkaline phosphatase, total bilirubin, and creatinine (vol. 84, p.31). Patients' cardiac status was monitored with ECGs and either radionuclide angiography or echocardiograms. These tests were performed at baseline, month 12, month 24, and month 36.

4.3.2 Safety Results

4.3.2.1 Deaths

There were no deaths reported while patients were on study drug or within 90 days of completing study drug administration (9/27/99 submission, p.17). In the Safety Update no deaths were reported although 11 subjects who completed the study (4-placebo, 1-5mg/m^2, and 6-12mg/m^2) were lost to follow up between the 24-month and 36-month evaluations (Safety Update, p.7).

4.3.2.2 Serious Adverse Events

In the study report, the sponsor defined a serious adverse event as *an experience that is life threatening or fatal (including any death that occurs within 30 days of the last dose, regardless of drug relationship; or which may be drug related irrespective of the time interval); results in permanent disability, congenital anomaly, or neoplasm; requires in-patient hospitalization; requires extended hospitalization; or is an overdose* (vol. 84, p.31). The sponsor reported that 20 (16%) of the mitoxantrone exposed subjects (10 in each dose group) experienced 21 SAEs and 6 (9%) of the placebo exposed subjects experienced 8 SAEs. The sponsor listed the subjects with SAEs in table 12.2.1.-3. Information from that table is provided below.

Serious Adverse Events from Study 031.0901

Treatment/Dose	Patient number	Event
Mitoxantrone 12mg/m^2	108	Osteonecrosis
Mitoxantrone 12mg/m^2	706	Osteonecrosis
Mitoxantrone 12mg/m^2	1304	Pulmonary Embolism
Mitoxantrone 12mg/m^2	1411	Urinary Tract Infection
		Renal Function Abnormal
Mitoxantrone 12mg/m^2	1424	Urinary Rentention
Mitoxantrone 12mg/m^2	1509	Endometritis
Mitoxantrone 12mg/m^2	1615	Hemorrhagic cystitis
Mitoxantrone 12mg/m^2	5303	Diarrhea
Mitoxantrone 12mg/m^2	5905	Unintended Pregnancy
Mitoxantrone 12mg/m^2	5910	Pharyngitis
Mitoxantrone 5mg/m^2	123	Back pain
Mitoxantrone 5mg/m^2	505	Pathological fracture
Mitoxantrone 5mg/m^2	1305	Enteritis
Mitoxantrone 5mg/m^2	1403	Seborrhea
Mitoxantrone 5mg/m^2	1511	Anxiety
Mitoxantrone 5mg/m^2	1513	Thoracic lymphadenopathy
Mitoxantrone 5mg/m^2	1609	Asthenia
Mitoxantrone 5mg/m^2	1610	Urinary Tract Infection
Mitoxantrone 5mg/m^2	1617	Carcinoma
Mitoxantrone 5mg/m^2	5911	Pharyngitis
Placebo	124	Depression
Placebo	1406	Hypochromic anemia
Placebo	1409	Abortion
Placebo	1612	Asthenia
		Back Pain
		Depression
Placebo	5304	Upper Respiratory Infection
Placebo	5602	Condition Aggravated

The sponsor provided narratives for these events in their 9/27/99 submission. The narratives for the two subjects in the mitoxantrone 12mg/m^2 group who developed osteonecrosis (*femur head, hip bone*) noted that both had been treated with corticosteroids in the past. The narrative for the subject with endometritis provided only the diagnosis and that this individual was hospitalized and received treatment. The sponsor's narrative for the subject with hemorrhagic cystitis stated that this event occurred following the first dose of study medication and was treated with antibiotics and vitamin C. Subsequent mitoxantrone doses were reduced to 10mg/m^2 and this subject finished the study and the event did not reoccur.

The sponsor provided a listing of all hospitalizations for subjects in this study (vol. 90, p.278). A review of that listing revealed that there were additional hospitalizations for reasons such as study drug administration and physical therapy that were not included in the SAE count/listings.

Serious adverse events were not discussed as a separate topic in the Safety Update. Instead, the sponsor provided risks for hospitalization by treatment group for months 25 through 36 (off drug) for those evaluated at month 36 (Safety Update, p.13). During this period, 33% (n=14) of placebo subjects, 28% (n=15) of 5mg/m^2 subjects, and 36% (n=15) of 12mg/m^2 subjects reported one or more hospitalizations. Listing 7 from the Safety Update provided reasons for these hospitalizations. Most hospitalizations were for MS attacks/disease progression or rehabilitation. There were no hospitalizations for cardiac or hepatic events.

4.3.2.3 Discontinuations

The sponsor reported that one patient randomized to each of the three study arms withdrew prior to receiving the first dose. Three subjects withdrew following the first dose of study medication. Subjects 1106 and 5311 refused further treatment, and patient 5004 withdrew for adverse laboratory events and worsening neurologic condition due to MS (vol. 84, p.45). I reviewed the narrative for this patient. This 35-year-old male was noted as having a clinically relevant decrease in WBC count (to $3.3 \times 10^9/L$) and an increased bilirubin (3.3mg/dL) at the evaluation 3 months following the first dose. WBC count and bilirubin were the only lab results included in the narrative and I could not locate data for this subject in the lab result listings. This subject's CRF did not have an end of study page and the lab data were incomplete.

An additional 39 subjects withdrew from the study, 17 in the placebo arm, 10 in the 5mg/m^2 arm and 12 in the 12mg/m^2 arm. The sponsor provided the reasons for discontinuation for those subjects in table 10.1.1.A. on p. 46 of vol. 84. I summarized that information in the table below.

Reasons for to Discontinuing from Study 31.0901

Reason for Withdrawal	Treatment Arm		
	Placebo n=64	Mitoxantrone 5mg/m^2 n=64	Mitoxantrone 12mg/m^2 n=60
Lack of Efficacy	8 (12.5%)	3 (4.7%)	4 (6.7%)
Patient Refusal	6 (9.4%)	3 (4.7%)	2 (3.3%)
Loss to Follow-up	1 (1.6%)	3 (4.7%)	0
Adverse Event	2 (3.1%)	0	5 (8.3%)
Other reasons	0	1 (1.6%)	1 (1.7%)

Other reasons included use of an excluded medication (subject 5601) and pregnancy (subject 5905).

I reviewed the narratives for the 5 mitoxantrone subjects who withdrew for adverse events. Subject 125 discontinued for major depression and suicidal ideation. Subject 1105 developed cardiac toxicity manifested by a decrease in the left ventricular fractional shortening (LVFS) to 22% (LVFS was 41% at baseline, lower normal limit 25%) by echocardiography. This abnormality was measured after 4 doses of drug had been administered. LVFS improved to 33% in this subject 1 year later. There was no mention if the subject became symptomatic. Subject 1308 discontinued for repeated episodes of nausea and vomiting that persisted despite ondansetron treatment and decreases in the dose of mitoxantrone. Subject 1411 discontinued following development of moderate renal insufficiency. I requested additional information about this event. In the 9/27/99 submission (vol.1, pp. 12-15) the sponsor described an episode of renal insufficiency (creatinine 4.17mg/dL) with evidence of urinary retention and hydronephrosis and improvement in renal function following bladder catheterization. The subject subsequently underwent sphincterotomy. The subject withdrew from the study following this event, reportedly at the suggestion of his urologist and nephrologist. Subject 5803 withdrew for repeated UTIs.

4.3.2.4 Treatment Emergent Adverse Events

On page 90 of vol. 82, the sponsor reported that during the 24 month study period, 98% (61) of the mitoxantrone 12mg/m^2 subjects, 96% (63) of the mitoxantrone 5mg/m^2 subjects, and 86% (56) of the placebo subjects reported at least 1 adverse event. The sponsor reported that the most common AEs were gastrointestinal followed by respiratory, skin, urinary tract, and female reproductive. The sponsor reported a difference in risk (p<.05) between placebo and mitoxantrone 12mg/m^2 for nausea, alopecia, urinary tract infections, menstrual disorders, and amenorrhea. The sponsor reported a difference in risk (p<.05) between placebo and mitoxantrone 5mg/m^2 for nausea, urinary tract infection, menstrual disorders, and amenorrhea. The sponsor included a table

that summarized the adverse events that occurred in more than 5% of the subjects in any arm of the study (vol. 84, p.104).

Table 12.1.2.A Adverse Events Reported in >5% of Patients in any arm of Study 31.0901

| | Treatment Group | | |
| | | Mitoxantrone | |
Preferred Term	Placebo (n=64) %	5mg/m^2 (n=65) %	12mg/m^2 (n=62) %
Nausea	20	55	76
Alopecia	31	38	61
Upper respiratory tract infection	52	51	53
Urinary tract infection	13	29	32
Menstrual disorder*	26	51	61
Stomatitis	8	15	19
Amenorrhea*	3	28	43
Leukopenia[†]	0	9	19
Arrhythmia	8	6	18
Diarrhea	11	25	16
Gamma GT increased	3	3	15
Urine abnormal	6	5	11
ECG abnormal	3	5	11
Constipation	6	14	10
Rhinitis	14	11	8
SGOT increased[†]	8	9	8
Back pain	5	6	8
Pharyngitis	9	8	6
Sinusitis	2	3	6
Granulocytopenia[†]	2	6	6
WBC abnormal[†]	2	8	6
Infection viral	6	6	6
Headache	5	6	6
Anemia[†]	2	9	6

* Female patients only
[†] Laboratory results reported as adverse events by the Investigator

I reviewed adverse event tables 12.1.4.-1, 12.1.4.-2 that listed all adverse events by patient, body system, and that provided investigator terms in order to further explore events listed above and to identify infrequently occurring events of concern. I identified 13 reports of SGOT increased for 11 mitoxantrone treated subjects. I then reviewed the lab listings, available narratives and CRFs for these subjects. The highest SGOT for any of these subjects was 152U/L (#1413) and none were associated with a bilirubin ≥ 2.0 mg/dL. The risk for bilirubinemia reported as an adverse event was 5% (n=3) for each of the three treatment groups. I identified the 6 mitoxantrone treated subjects with AEs of elevated bilirubin. The highest bilirubin for any of the mitoxantrone subjects with an AE of bilirubinemia was 25.5 (units not listed, likely μmol/L since event was described as mild). The bilirubin values for the remaining 5 mitoxantrone subjects were below 2.2mg/dL. Except for patient 1516 (bilirubin 1.4mg/dL; SGOT 53U/L, ULN 37 U/L), none of the subjects with increased bilirubin reported as an AE had associated increases in SGOT.

The sponsor summarized the cardiac adverse event data from this study in section F.4.9 (vol.82, p. 94). They reported cardiac adverse events by treatment and dose. Nine percent (n=6) of placebo patients had a heart rate/rhythm body system category AEs compared to 6.2% (n=4) of the subjects in the 5mg/m^2 group and 21% (n=13) of the subjects in the 12mg/m^2 group. Within this category, the greatest difference between treatment groups was for arrhythmia (8% for

placebo, 6% for 5mg/m² and 17% for 12mg/m²). Almost 5% (n=3) of placebo subjects experienced an adverse event included under the cardiovascular body system category compared to 12.3% (n=8) of the 5mg/m² group and 12.9% (n=8) of the 12mg/m² group. Within this category the greatest difference between groups was for ECG abnormal (3% of placebo subjects, 5% of 5mg/m² subjects and 11% of 12mg/m² subjects). The preferred term arrhythmia subsumes the AEs captured as *cardiac function rhythm* in the AE checklist and the event ECG abnormal subsumes the AEs captured as *cardiac function conduction* in the AE checklist. Since investigators were not required to record the actual event and these terms are not specific, I am uncertain about the nature of these events.

Subject 5903 had an adverse event of cardiac function decreased and I requested a narrative for this subject from the sponsor. This 55-year old male had a baseline LVEF of 58%. At his 12-month evaluation, his LVEF was 51% and a cardiologist considered the LVEF to be normal. His LVEF 3 months later was 56% and the end study LVEF was 52%. This subject had no clinical evidence of congestive heart failure.

Four subjects had AEs of CPK increased. Three of these subjects were in the mitoxantrone group (709, 712, and 1516) and for 2 of these subjects (709, 1516), the CPK was >100U/L. I asked the sponsor for narratives for these 2 subjects. Subject 709 a 50 year old female randomized to mitoxantrone 12mg/m² every 3 months, had an elevated CPK that prompted the investigator to decrease the dose of study medication. The sponsor reported, in the narrative (vol. 1 p.32, 9/27/99 submission) that this subject entered the study with normal lab test results except for a mildly elevated GGT. During the study, she had the following chemistry test results:

Selected Lab results for Subject 709, from study 31.0901

Date of Test	CPK (U/L)	GGT (U/L)	LDH (U/L)	SGOT (U/L)
10/20/93	N/A	21	N/A	10
1/19/94	N/A	20	N/A	14
4/20/94	N/A	46	N/A	9
7/13/94	156	18	N/A	7
10/19/94	318	14	312	19
11/4/94	108	N/A	219	N/A
11/14/94	105	N/A	<240	N/A
1/18/95	130	14	212	15
4/19/95	123	15	N/A	12
7/12/95	113	15	N/A	12
10/18/95	72	17	N/A	11

Lab normal ranges: CPK: 10-70 U/L, GGT: 4-18 U/L, LDH: 120-240 U/L, SGOT: 0-15U/L

Isoenzyme results for CPK and LDH were not reported. Study medication was reduced to 10mg/m² on 10/19/94 because of the elevated CPK and LDH. The sponsor stated that during the study no muscular anomalies were reported. They commented that mild cardiac function abnormalities (ECG abnormal) were identified on 8/22/94, 8/27/94, and 10/19/94 but these findings were not described. An echocardiogram was reported for 10/19/94 (the same date as the highest recorded CPK above) and documented an EF of 67% and this subject's lowest recorded EF was 62% (end study). This subject completed the study. The investigator and the sponsor considered this event to be remotely related to study drug and the sponsor commented that "there is no evidence from other trials or post-marketing reports that mitoxantrone induces CPK elevation" (vol. 1, p. 33, 9/27/99 submission).

Subject 1516, a 54 year old male, had abnormalities of several laboratory parameters (bilirubin 1.5xULN, SGOT 1.4xULN, SGPT 81U/L) during the study. The sponsor reported a single CPK

of 381U/L during month 12. The reason for performing this test was not given. The CPK was not fractionated and follow up CPKs were not available. The subject's dose was reduced during the study for leukopenia but not for chemistry result abnormalities. This subject received 8 doses of mitoxantrone and completed the study.

I identified a subject (1103) with a preferred term of hepatocellular damage and I requested a narrative description of this event from the sponsor. This 43 year old female was randomized to mitoxantrone 5mg/m^2 every 3 months. During the study she was diagnosed with biliary colic or colic-like pain on several occasions and was treated with hyoscine and gallstone lithotripsy (hospitalization, although not included as a serious adverse event). This subject's highest bilirubin was 0.8 mg/dL (baseline) and highest SGOT was 18 U/L (baseline) and highest recorded SGPT was 26 U/L (vol. 1, pp. 34-36, 9/27/99 submission).

There were no AEs suggestive of convulsions, rhabdomyolysis, serious skin reaction, or acute hepatic failure.

4.3.2.5 Dose Adjustments

In table 12.1-4 (vol. 86) the sponsor provided a listing of the number of doses each subject received by treatment group in study 31.0901. Eighty six percent (56/65) of those randomized to 5mg/m^2, 77% (48/62) of those randomized to 12mg/m^2, and 75% (48/64) of those randomized to placebo received the protocol intended eight courses of therapy. Table 12.1-5 provided summary data for cumulative dose received in this study. The mean cumulative dose for the 12mg/m^2 group was 82.61 mg/m^2 and for the 5mg/m^2 group was 37.23mg/m^2. The sponsor reported that approximately 9% (n=6) of those in the 5mg/m^2 arm had their dose adjusted during the study compared to 45% (n=27) of those in the 12mg/m^2 arm (vol. 82. p.88). They summarized the number of adjustments by dose group in table F.4.4.A. That table is reproduced below.

Table F.4.4.A. Number of Patients with Dose Adjustments in the Two Mitoxantrone Groups

No. of Dose Adjustments	Mitoxantrone Group	
	5mg/m^2	12mg/m^2
0	59 (90.8%)	35 (55%)
1	4 (6.2%)	14 (23.3%)
2	1 (1.6%)	3 (5%)
3	0 (0%)	7 (11.7%)
4	1 (1.6%)	3 (5%)
Total no. of patients	65 (100%)	62 (100%)

The reasons for dose adjustments were hematological toxicity (15 adjustments in 9 patients, all 12mg/m^2 group); grade 2-3 non-hematological toxicity (10 adjustments in 6 patients in the 5mg/m^2 group and 36 adjustments in 22 patients in the 12mg/m^2 group); severe infection* (subject 1419, 12mg/m^2); and unknown (1 in the 12mg/m^2 group). There were 4 patients (all in the 12mg/m^2 group) who had dose adjustments for both hematologic and non-hematologic toxicity. The investigator was only required to indicate whether the toxicity leading to dose adjustment was hematologic or non-hematologic. A description of the toxicity leading to dose adjustment was not captured. (Source-Tables 12.1-1, 12.1-2, 12.1-3, 12.1-3.1 and 12.1-3.2.) *NDA vol. 88, p. 91

I requested additional information about subject 1419 who was identified as having a dose adjustment for severe infection. In the 9/27/99 response, the sponsor reported that after reviewing the CRF and adverse event listings, they were unable to confirm that this event was severe. They were able to identify only mild and moderate adverse events for this subject.

4.3.2.6 Lab testing
The parameters tested and the schedule for collection of labs were discussed above.

Hematology Results
For their analysis of lab data, the sponsor provided a summary table for hematological lab results. The table provided, for each of the 3 treatment arms, the mean (SD), median, minimum, and maximum values for the tested parameters for baseline and then the on study maximum change.

The sponsor also provided tables in the appendices that summarized the mean values, mean changes from baseline, and extreme values for laboratory parameters by study month (12.3.3-2 through 12.3.3-10). I have arbitrarily selected to display the values for month 12 (following 4 doses) and end study mean change values.

Hematology Mean Changes from Baseline

Parameter	Placebo		$5mg/m^2$		$12mg/m^2$	
	Month 12	End	Month 12	End	Month 12	End
Hemoglobin	0.1	0	-0.1	-0.1	-0.2	-0.2
Platelets	1.3	4.1	-2.8	-6.1	-21.9	-21
WBC	0.1	0.3	-0.2	-0.2	-0.9	-0.8
Granulocytes	0.5	0.9	-0.5	0.6	-0.4	-0.4

Granulocyte analysis based on n=13 for $12mg/m^2$, n=15 for $5mg/m^2$, and n=15 for placebo

The mean change from baseline analysis suggests a dose response for decrease in WBC and platelets. There were few individuals with granulocyte counts in this study.

The sponsor also provided tables with hematological result outliers (tables 12.3.3.1-1 through 12.3.3.1-5). They stratified by whether the baseline value was within, above or below the normal range and then provided the number above or below the normal range during the study. I summarized the risk for having an outlier among those subjects with normal results at baseline.

Risk of outliers for subjects normal at baseline, by treatment

Analyte	Placebo	$5mg/m^2$	$12mg/m^2$
Hemoglobin	18% (10/57)	22% (13/60)	22% (12/55)
Platelets	5% (3/60)	8% (5/61)	11% (6/57)
WBC	7% (4/55)	22% (13/58)	37% (19/52)

This outlier analysis supports a mitoxantrone related increased risk for low WBC count and suggests a relationship between dose and low platelet count.

In order to examine the data more closely for evidence of low granulocyte counts, I reviewed the hematology listing for study 31.0901 provided by the sponsor (Appendix VIII, vol. 90). The data listing included WBC, %neutrophils and in a few cases granulocyte counts. When granulocyte counts were provided, they were used in this analysis. When a granulocyte counts was not provided, I calculated one by multiplying the WBC count by the % neutrophils. Rarely, only the WBC was provided and when that happened there was no way to estimate the granulocyte count. In some cases there were counts provided that were likely data entry errors (generally abnormally high, probably related to use of different units). I identified patients with neutrophil counts less than $2.0x$ $10^9/L$ during the study.

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Neutrophil Counts <2.0x 10⁹/L for Patients Enrolled in Study 031.0901

Patient	Gender	Granulocyte Count	Month/dose group
1401	Male	1.71	9/12
1408	Female	1.9	15/12
1411	Male	1.05	9/12
1416	Male	1.81	6/12
1419	Female	1.75	12/12
		1.8	15/12
1424	Male	1.7*	12/12
1516	Male	1.9	21/12
		1.9	24/12
1608	Female	1.8	9/12
5805	Female	1.8	6/12
5811	Female	1.6	21/12
5902	Male	1.8	18/12
103	Female	1.8	15/5
1418	Female	1.9	15/5
1605	Female	1.9	24/5
1609	Male	1.8	6/5
1617	Male	1.8	18/5
		1.9	21/5
		1.8	24/5
5810	Female	1.9	18/5
5906	Female	1.5	12/5
		1.4	12/5
		1.5	12/5
		1.6	15/5
		1.6	15/5
		1.7	18/5
		1.6	18/5
		1.9	24/5
1406	Male	1.8	21/P
1423	Female	0.8	9/P

*total WBC count provided, there was no differential reported for this result
Patient 714 had a granulocyte count of 0.15 listed for month 12 which was not in agreement with the WBC count (4.9) and the % neutrophils (59%)
Patient 1412 had a granulocyte count of 63.8 listed for month 6 that is incorrect
Patient 5813 had a granulocyte count of 1.3 listed or month 9, which was not in agreement with the WBC count (11.4) and the % neutrophils (64%)
Patient 5002 had a granuiocyte count of 2,838 reported for month 0

No patients had a documented neutrophil count less than 0.5x 10⁹/L. Patients randomized to the 12mg/m² mitoxantrone dose group had the highest risk of a neutrophil count <2.0x 10⁹/L (18%, 11/60) followed by the 5mg/m² mitoxantrone dose group (11%, 7/64) and then the placebo group (3%, 2/64).

I reviewed the lab listings to identify subjects with platelet counts less than 100,000/mm³. No subjects in the 12mg/m² had a platelet count ≤100,000/mm³ compared to 1 in the 5mg/m² group (94,000/mm³ at final visit) and one in the placebo group (lowest 73,000/mm³).

Chemistry Results
The sponsor commented that mean creatinine and bilirubin levels did not change during the study. The sponsor reported increases in mean SGOT compared to baseline in the mitoxantrone group and placebo group. The mean changes for creatinine, bilirubin and SGOT are summarized

below. The sponsor provided the mean changes for each of the protocol specified lab collection periods (Tables 12.3.3-11 through 12.3.3-15). I have chosen to display the values for month 12 and the end study mean change values.

Chemistry Mean Changes from Baseline

Parameter	Placebo		5mg/m²		12mg/m²	
	Month 12	End	Month 12	End	Month 12	End
Creatinine	0.1	0.1	-0.1	0.1	-0	0
Bilirubin	0.1	0.3	0.1	0.3	0	-0.1
SGOT	-0.5	8.2*	-0.8	1.4	2.2	2.3

*The mean change for SGOT in the placebo group is influenced by a single patient with SGOT of >500. The median change for the placebo group at end study was –1.0, compared to 1.0 in the 5mg/m² group and 2.0 in the 12mg/m² group.

The sponsor also provided tables (12.3.3.1-11 through 12.3.3.1-15) with chemistry result outliers (results outside the laboratory normal range). They stratified by whether a subject's baseline value was within, above or below the laboratory normal range and then provided the number of subjects with results above or below the normal range during the study. I summarized data from those tables below.

Risk of outliers for subjects normal at baseline, by treatment

Analyte	Placebo	5mg/m²	12mg/m²
Creatinine	7% (4/59)	10% (6/59)	11% (6/56)
Bilirubin	19% (11/57)	17% (10/59)	11% (6/55)
SGOT	15% (9/60)	27% (16/59)	30% (17/56)

There did not appear to be large differences in risk for creatinine or bilirubin outliers between treatment groups but there appeared to be a dose response for SGOT outliers. Since the sponsor used lab results greater than the upper limit of normal to define outliers, I analyzed the lab results for more extreme outliers to look for differences by treatment. I identified subjects normal at baseline who had an SGOT result >100U/L during the study. One subject from the mitoxantrone 12mg/m² group (1413, SGOT 152U/L), and 1 from the placebo group (404, SGOT 595U/L) met these outlier criteria. Considering more extreme SGOT outliers there did not appear to be differences in risk by treatment group in this study.

For bilirubin, I identified those subjects normal at baseline and with a bilirubin >2.0mg/dL during the study. I identified 1 subject from the 12mg/m² group (5815, bilirubin 6.8), one from the 5mg/m² group (5302, bilirubin 2.11), and three from the placebo group (404, bilirubin 14.4; 1102, bilirubin 2.1; 5002, bilirubin 8.8) that met these criteria.

4.3.2.7 Vital Signs

There was no analysis of vital sign data from study 31.0901 in either the ISS or the study report. The sponsor reported in their 9/27/99 submission that vital signs were only recorded at baseline in this trial.

In the Four Month Safety Update the sponsor provided an analysis of baseline to month 24 data for the number of days with temperature above 38°C by treatment group. There was no discussion of the methods used to capture temperatures. The sponsor comments that there were no clinically relevant differences among treatment groups for the number of days with temperature above 38°C at any of the time points evaluated (p.14, Safety Update). The sponsor did not report the number of subjects with temperature elevations above 38°C by treatment group.

4.3.2.8 Cardiac Monitoring Results

The sponsor did not provide an analysis of mean change from baseline for ECG intervals. In the study report, the sponsor noted that 7.8% (n=5) in the placebo group, 9.2% (n=6) in the 5mg/m^2 group, and 11.3% (n=7) in the 12mg/m^2 group had an abnormal resting ECG at month 12 (vol. 84, p.118). I reviewed the listing of diagnoses for abnormal ECGs in table 12.4.1.2.-2. In the 12mg/m^2 group, the abnormalities were bradycardia, repolarization disturbances, sinus tachycardia (2), tachycardia, sinus arrhythmia, and incomplete right block. The abnormalities for the 5mg/m^2 group were ventricular extrasystole (2), incomplete RBBB, a negative T and P wave, repolarization abnormality, and an untranslated diagnosis. In the placebo group there were 3 ECG diagnoses in German that were not translated to English, and one diagnosis of poor R wave progression and one of sinus arrhythmia. The ECG findings were considered not clinically relevant.

The sponsor summarized echocardiograph data collected from this trial in table F.4.9.B. in the ISS. Information from that table is provided below.

Summary of Echocardiography Results from Study 31.0901

Value below lower limit of center	Value below 50%	Decrease≥10% compared to baseline	Treatment Group		
			Placebo N	Mitox 5 N=	Mitox 12 N
No examination			5	5	7
No	No	No	48	49	38
No	No	Yes	9	7	12
Yes	No	No	0	0	1
Yes	No	Yes	1	2	1
Yes	Yes	Yes	1	2	3

Decreases in EF of at least 10% from baseline appeared to occur commonly in all 3 treatment groups. Eight percent (n=5) of those exposed to 12mg/m^2 had an EF below the local limit of normal compared to 6% (n=4) in the 5mg/m^2 group and 3% (n=2) in the placebo group. As stated above, there was a single subject (1105, 12mg/m^2 group) who discontinued from the study for decrease in ventricular function.

In the Four Month Safety Update, the sponsor summarized ejection fraction data that were collected at month 36 (p.6). The sponsor commented that they did not have month 36 data for 7 subjects who had abnormalities during the study. They did not have additional information for subject 1105 who discontinued for decrease in ejection fraction. Subjects 1520 and 5910, who were identified with treatment emergent EF abnormalities in the ISS (below local normal limit), had increases in ejection fraction off drug and were considered normal at month 36. There were four subjects who had normal ejection fractions during the first 24 months of the study but were considered abnormal at month 36. Those subjects and their echo results are listed below.

Ejection fraction data for subjects normal on drug but abnormal at month 36

Subject	Last on treatment EF	Month 36 EF
501 (5mg/m^2)	80%	53%
5302 (5mg/m^2)	61%	58%
5401 (5mg/m^2)	56%	45%
408 (12mg/m^2)	57%	40%

The sponsor did not provide additional information (ex. clinical findings, treatment etc.) for these subjects.

Sponsor's Safety Summary

In their summary and conclusions regarding safety in this study, the sponsor commented that the drug was well tolerated and that the adverse events and laboratory findings were consistent with the known safety profile for mitoxantrone when used in cancer patients. They pointed out that the leukopenia was significantly more common in the mitoxantrone group but was not associated with an increased risk of infection. They noted that serious cardiotoxicity was not reported (vol. 84, pp. 119-122).

4.4 Safety in Study 31.0902

The sponsor summarized safety data from study 31.0902 in section F.5 (vol. 82, p. 100). The study report for this trial is provided in vol. 93.

4.4.1 Study description

This study was a Phase II single blinded controlled trial with subjects randomized to mitoxantrone plus methylprednisolone or methylprednisolone alone. The study was conducted at five centers in France between 4/92 and 3/95. The studied population included MS patients aged 18 to 45 with disease duration of ≤ 10 years. To be included, subjects had to have a baseline LVEF >50% by radionuclide angiography or >40% by echo. Patients were excluded from the study if they were pregnant or breast feeding, had received cardiotoxic drugs, had concomitant illnesses, or had been treated with immunosuppressive agents for a duration >3 months during the preceding year or had received immunosuppressive therapy within the prior 3 months.

Eligible patients (n=85) received methylprednisolone 1g monthly for two months and underwent monthly MRIs with gadolinium enhancement. Those patients with evidence of new lesions during the triage period were then randomized to receive methylprednisolone alone at a dose of 1g or mitoxantrone given at a fixed dose of 20mg (the equivalent of 12-14mg/m^2) plus methylprednisolone 1g. The treatments were to be administered monthly for six courses for a total dose of 120mg of mitoxantrone. Dose reduction was not permitted but treatment delay was allowed under specific conditions.

Safety monitoring included monthly physical examinations, monthly serum chemistries for all subjects, weekly CBCs for mitoxantrone subjects, monthly CBCs for control group subjects, and baseline and end of study ECGs and echocardiograms.

Of the 85 patients who entered the triage period, 44 were randomized and 42 continued into the treatment period, 21 to the methylprednisolone plus mitoxantrone arm and 21 to methylprednisolone alone. The mean age for the 21 mitoxantrone+methylprednisolone patients patients was 31.4 ± 8.3 years compared to 32.3 ± 8.1 years for the methylprednisolone subjects. In the mitoxantrone+methylprednisolone group there were 6 males and 15 females while in the methylprednisolone group there were 10 males and 11 females (vol. 93, p.37). The sponsor converted the dose in mg to mg/m^2 to allow comparison with data from other trials. The overall cumulative mean dose was 81.2mg/m^2 and the range was 61.6 to 101 mg/m^2 (vol. 93, p.44).

4.4.2 Safety Results

4.4.2.1 Deaths

The sponsor reported that there were no deaths reported while patients were on study drug. There was no long-term follow up beyond the end of the study (vol. 82, p.85 table F.2.).

4.4.2.2 Serious Adverse Events

The sponsor reported that no serious events were reported to the French regulatory agency but the definition of a serious adverse event was not provided in the study report. I asked the sponsor to provide the criteria used to determine if an adverse event was serious. In their 9/27/99 submission they stated that an adverse event was considered serious if the event resulted in death or placed the patient's life at risk, resulted in a permanent handicap, or resulted in hospitalization or prolonged a hospitalization.

4.4.2.3 Discontinuations

The sponsor reported that one mitoxantrone + methylprednisolone subject was withdrawn on day 1 following the first dose of medication (due to increased ALT and AST, attributed to fluoxetine). One subject in the methylprednisolone group was withdrawn on day 21 for rapid disease progression. Neither of these patients was included in the analyses because they did not undergo MRI analyses after month 0 (vol.93, p.31). During the treatment period, 5 subjects discontinued from the study. All five were in the methylprednisolone arm and the discontinuations were for deterioration and lack of efficacy (vol. 93, p.35).

4.4.2.4 Treatment Emergent Adverse Events

The sponsor summarized the treatment emergent adverse events in table F.5.7. That table is reproduced below.

Table F.5.7. Number of Patients with Adverse Events (Listed by Body System)

Adverse Events	Methylpred (n=21)		MITOX + Methylpred (n=21)	
	No. Pts (%)	No. Events	No. Pts (%)	No. Events
Digestive System				
Nausea	-	-	6 (29)	21
Stomach burning or epigastric pain	1 (5)	1	2 (10)	2
Abdominal pain	-	-	1 (5)	2
Gastralgia	-	-	2 (10)	4
Gastroenteritis	-	-	1 (5)	1
Retrosternal burning	-	-	1 (5)	1
Cytolytic and cholestatic hepatitis	1 (5)	1	-	-
Hemorrhoid	1 (5)	1	-	-
Neurologic System				
Asthenia	-	-	5 (24)	14
Insomnia	-	-	1 (5)	2
Anorexia	-	-	1 (5)	1
Depression	-	-	1 (5)	1
Faintness	-	-	1 (5)	1
Headache	1 (5)	1	-	-
Genitourinary system				
Amenorrhea	-	-	8 (53)*	11
Urinary infection	1 (5)	2	4 (14)	6
Menorrhagia	-	-	1 (7)*	1
Cutaneous system				

Alopecia	-	-	7 (33)	7
Herpes simplex	-	-	1 (5)	3
Aphthosis	-	-	2 (10)	2
Mycosis	-	-	2 (10)	2
Urticaria	-	-	1 (5)	1
Eczema	1 (5)	1	-	-
Photosensitivity	1 (5)	1	-	-
Respiratory system			-	
Throat infection	1 (5)	1	3 (14)	4
Pharyngitis	-	-	2 (10)	3
Rhinitis	-	-	2 (10)	3
Dyspnea	1 (5)	1	-	-
Laryngitis	1 (5)	1	-	-
Flu syndrome	1 (5)	1	-	-
Cardiovascular system				
Tachycardia	-	-	1 (5)	3
Palpitation	1 (5)	1	-	-
Other				
Hot flash	-	-	1 (5)	3
Periarthritis	-	-	1 (5)	1
Conjunctivitis	-	-	1 (5)	1
Contact lens intolerance	-	-	1 (5)	1
Edema	1 (5)	1	-	-
TOTAL	6 (29)*	14	18 (86)*	101

* Denominator is for female patients only (n=15)
* Excludes double-counting; patients may have had more than one event but are only counted once

The sponsor reported that all of the events in the mitoxantrone+methylprednisolone subjects resolved quickly with the exception of amenorrhea (8), alopecia (2), mycosis (2), asthenia (1), and retrosternal burn (1).

4.4.2.5 Lab testing

As stated above, hematological lab testing was performed weekly from month 0 through 6 in the mitoxantrone group and monthly in the methylprednisolone group. Outlier and mean change from month 0 analyses were provided. The outlier analyses classified results as potentially clinically significart abnormalities (PCSAs) if they met pre-specified criteria. Those criteria were provided in vol. 95, p.35 and are summarized below.

Criteria for Potentially Clinically Significant Abnormalities

Parameter	PCSA
ALT, AST	>2 ULN
ALP	>1.25 ULN
Total bilirubin	>2 ULN
Conjugated bilirubin	>5 μmol/L
Creatinine	>30% increase from baseline
Total cholesterol	>2 mmol/L
Triglycerides	>2.5 mmol/L
Fasting glucose	$\geq$ 7.8 mmol/L
(glucose oxidase method)	<3.3 mmol/L
Potassium	<3.5
	>5.5
Hemoglobin	Female <11g/dL
	Male <12g/dL

WBC	<3,000/mm³
Neutrophils	<1,500/mm³
Eosinophils	>500/mm³
Platelets↓	<100,000/mm³

Hematology

Mean change from baseline

The sponsor provided a table with the mean values for laboratory parameters by treatment group for each month of the study. In the following table, I display the month 0 and month 6 mean values and the mean change observed.

Parameter	Methylprednisolone			Mitoxantrone + Methylprednisolone		
	Month 0	Month 6	Mean Δ	Month 0	Month 6	Mean Δ
Hemoglobin	13.69	13.52	-.17	13.41	13.1	-.31
WBC	7.31	6.96	-.35	6.51	4.54	-1.97
Neutrophils	4.25	4.15	-.1	3.97	2.84	-1.13
Platelets	267.7	247.62	-20.08	246.14	216	-30.14

Mitoxantrone treated subjects experienced greater mean decreases from baseline for the above hematologic parameters compared to the control subjects.

Outliers

The sponsor provided a summary table describing decline in WBC count and neutrophils following treatment (table F.5.10.1, vol. 82, p.105). Forty-eight percent (10/21) of the mitoxantrone treated subjects developed a WBC ≥1.0 to <2.0 x10⁹/L and none developed a WBC count <1.0 x10⁹/L at any point during the study. Using the lab listings, I identified 19 subjects (90%) with a neutrophil count ≤1.0 x10⁹/L during the study and 9 subjects (43%) had a neutrophil count <0.5 x10⁹/L during treatment. All but 3 of the patients (202, 402, 404) who developed a neutrophil count <0.5 x10⁹/L had neutrophil counts >0.5 x10⁹/L when tested the following week. Subject 202, had a neutrophil count of 0.43 x10⁹/L during week 2 of month 1, which declined to 0.29 x10⁹/L the next week. During month 6, this same patient had a neutrophil count of 0.4 x10⁹/L during week 2 that increased slightly to 0.48 x10⁹/L during week 3. Two patients (402, 404) had neutrophil counts <0.5 x10⁹/L with a missing value at the next visit. From the summary tables and lab listings, there were no subjects identified with neutrophil counts <0.5 x10⁹/L at week 4 although there were missing values.

To examine the risk of low neutrophil count over time, I identified subjects with neutrophil counts ≤ 1.0x10⁹/L and ≤ 0.5x10⁹/L by study month. Those results are included in the following table.

Risk of Low Neutrophil Count Stratified by Month, Study 31.0902

Study Month	% (n) subjects with neutrophil count ≤1 x 10⁹/L	% (n) subjects with neutrophil count ≤0.5x10⁹/L
1	48% (10)	10% (2)
2	52% (11)	19% (4)
3	48% (10)	19% (4)
4	57% (12)	24% (5)
5	57% (12)	38% (8)
6	57% (12)	29% (6)

These results suggest that the risk for neutrophil count ≤1.0x10⁹/L persisted and the risk for experiencing a neutrophil ≤0.5x10⁹/L increased during the study.

No mitoxantrone-exposed subjects had a platelet count less than 100,000/mm^3 during the study. Five mitoxantrone-exposed subjects had a hemoglobin <10g/dL at any time during the study compared to 10 subjects in the control group (vol.93, p.69).

The sponsor stated that "the hematologic abnormalities were reversible without further treatment, did not lead to any clinical event, and did not result in transfusion of blood products." (vol. 82, p.106)

Chemistry
The investigators collected serum chemistry labs monthly from patients enrolled in this study. The chemistry labs collected were glucose, sodium, potassium, calcium, alkaline phosphatase, AST, ALT, Gamma GT, urea, creatinine, uric acid, and total protein.

Mean Change from baseline
The sponsor provided a table with the mean values for laboratory parameters by treatment group for each month of the study. In the following table, I display the month 0 and month 6 mean values and the mean change observed.

Parameter	Methylprednisolone			Mitoxantrone + Methylprednisolone		
	Month 0	Month 6	Mean Δ	Month 0	Month 6	Mean Δ
Creatinine	84.95	84.71	-.24	75.25	76.53	1.28
AST	15.5	14.67	-.83	17.8	22.15	4.35
ALT	19.3	18.6	-.7	32	23.47	-8.53
Alkaline Phos	67.8	64.6	-3.2	58.05	66.33	8.28

Compared to the control group, mitoxantrone exposed subjects had greater mean increases in creatinine, AST and alkaline phosphatase and a greater mean decrease in ALT.

The sponsor identified patients who developed a chemistry outlier (meeting PCSA criteria). The following table summarizes the outliers for chemistry tests.

Patients with Serum Chemistry Test Outliers

Parameter	Methypred (month)	MITOX+ Methlpred (month)
Glucose	207, high (M-1) 309, low (M6)	306, high (M6) 412, high (M6)
Potassium	103, low (M-1) 105, low (M-2) 501, low (M0)	206, low (M2) 208, low (M-1,M0) 404, low (M0, M3, M4, M5)
Alkaline Phosphatase	407, high (M2)	208, high (M5, M6)
AST		402, high (M1,M2) 412, high (M6)
ALT	407, high (M2)	402, high (M-1,M0,M1,M2)

I reviewed the sponsor's submitted listings of all test results to further examine the transaminase abnormalities identified above. For subject 402, AST and ALT were normal at 2 months prior to randomization and then were elevated at 1 month prior to randomization (AST 67U/L, ALT 182U/L). The highest ALT (375U/L) occurred in the month following the first treatment and the highest AST (177U/L) occurred during the second month of treatment. Both AST and ALT declined thereafter and were 18U/L and 47U/L respectively during month 6. Total bilirubin was not measured in this study. Patient 412 had a single elevated AST result (102U/L) during month 6 and ALT was normal throughout the study.

4.4.2.6 Vital Signs

Vital signs (SBP, DBP, and HR) were recorded monthly. In the sponsor's analysis of these data, they identified, by treatment, the number of subjects meeting outlier criteria at months 0 and 6. The outlier criteria included: SBP ≤90mmHg or ≥160mmHg, DBP ≤50mmHg or ≥95mmHg, and HR ≤4⊃bpm or ≥100bpm. There was a slight numerical excess for SBP outlier in the mitoxantrone group at both month 0 (3 v. 1) and month 6 (5 v. 1) but no marked differences were noted for DBP or HR (Table 7.1.2.A. vol.93, p. 64). The sponsor also provided a table (7.2.1.B.) that identified the number of patients by treatment that had outliers for change in a vital sign at any time during the study. Information from that table is provided below.

Vital Sign Changes Compared to Month 0

Parameter	Change	Treatment Arm	No. of Patients	No. of patients with abnormal value
SBP	↓ 20 mmHg	MP	5	0
		MITOX+mP	10	4
DBP	↓ 15 mmHg	MP	6	0
		MITOX+mP	9	3
HR	↓ 15 bpm	MP	4	0
		MITOX+mP	9	0
	↑ 15 bpm	MP	3	1
		MITOX+mP	6	0

The data describe an increase in risk for decreases in SBP, DBP, and HR for mitoxantrone exposed subjects. Beginning on p. 94 of vol. 95, the sponsor provided the vital sign measurements for the study subjects. The lowest recorded systolic BP was 90mmHg (mitoxantrone n=8, methylprednisolone n=4). The lowest recorded diastolic BP was 50mmHg (mitoxantrone n=6, methylprednisolone n=6). No study patients had a recorded heart rate below 50 bpm. Among mitoxantrone exposed subjects, the highest systolic BP was 170mmHg (#402, month4) and there were no other SBPs>160mmHg. There were no DBP recordings >100mmHg. No mitoxantrone subjects and 2 methylprednisolone subjects had recorded heart rates>100bpm. The fact that all BPs ended in either 0 or 5 raises questions about the validity of the blood pressure measurements.

4.4.2.7 Cardiac monitoring

Cardiac monitoring included electrocardiograms and echocardiograms at month -2 and month 6. The sponsor commented that significant cardiotoxicity was not reported in any patient. All ECGs in both groups were reportedly normal except for one patient in the mitoxantrone +methylprednisolone group who had an inverted T wave at Month 6 (vol. 93, p.63). No treatment emergent echocardiographic abnormalities were noted in either group (3 patients in the mitoxantrone group had mitral valve prolapse noted at baseline).

Three episodes of tachycardia occurred in one mitoxantrone patient (#506). The sponsor was asked to explain these events. They responded in the 9/27/99 submission that this subject experienced these events "on different dates in Months 2,3, and 4". In addition, they stated that "The events were mild, intermittent and each had a duration of 7 days. All events were reported to have resolved without requiring treatment." Additional information about the rate, rhythm etc, were not provided (9/27/99, p.15).

Sponsor's Safety Summary
In their safety summary section for this study report, the sponsor acknowledged that AEs were more frequent among mitoxantrone subjects and that most of these events were expected based on the known safety profile of mitoxantrone. They noted that neutropenia was the most frequent lab abnormality in the mitoxantrone group but that no significant infections were associated with neutropenia (vol. 93, p.72).

4.5 Safety Data from Retrospective Analysis: Study 31.0903
The safety data summarized for the cohort of MS patients treated in a German clinic was located in vol. 97 of the NDA, and also beginning on p. 107 of the ISS.

4.5.1 Report Description
For the purpose of providing long term safety data, the sponsor conducted a retrospective analysis of a cohort of MS patients who were treated with mitoxantrone in a clinic in Germany between November 1988 and September 1998. The clinic is an academically affiliated referral center that treats MS patients. A CRF was used to capture data from the clinic medical chart and the sponsor did not have access to the source documents (vol. 97, p.15). The CRF was designed to capture events such as cardiotoxicity, malignancy, amenorrhea, pregnancies, infection, and treatment with antibiotics. The CRF also captured the following lab data: leukocyte counts, lymphocyte counts, granulocyte counts, and immunoglobulin concentrations. The CRFs did not capture information about severity of an adverse event. The sponsor commented that attempts were made to obtain follow up information on patients who were not currently being treated at the clinic at the time of the review (vol. 97, p.13).

The sponsor identified a total of 454 patients treated during the 10-year interval. Patients with a history of cardiac disease (not defined) were excluded from treatment with mitoxantrone (vol.97, p.15). No other treatment exclusion criteria were mentioned. The standard dose of mitoxantrone used during this period was 12mg/m^2 administered every 3 months. Patients had their dose of mitoxantrone adjusted at the discretion of their treating physician. Doses were adjusted downward in patients demonstrating responses or in patients developing toxicity (ex. lymphocyte count <900). Other MS treatments and symptomatic treatments were administered but CRFs did not capture information about concomitant medications (vol. 97, p.16).

Patients received a mean of 4.4 doses of mitoxantrone (range 1 to 17). Eighty five percent received at least 2 doses and 64% received at least eight doses. Two patients received 17 doses. The mean dose administered was 9.81 mg/m^2 and the mean cumulative dose was 43.52 mg/m^2. Ninety three percent (424/454) received a cumulative dose <100mg/m^2 (vol.97, p.44). Six patients received a cumulative dose of at least 140mg/m^2 and the highest recorded cumulative dose was 183.3mg/m^2. The average number of months since first dose (time in study) was 47.4 months and the longest follow up time was 121 months.

4.5.2 Safety Results

4.5.2.1 Deaths
The sponsor identified a total of 20 deaths in the cohort (4%). On p.45 of vol.97, the sponsor provided a death summary table listing the causes of death. Eight deaths were attributed to *pneumonia*, 5 to *insufficiency of breath*, 3 were unknown, and the remaining 4 were attributed to *bladder dysfunction/infections, cachexia, heart failure, and pulmonary infection+cardiomyopathia*. The sponsor provided narratives for the deaths in their 9/27/99 submission. For some of the deaths, the sponsor reported that the cause of death was obtained by telephone conversations with family members.

The sponsor analyzed the interval between last dose and death for these patients. Three patients died within 19 months of last dose (2 months-bladder dysfunction/infection, 8 months-pneumonia, and interval not specified- insufficiency of breath) and 11 died more than 3 years after their last dose.

4.5.2.2 Serious AEs

The sponsor reports that no serious adverse events were reported to the German regulatory agency.

4.5.2.3 Discontinuations

The sponsor reported that 341 patients discontinued treatment with mitoxantrone during the 10 year period and the remaining 113 patients are continuing to receive mitoxantrone. Seventy-seven patients discontinued for *treatment success* and 44 for *treatment failure*. Twenty patients reached a cumulative dose considered maximal by the treating physician. Thirty-four patients discontinued for *adverse events*. One hundred forty-seven patients discontinued for *other* reasons (not described). Information about reason for discontinuation was not known for 4 patients and was not completed for 15 patients (vol. 97, p.21). The sponsor included a listing of reasons for mitoxantrone termination (listing 4.2, vol. 97, pp277-314). This listing included a column titled *Specify*, which appeared to further explain the reason for discontinuation. If the reason for discontinuation was *adverse event*, *Specify* would list the event (ex. lymphopenia, cardiotoxicity, etc.). I identified a total of 32 discontinuations due to *adverse events*. Nine were for leukopenia, 5 for lymphopenia, 5 for cardiac events, 3 for infection, 3 for vomiting, and one each for general weakness, reduced condition, increased liver enzymes, hepatitis C, very bad general condition, skin necrosis, and no event listed. A majority of the discontinuations classified as *patient refusals* did not include information about why the patient refused (n=109). For those *patient refusals* with a reason, desire to become pregnant was most frequently noted (n=8). There were discontinuations classified as *patient refusals* that included information suggesting an adverse event may have been involved (#67- vomiting, #260-alopecia, #266 infections, #302 low leukocytes, #369 decreased left ventricular ejection fraction, #385 vomiting, #439 low leukocytes). In addition, there were four discontinuations listed under *treatment failure* that had information suggesting an adverse event was involved (#176 leucopenia, #395 ongoing lymphopenia, #408 multiple infections, #416 alopecia). There were no narrative summary descriptions provided for the adverse events leading to discontinuation.

4.5.2.4 Treatment Emergent Adverse Events

All treatment emergent adverse events were not collected during this retrospective review. As described above, the review focused on specific events such as infections, cardiotoxicity, menstrual cycle abnormalities, secondary leukemia, and hematology results, blood chemistry results and immunoglobulin levels.

Infections

The sponsor reported that 38% (171) of patients in the cohort had a recognized infection during the observation period. Eighty six percent of these were classified as UTIs, 2% were URIs, <1% were sinusitis, and 12% were unknown. The sponsor noted that the severity and outcome of infections were not reported. The sponsor did not state, which if any of these infections occurred in the setting of decreased WBC counts. The sponsor provided a listing of infections that only included the patient number, the site of infection and whether or not antibiotics were administered.

Cardiotoxicity
Patients with a history of cardiac disease were excluded from treatment with mitoxantrone. This was not a trial with formally delineated schedules of monitoring for cardiac toxicity. The sponsor reported that echocardiograms were performed to assess clinical findings suggestive of cardiac toxicity and in patients exceeding the cumulative dose of 140mg/m^2 to monitor cardiac function before each course of therapy (vol. 97, pp 15-16). Forty-five percent (203/454) of patients had at least one echocardiogram (number of patients studied for each indication was not provided). Since there were only 6 subjects who were treated with cumulative doses exceeding 140mg/m^2, there were a large number of echocardiograms performed for reasons not explained. Forty-three of the 203 patients studied (21%) had abnormal echocardiogram results. Abnormalities included ventricular dilation/dysfunction (14%, 29/203 patients studied), pericardial effusion, and valvular abnormalities. The severity of LV dilatation/dysfunction was not recorded on the CRF.

The sponsor reported that ECGs were routinely performed prior to administering a dose of drug. For hundred and fifty three of the 454 patients had at least one ECG and the mean number per patient was 4.3. Thirty-two percent of patients (143/453) had abnormalities detected on ECG. Conduction block was the most common abnormality, and was observed in 17% (79/453) of the patients. Extrasystoles were seen in 5% of the patients, ST-T repolarization abnormality in 4% and ventricular hypertrophy in 2%. No other ECG abnormality was recorded in more than 1% of patients. I reviewed listing 5, which provided the diagnoses for the ECGs. Most of the events categorized as conduction blocks were bundle branch blocks.

The sponsor reported that 7 patients developed cardiotoxicity. The identified events included arrhythmia, decreased ventricular ejection fraction, diastolic functional disturbance, mitral insufficiency, and decreased contractility of the left ventricle. Two of the patients with cardiotoxicity died and one of the deaths was attributed to pulmonary infection and cardiomyopathy and the other to respiratory failure associated with an upper respiratory tract infection. The cumulative dose for the patients developing cardiotoxicity (except for the arrhythmia patient who dc/d after one dose) was between 41mg/m^2 and 130mg/m^2. The sponsor provided narrative summaries for the deaths in the 9/27/99 submission. I reviewed the narratives for the subjects with cardiotoxicity who died.

Subject 281, a 42 year old male MS patient, was treated in the clinic with mitoxantrone, cumulative dose of 155mg (91mg/m^2) over a 2 year period (5/90-4/92). The narrative reports that the patient's family doctor administered an additional 120mg over a 2-year period (1/94-2/96). Two months after his last dose, he was admitted for cardiogenic shock and died of cardiac insufficiency.

Subject 369, a 41 year old male MS patient was treated with a cumulative dose of 100mg (50mg/m^2). An echocardiogram noted diffuse hypokinesia of the left ventricle with some reduction of ejection fraction at rest. Mitoxantrone was stopped. The patient died during the next year (date not provided) and the death was attributed to respiratory insufficiency during an upper respiratory tract infection.

Malignancies
The sponsor identified one patient who was diagnosed with a malignancy after initiating treatment with mitoxantrone (carcinoma of the cervix). The sponsor did not identify any patients in the cohort who developed secondary leukemia.

Effect on Fertility and Menstrual Cycle
The sponsor reported that 33/276 (12%) women in the cohort experienced amenorrhea and that none of these events were listed as a cause for discontinuation. After discontinuing therapy, 27% of the women with amenorrhea recovered (time to recovery not known). They did not state the length of follow up off drug for those women with persistent amenorrhea. Four pregnancies

occurred in women who were receiving mitoxantrone. Mitoxantrone was discontinued when it was discovered that the women were pregnant. Five females became pregnant following their last dose of mitoxantrone. Six of the nine pregnancies resulted in normal children, the outcome of 2 pregnancies was not known and 1 woman had not yet given birth at the time of the report.

Hematology
The sponsor reported that lab samples were collected prior to each administration of mitoxantrone. Twenty-eight patients had WBC counts $\geq 1,000/mm^3$ and $<2,000/mm^3$ and none had WBC counts $<1,000/mm^3$. The sponsor reported that 12 patients had absolute neutrophil counts $<500/mm^3$ and that 62 patients had absolute neutrophil counts between 500 and $1,000/mm^3$. The sponsor did not describe these events or note if any of these patients required hospitalization or treatment.

Sponsor's Safety Summary
In their discussion and conclusions section of this study report, the sponsor commented that the safety data collected suggest that mitoxantrone is well tolerated in this population. They did not identify any unique or unexpected adverse events based on the drugs known safety profile in cancer patients. They felt there was less hematologic toxicity in these MS patients compared to the experience with cancer patients (vol.97, p.32).

4.6 Safety Data from MS Studies Published in Peer-Reviewed Journals
In section F.7 of the ISS, the sponsor presented safety data from 3 studies (one randomized controlled trial, two open label trials) that appeared in peer reviewed journals. The sponsor noted no previously unidentified adverse events.

4.7 Post Marketing Safety
The sponsor provided a listing of the types of spontaneous post marketing reports for mitoxantrone that had more than 5 occurrences but did not review individual reports (vol. 82, p. 115). I contacted Mary Mease in the Division of Drug Risk Evaluation I (OPDRA) and requested a query of the FDA AERS database to identify the mitoxantrone post marketing adverse event reports. She provided a listing of 598 reports. From this listing, I identified events of interest and requested the actual MedWatch forms for review. The requested reports were for events related to rhabdomyolysis, renal failure, hepatic failure or injury, and congestive heart failure.

Elevated CPK/Rhabdomyolysis
The two patients with reports of elevated CPK were diagnosed with acute myocardial infarction and had elevation of the MB isoenzyme. There was one report of rhabdomyolysis. The report described a 46-year-old female who developed rhabdomyolysis and renal failure following the first course of mitoxantrone and cyclophosphamide. The reporter did not identify a clear cause but did describe a decrease in muscle phosphorylase activity in this patient, which may have contributed to the event. This case resulted in a literature report. There was one report of myositis. This report described a patient who developed proximal muscle weakness and muscle pain but did not suggest a clear case of rhabdomyolysis.

Liver failure/Acute Liver Injury
There were reports for 5 patients with serious acute liver injury or liver failure. In four of the reports it appeared that the liver failure occurred as part of multi-organ failure rather than as a primary event. For the remaining case, which was reported in the literature, a 15 year old female who was treated with Ara-C and mitoxantrone for relapse of AML developed elevated liver enzymes (ALT 110U/L, ALP 2x ULN) 14 days after the first dose. After normalization of transaminases, she received a second course of Ara-C and mitoxantrone, at a reduced dose:

Twenty-five days later, she was readmitted for jaundice, and grade I encephalopathy and had an AST=4,500U/L, ALT=3,330U/L and a bilirubin=2.6mg%. Her course progressed to hepatic coma and she died. Post-mortem liver histology revealed massive hepatocellular necrosis. Hepatic dysfunction appears in the boxed warning, as well as a list of "most frequent adverse reactions" in the labeling for Ara-C.

Renal Failure/Insufficiency
There were reports for 15 patients with renal failure occurring in the setting of multi-organ failure, following treatment with other nephrotoxic agents (ex. amphotericin B, gentamicin) as a result of tumor lysis syndrome, or with inadequate information to describe the event. In none of the spontaneously reported cases did acute renal failure appear to be the primary event.

Cardiac Toxicity
There was one report of cardiotoxicity in a patient treated for MS and that case is described below. The remaining cases occurred in patients treated for cancer. Many of the cases in cancer patients are potentially confounded by the use of other therapies associated with cardiac toxicity (ex. anthracyclines, radiation). I reviewed the cardiotoxicity dose relationship, specifically in cancer patients not previously treated with anthracyclines or radiation. The current mitoxantrone labeling suggests that risk for cardiotoxicity is low in patients not previously treated with anthracyclines or radiation and who have received cumulative doses below 160mg/m^2. I reviewed the spontaneous reports to look for events of cardiotoxicity occurring at lower doses.

Spontaneous Report of Cardiotoxicity in an MS Patient
I identified a single spontaneous report (Belgium) of heart failure in a patient treated for Multiple Sclerosis. This 32-year-old female, treated concomitantly with lithium, developed massive cardiac failure unresponsive to inotropic therapy 2 months following her last dose of mitoxantrone. She had received a cumulative dose of mitoxantrone of 170-180mg/m^2. She died prior to a planned heart transplant.

Spontaneous Reports of Cardiotoxicity in Cancer Patients
I identified reports for 56 mitoxantrone patients with either decrease in EF or CHF and without mention of an acute myocardial infarction. In many of these cases, patients were concomitantly or had in the past received treatment with anthracyclines or had received radiation therapy to the chest. Most reports contained some information about dose but there were reports where it was not possible to determine the cumulative mitoxantrone dose that a patient had received. There are cases that document development of decreased EF or CHF with relatively low doses of mitoxantrone. Some of those cases are discussed below.

ID#1210700 This 59 year old female was treated with mitoxantrone for AML and developed pulmonary edema with an EF of 30% after the first course of mitoxantrone (10mg/m^2). The report did not mention if this patient had previous treatment with an anthracycline or radiation.

ID#562799 This 85 year old female was treated with mitoxantrone for ovarian cancer and developed a clinical picture of cardiac failure with pulmonary edema and then sudden death the day following her first dose (14mg/m^2).

ID#924127 This female (age unknown) was treated with mitoxantrone for ALL and had a documented drop in EF from 40% pre-treatment to 25% following 80mg/m^2.

ID#3198292 This 76 year old male treated with mitoxantrone for prostate cancer developed heart failure following 2 courses of therapy (dose not reported).

These cases illustrate that there have been cardiac events in patients receiving low doses of mitoxantrone although the exact relationship between drug and event in these cases is not clear. In addition, for at least 2 of the 4 cases the reports documented that the patients were >75 years old and the prevalence of heart disease in this age group is expected to be high.

4.8 Withdrawal/Abuse
The sponsor comments that there is no evidence of withdrawal effect in any controlled study of mitoxantrone in patients with MS or cancer patients (vol. 82, p. 147). Product labeling contains no information regarding withdrawal or abuse.

4.9 Human Reproductive Data
Current labeling states that mitoxantrone is pregnancy category D. The warning section states that mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Low fetal birthweight and retarded kidney development was observed in rats at .05 fold the recommended human dose on a mg/m^2 basis. An increased incidence of premature delivery was observed in exposed rabbits at .01 fold the recommended human dose on a mg/m^2 basis. Mitoxantrone was not teratogenic in rabbits.

4.10 Drug-Drug interactions
The sponsor reported that drug–drug interactions were not evaluated during the controlled trials of mitoxantrone in MS (vol. 82, p.147). The product labeling that there is no evidence for drug-drug interactions when mitoxantrone is administered with corticosteroids.

4.11 Overdose
The product labeling states that there is no specific antidote for mitoxantrone. It mentions four patients who died from severe leukopenia with infection following single bolus injections of 140-180mg/m2. It also states that because of extensive tissue binding, it would be unlikely that peritoneal or hemodialysis would mitigate toxicity.

In the ISS, the sponsor reported alterations in cardiac function in three patients receiving accidental mitoxantrone overdoses. A 44-year-old patient with leukemia previously treated with daunorubicin was given a $100mg/m^2$ bolus injection of mitoxantrone and developed clinical signs of CHF 4 months after the event. A 72-year-old female with breast cancer was given a $100mg/m^2$ dose of mitoxantrone and $500mg/m^2$ dose of cytoxan during her fourth course of therapy (total cumulative mitoxantrone dose $130mg/m^2$). Prior to death from pulmonary metastases, she developed clinical signs of low cardiac output. A 9-year-old with AML was given a $110mg/m^2$ dose of mitoxantrone over 2 days in combination with Ara-C. Sequential echocardiograms showed decrease in the shortening fraction, which returned to normal within 25 weeks and was not associated with clinical symptoms. In addition, the sponsor reported that a 73 year old woman with small cell lung cancer was given a $183mg/m^2$ dose of mitoxantrone in combination with cytoxan and vincristine and had a normal EF one month after the event.

5.0 Review of Systems
5.1 Cardiovascular
The sponsor acknowledges that mitoxantrone use is associated with cardiac toxicity, predominantly declines in left ventricular function or development of CHF, and comments that the mechanism of injury is not fully understood (vol.82, p. 117). The current mitoxantrone product labeling includes warnings about cardiotoxicity. In their proposed changes for labeling, pending approval for an MS treatment indication, the sponsor would add that as in patients with cancer, functional cardiac changes may occur in patients with MS treated with NOVANTRONE.

They would also state that no major clinical cardiotoxicity was observed in the Phase III trial but that 5/62 (8%) receiving 12mg/m^2 had decreased LVEF below the normal range.

Animal studies
Mitoxantrone caused vacuolization, dilation of the sarcoplasmic reticulum, mitochondrial swelling, and myofibrillar disruption of cardiac myocytes in mice and spontaneously hypertensive rats (vol. 82, p.118). Other findings in animals have included ECG abnormalities in monkeys, dose related impairment of contractility in rabbits, but no progressive anthracycline-like lesions on endomyocardial biopsy specimens of beagle hearts[1].

Myocardial biopsy findings in humans
Benjamin et al.[2] examined endomyocardial biopsy specimens from 66 mitoxantrone treated patients, 37 of whom were not previously treated with doxorubicin. The investigators reported that 6 of these 37 patients reached cumulative mitoxantrone doses >100mg/m^2. Three of the 37 patients had normal biopsies. The remaining patients had biopsies demonstrating histological changes resembling those caused by anthracyclines including dilatation of the sarcoplasmic reticulum, and myofibrilar dropout. The investigators considered these changes minor and rarely expected to be of clinical significance in the absence of other cardiac abnormalities. Dukart and Barone[3] identified 3 mitoxantrone treated patients with anthracycline like changes on biopsy but also reported that endomyocardial biopsy specimens from 2 patients who developed CHF following mitoxantrone treatment and from 4 adult patients who received substantial cumulative doses of mitoxantrone did not have anthracycline-like changes.

Cardiotoxicity in Cancer Patients Treated with Mitoxantrone
Most of the mitoxantrone treatment experience is in cancer patients. The current mitoxantrone labeling states that in a comparative trial conducted in adult patients with previously untreated acute nonlymphocytic leukemia (ANLL), mitoxantrone or daunorubicin administered in combination with cytarabine resulted in CHF in 6.5% of patients in each treatment arm. In this trial, mitoxantrone was administered in a dose of 12mg/m^2 daily for 2-3 days, at intervals of 4 to 6 weeks. Mitoxantrone's label also references data from use in hormone resistant prostate cancer. Seven of 128 (5%) treated patients (median dose 12mg/m^2, every 3 weeks, given with low dose prednisone) experienced cardiac events (CHF, decreased LVEF, or myocardial ischemia). In a second study, 18 of 112 (16%) patients had a reduction in cardiac function, 5 had cardiac ischemia, and 2 developed pulmonary edema. Data from other treated populations suggested a 2.6% risk of CHF, and a 13% risk of decreased LVEF for patients treated with a cumulative dose of 140mg/m^2.

The sponsor provided a collection of published articles discussing mitoxantrone associated cardiotoxicity in cancer patients. Information from those articles is summarized below. Additional articles identified through Medline searches are referenced as well.

I reviewed 4 publications that examined the relationship between CHF risk and cumulative dose in cohorts of more than 700 patients treated for cancer. Although not completely clear, there is likely overlap in the populations for some of these analyses.

Crossley[4] examined risk by cumulative dose in 1,228 subjects from clinical trials with sufficient information about dose and compared risk in those treated with mitoxantrone and anthracyclines to those with mitoxantrone and no prior anthracycline by plotting CHF risk against cumulative dose. The curve for those without prior anthracycline treatment demonstrated roughly a 2% CHF risk through 120mg/m^2 followed by a slight increase in risk and then a steep rise in risk above

160mg/m^2. There appeared to be few patients (15) treated with cumulative doses greater than 160mg/m^2.

Dukart and Barone[3] analyzed the cumulative dose and CHF risk relationship for 774 patients from a European study pooled with information from subjects in SWOG phase II studies. The curve for those with no prior doxorubicin treatment suggested a risk of roughly 1-2% up to 160mg/m^2 with a steep increase above this dose. Although not quantified, the authors noted that there were few subjects who were treated with large cumulative doses. They also recognized that some patients had cardiac function monitoring and may have been withdrawn from treatment for cardiac changes prior to developing CHF.

Posner[5] examined the cumulative dose and CHF risk relationship in 1,211 patients with adequate dose information from the sponsor's clinical trials database. The risk for those without prior doxorubicin treatment was approximately 2% through 120mg/m^2, increased slightly thereafter and then the risk appeared to increase steeply at 160mg/m^2. The author admitted that the sample size above 160mg/m^2 was small.

Mather et al[6] explain that when the dose response relationship is examined by using a Kaplan Meier curve with final cumulative dose instead of time to event, the result could confound a time effect if one exists. They point out that this method would produce a dose response even if one doesn't exist because the duration of exposure to the background risk of cardiotoxicity is longer in those surviving to receive higher cumulative doses. Further, when there are dose and time effects, the method underestimates risk at low dose levels because of short survival times and overestimates risk at high dose levels because of longer survival times. They analyzed data from 801 cancer patients treated with mitoxantrone, in which 12 events of CHF and 12 of decrease in EF were observed. These events were grouped as a single outcome of cardiac toxicity. Using proportional hazards to analyze cumulative dose as a time dependent covariate, they demonstrated that cumulative dose of mitoxantrone was significantly associated with increased risk of cardiac toxicity. They estimated a cardiotoxicity risk of 4% for low cumulative dose schedule (24mg/m^2 by 60 days), 6% for a medium dose schedule (60mg/m^2 by 120 days) and 15% for a high dose schedule (120mg/m^2 by 300 days). For a subset of patients without previous doxorubicin exposure, they provided a graph depicting a risk of cardiotoxicity of approximately 1% for 100mg/m^2 and 2% for 150mg/m^2.

There were additional publications describing cardiotoxicity in large cohorts but without examination of cumulative dose and risk relationships. Foster, Lev, and Bergman[7] reported on 633 adults treated in phase II trials sponsored by NCI. In this cohort, 4 subjects developed CHF and 2 had decreases in LVEF. The cumulative doses in the 4 with CHF were 60mg/m^2, 75mg/m^2, 135mg/m^2, and 140mg/m^2 and all 6 of the subjects with evidence of cardiotoxicity had prior treatment with doxorubicin. Gams and Wesler[8] reported the experience of a cohort of 766 patients who received mitoxantrone 5mg/m^2 once a week in Southeastern Cancer Study Group Phase II clinical trials. They identified 1 subject who developed CHF after receiving 100mg/m^2 of mitoxantrone and prior doxorubicin, and 8 subjects who developed LVEFs less than 50% with cumulative mitoxantrone doses of 25-110mg/m^2. Three of these patients had prior treatment with doxorubicin.

In addition, there have been several publications discussing cardiotoxicity associated with mitoxantrone in smaller cohorts of subjects (10-116 patients) treated for a variety of malignancies using different dosages and schedules. Risks of decreases in ejection fraction ranged from 10% to 43% and for CHF ranged from 0 to 7%.[9,10,11,12,13,14,15,16,17]

To examine the issue of late occurring cardiotoxicity, Aviles[18] et al studied patients previously treated for Hodgkin's disease with one of 3 cardiotoxic chemotherapeutic agents (mitoxantrone, epirubicin, or doxorubicin), who did not receive mediastinal radiotherapy, or treatment with cyclophosphamide. Volunteers in remission were examined a median of 6.7 years following their last dose. The authors reported that 7.5% (3/40) mitoxantrone patients had developed CHF and that 42.5% (17/40) developed cardiac toxicity (defined as LVEF<45% or a decrease in LVEF of at least 15% compared to pretreatment). The median mitoxantrone cumulative dose among the CHF patients was 106mg/m^2 (range 70-135mg/m^2) and among the patients with cardiotoxicity was 131mg/m^2 (range 90-155mg/m^2). The authors did not state whether or not end of treatment LVEF evaluations were performed so it is not possible to comment on the time course of the asymptomatic decreases in ventricular function. They explained that CHF developed in the patients 3-5 years following last dose.

Cardiotoxicity in the MS NDA database
There were no deaths attributable to cardiac events in either the phase II or the phase III MS trial. In the German retrospective cohort, there were 2 deaths in patients with evidence of cardiotoxicity. Additional deaths were attributed to insufficiency of breath in the German cohort and based on the limited available data I cannot rule out cardiac etiologies for these events. There were no serious cardiac adverse events reported for any of the MS NDA trials. One subject withdrew from the phase III trial for echocardiographic changes (decreased fraction shortening from 41% at baseline to 22% following 5 doses of study drug) that improved off drug. In the phase II trial, there were no withdrawals for cardiac related adverse events and the only reported cardiac AE in the mitoxantrone group was for tachycardia. In the German cohort, 5 patients discontinued treatment for cardiac events.

The NDA studies contained additional cardiac information in the form of ejection fraction monitoring (by echocardiography or radionuclide angiography) and ECGs. In the phase III MS trial, there was an increased risk of decreases in ejection fraction below the local normal limit compared to baseline for the 12mg/m^2 group (8%) compared to the 5mg/m^2 group (6%) and the placebo group (3%). In the phase II trial the sponsor reported that there was no evidence of cardiotoxicity in either treatment group. In the German cohort, ECGs and EF measurements were not part of a protocol and were not systematically performed and the severity of identified abnormalities was not captured. Neither the phase II nor the phase III trial was capable of detecting late occurring events (beyond 1 year) and the ability of the review of the German cohort to detect late occurring cardiac events is not clear.

Cardiotoxicity in Non NDA MS Published Studies
The sponsor identified 8 published single arm studies where mitoxantrone was used to treat MS patients. Four studies were silent about cardiac events and it is unclear if any occurred. The remaining 4 studies mentioned cardiotoxicity and the findings are summarized below.
Noseworthy et al[19] described the experience of 13 patients treated with mitoxantrone 6-20mg/m^2 every 3 weeks for seven courses. Cardiac monitoring consisted of baseline and week 21 MUGA scans and ECGs. The investigators mentioned that no patients developed clinical or laboratory evidence of cardiac toxicity.
Ruggero and Marciano[20] treated 14 MS patients with mitoxantrone 8-10mg/m^2 every 3 months for a mean of 14 months (range 5-21) and noted that no cardiotoxicity was observed. The monitoring methods were not discussed in this abstract.
Mesaros et al[21] treated 23 patients with 6 monthly treatments of 20mg of mitoxantrone and 1g of methylprednisolone and stated that there was no evidence of cardiotoxicity. The monitoring methods were not discussed in this abstract.

Gonsette[22] treated 68 patients with an unspecified dose/schedule of mitoxantrone with most followed up to 6 years. They reported that 11.7% (8/68) developed cardiotoxicity (mostly decreases in LVEF). The cumulative dose range for these 8 patients was 94-207mg/m^2. One patient who developed cardiotoxicity died. This patient had been treated with a cumulative mitoxantrone dose of 207mg/m^2. Two months after the last infusion she developed progressive heart failure and died.

In a randomized placebo controlled trial not submitted as part of the NDA, Millefiorini et al[23] treated 27 patients with mitoxantrone at a dose of 8mg/m^2, monthly for 1 year (cumulative dose 96mg/m^2). ECGs were performed monthly and echocardiograms were performed at baseline and at months 6 and 12. The investigator found no cardiotoxicity and no significant differences in ECGs or echocardiographic parameters during the follow up.

5.2 Hematologic
Bone Marrow Suppression
The mitoxantrone product labeling has a black box and bolded warnings discussing bone marrow suppression. In the adverse events section, under the Hematologic heading and Multiple Sclerosis subheading, the sponsor proposes the following statement:

> "In the Phase III study, 32% of patients treated with 12mg/m^2 NOVANTRONE every 3 months had leukopenia and 10% had thrombocytopenia at some point during the study. In the Phase II study, in which NOVANTRONE was administered at a dosage of 20mg every month, Grade 4 neutropenia was observed in 43% of patients at some point during the study and platelet counts less than 100,000/mm^3 were not observed. Neutropenia occurred within 3 weeks after NOVANTRONE administration and was always reversible."

The mitoxantrone labeling notes that in the 2 prostate cancer trials, grade 4 neutropenia (ANC<500/mm^3) was observed in 23% and 54% of mitoxantrone exposed subjects and that neutropenic fever occurred in 10% and 11% of mitoxantrone subjects.

In reviews describing the experience in treatment of cancer, Faulds et al[24] and Poirier[25] both identify myelosuppression, predominantly declines in WBCs, as the most common dose limiting toxicity. These sources note that the WBC nadir occurs by day 10-14 of treatment and recovery generally occurs by day 21.

Data from the MS trials
There were no deaths from hematologic treatment emergent adverse events in the phase II or phase III trial. There were no hematologic SAEs in the phase II or phase III trial. No subjects withdrew for hematologic AEs in either of these studies. In the German cohort, nine patients discontinued drug for leukopenia and 5 discontinued for lymphopenia. In the phase III trial, there was an increased risk of low white blood cell count and low platelet count outliers when comparing mitoxantrone and placebo treated subjects. The estimates of risk for declines in WBC counts in this study likely underestimate the true risk since labs were not performed when declines in WBC are expected to occur. The protocol for this trial required dose adjustments for hematological abnormalities. Thirteen subjects (all in the 12mg/m^2 group) had dose adjustments for hematological toxicity during this study. The sponsor did not identify any patients with fever and neutropenia. In the phase II trial, which included weekly blood testing, 48% (10/21) of mitoxantrone subjects had a WBC count between 1.0 and 2.0 x 10^9/L and none had a WBC count < 1.0 x 10^9/L. Forty-three percent (9/21) had a neutrophil count <0.5 x 10^9/L during the study. One subject had a neutrophil count less than 0.5x 10^9/L that persisted for 2 weeks. The sponsor reported that the hematologic abnormalities were reversible without further treatment and did not lead to any clinical event. In the German cohort, 28 patients had recorded WBC counts between 1.0 and 2.0 x 10^9/L and none had a WBC < 1.0 x 10^9/L. In addition, 63 patients had neutrophil

counts between 0.5 and 1.0 x 10^9/L and 12 patients had neutrophil counts <0.5x 10^9/L. Labs were usually collected prior to administration of a dose in the German cohort. Since declines in WBC counts are generally expected 7-14 days following administration, the risk observed in the German cohort likely underestimates the true risk of WBC decline.

Treatment Emergent Leukemia
The proposed product labeling states that topoisomerase II inhibitors including mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia. There is no risk estimate for mitoxantrone treatment related leukemia in labeling.

The sponsor provided an overview of the topic of treatment related leukemia. Two types of treatment related leukemia were described. The first (associated with alkylating agents like cyclophosphamide as well as radiation, and agents targeting topoisomerase II) is characterized by a latency of 3-5 years and has a pre-leukemic phase and a poor prognosis. The second type (associated with agents targeting topoisomerase II, specifically etoposide, anthracyclines, and mitoxantrone) is characterized by a myelocytic or monocytic morphology, a latency period of <3 years, and a more favorable prognosis.

Experience in Cancer Patients
Cancer patients are often treated with combinations of agents. In those patients developing treatment emergent leukemia, it is difficult to determine the risk attributable to any particular agent.

The sponsor reviewed 6 publications [26,27,28,29,30,31](studies and abstracts) that examined treatment emergent leukemia in breast cancer patients. These patients were treated with mitoxantrone as well as a variety of other chemotherapeutic agents (ex. cyclophosphamide, 5-flourouracil, methotrexate, and mitomycin), tamoxifen, and in some cases radiation therapy. Leukemia risks varied between 0.3% and 5% in these reports and average follow up ranged from 1.5 years to 6 years. The sponsor also provided a case report[32] for a patient with Non Hodgkin's lymphoma who developed AML following treatment with mitoxantrone, procarbazine, cyclophosphamide, doxorubicin, and etoposide.

The sponsor summarized the experience in cancer patients by stating that the clinical courses of the patients were consistent with the involvement of topoisomerase II inhibitors in the induction of therapy related AML. They also acknowledged that with the use of other lukemogenic treatments, the effect of mitoxantrone alone could not be isolated (vol. 82, p.136).

Experience in MS patients
The sponsor noted that leukemia was not identified in either of the NDA studies or in the German cohort. The sponsor did provide a case report for an MS patient previously treated with mitoxantrone who developed leukemia[33]. This patient had received a cumulative dose of 87.5mg/m^2 and developed APL 5 years after the last mitoxantrone dose.

The sponsor states that the relationship between mitoxantrone treatment and the risk of treatment related leukemia is not well established. The sponsor goes on to say that the risk is small to negligible in the relatively small numbers of patients with MS who have been treated with mitoxantrone (vol. 82, p.137).

5.3 Reproductive
The product labeling advises against becoming pregnant while being treated with mitoxantrone. Mitoxantrone is pregnancy category D and the sponsor warns that it may cause fetal harm if

administered to a pregnant woman. In the adverse reactions section of the proposed labeling, under the Multiple Sclerosis subheading, the sponsor would state that "In the Phase II clinical study, clinical adverse events most frequently reported in the NOVANTRONE group included amenorrhea (53% of female patients)..."

In the sponsor's Phase III MS clinical trial (031.0901) events such as amenorrhea, dysmenorrhea and other menstrual disorders occurred more frequently in the mitoxantrone treated groups than the placebo treated group (vol. 82, p.140). Menstrual disorder (mostly irregular menstruation) and amenorrhea both appeared to exhibit dose response relationships and the risk in the highest dose group was more than doubled the risk in the placebo group. Endometritis and pregnancy were the 2 reproductive serious AEs occurring in mitoxantrone subjects. No reproductive disorder AEs led to discontinuation from this study. In the Phase II NDA study (031.0902), 53% (8/15) of the women treated with mitoxantrone experienced amenorrhea compared to 0/11 in the placebo group. Onset ranged from month 2 to month 6. In the German cohort (031.0903), 12% (33/276) of the women treated reported amenorrhea. The sponsor reported that none of the women discontinued for this event and that 27% of those who developed amenorrhea recovered after stopping drug. Four pregnancies were reported to have occurred during treatment with mitoxantrone and there were 5 additional pregnancies that occurred after patients' last dose of mitoxantrone. Of these 9 pregnancies, 6 resulted in normal children and 1 woman had not given birth. The outcome of the remaining 2 pregnancies was not mentioned.

Experience in MS published trials
Noseworthy et al[19] noted that 4/7 female subjects treated with mitoxantrone 8mg/m^2 every 3 weeks for 7 courses developed amenorrhea with onset during month 1 or 2. All four resumed menstrual cycles following mitoxantrone discontinuation. Ruggero and Marciano[20] noted that 1/9 female subjects treated with mitoxantrone 8-10mg/m^2 every 3 months for a mean of 14 months developed amenorrhea and the authors did not comment about reversibility. Millefiorini[23] reported that 5/17 female patients treated with mitoxantrone 8mg/m^2 monthly for a year developed amenorrhea, which resolved when treatment was stopped.

Experience in Published Cancer Trials
Hagemeister et al[34] reported the experience of 18 women treated for Hodgkin's lymphoma with mitoxantrone, vinblastine, vincristine, prednisone, and chest and abdominal radiation. Eight of the 18 women received oral contraceptives and reported no menstrual dysfunction. Six of the remaining women had amenorrhea with return of menses within 6 months of ending therapy. Two patients developed early menopause and 2 noted no dysfunction.

Meistrich et al[35] reported that sperm counts and motility declined significantly in male patients treated for Hodgkin's lymphoma with mitoxantrone, vinblastine, vincristine, prednisone, and in some cases chest and abdominal radiation. In patients followed for 1 year, sperm counts and motility recovered to normal levels.

In their summary, the sponsor noted that the effects of mitoxantrone on fertility are not fully known. The above evidence from different populations suggests mitoxantrone can interfere with menstruation in a substantial percentage of treated women.

5.4 Gastrointestinal System
The product labeling states that nausea and vomiting occurred acutely in most patients and may have contributed to reports of dehydration, but were generally mild to moderate and could be controlled through the use of antiemetics. Stomatitis/mucositis occurred within 1 week of therapy.

There were no deaths attributable to treatment emergent GI events in either the phase II or the phase III MS trial. There were two GI SAEs in the phase III trial, diarrhea in a subject in the 12mg/m² group and enteritis (s. .nonella) in a subject in the 5mg/m² group. A subject withdrew from the phase III trial for nausea and vomiting that persisted despite ondansetron treatment. No subjects withdrew for GI treatment emergent adverse events from the phase II study. At least 3 patients from the German cohort discontinued mitoxantrone for vomiting. GI treatment emergent adverse events were commonly reported in the NDA studies. Nausea (term subsumed both nausea and vomiting events) occurred in 76% of those receiving the 12mg/m² dose compared to 55% receiving 5mg/m², and 20% in the placebo group in the phase III trial. In the phase II trial, 29% of mitoxantrone treated subjects developed nausea/vomiting compared to 0 in the control group. Stomatitis was another GI treatment emergent adverse event that occurred more frequently in the phase III trial among mitoxantrone treated subjects. Nineteen percent of those in the 12mg/m² group, 15% in the 5mg/m² group, and 8% in the placebo group developed stomatitis. One subject treated with mitoxantrone had stomatitis that was classified as severe (subject 5902, 12mg/m²) and the remaining mitoxantrone treated subjects had events that were described as either mild (n=16) or moderate (n=4). Stomatitis was not reported in the phase II trial.

From the lab data collected during the phase II and phase III trials, there was no evidence of increased risk of elevated bilirubin or of extreme SGOT elevations (>100U/L) when comparing the mitoxantrone and control groups. Based on the number of subjects enrolled, the ability to detect small differences in risk is limited. There were no reports of hepatic failure or hepatic necrosis in these studies.

5.5 Respiratory
There were no deaths due to treatment emergent respiratory adverse events in the phase II or phase III trial. In the German cohort there were 8 deaths attributed to pneumonia and 5 to insufficiency of breath. There were 2 serious AEs of pharyngitis and 1 pulmonary embolism among mitoxantrone treated subjects in the phase III trial. There were no serious respiratory AEs in the phase II trial. Sinusitis was the only respiratory related AE that occurred more commonly in the mitoxantrone subjects (6% in the 12mg/m² group, 3% in the 5mg/m² group) compared to placebo subjects (2%) in the phase III trial. In the phase II trial, throat infection (15%, n=3 v. 5%, n=1), pharyngitis (10%, n=2 v. 0) and rhinitis (10%, n=2 v. 0) were the respiratory AEs occurring more commonly in the mitoxantrone treated group.

The adverse event section of the product labeling mentions that interstitial pneumonitis has been reported rarely in cancer patients receiving combination chemotherapy that included mitoxantrone.

5.6 Nervous System
There were no deaths or discontinuations for treatment emergent AEs attributable to the Nervous System in the phase II or III MS trials. There was one Nervous system SAE in the phase III trial, asthenia in a subject in the 5mg/m² group. Asthenia (24%, n=5) was the only Nervous system AE occurring in more than 1 mitoxantrone treated subject in the phase II trial. Nervous system AEs were infrequently reported in the phase III trial.

5.7 Skin
The package insert states that there have been rare reports of tissue necrosis following extravasation and that skin discoloration has been reported. There were no deaths attributable to skin AEs in the phase II or III MS trials. In the phase III MS trial, one subject in the 5mg/m² group had a SAE attributed to seborrhea. There were no skin SAEs in the phase II trial. Alopecia was commonly reported in the phase III trial and there appeared to be a dose response

relationship for this event. In the phase II trial, alopecia was reported by 33% (n=7) mitoxantrone subjects and no methylprednisolone subjects.

5.8 Metabolic/Endocrine
The sponsor provided no evidence of increased risk for metabolic endocrine adverse events associated with mitoxantrone treatment.

5.9 Renal
There were no deaths from renal treatment emergent adverse events in the phase II or Phase III trial. In the German cohort, 4 deaths were attributed to bladder dysfunction/infection. In the phase III trial, there were 4 mitoxantrone and no placebo patients with serious renal adverse events (renal insufficiency, urinary tract infection, urinary retention, and hemorrhagic cystitis). There were no serious renal AEs in the phase II trial. Two subjects discontinued from the phase III trial for renal AEs (renal insufficiency, repeated UTIs.). Urinary tract infection occurred in 32% of subjects in the $12mg/m^2$ group, 29% in the $5mg/m^2$ group, and 13% of the placebo group in the phase III trial. In the phase II trial, 14% (n=4) of mitoxantrone subjects experienced a UTI compared to 5% (n=1) of placebo subjects. In the phase III trial, the risk for creatinine outliers (above ULN) was comparable between the three treatment groups (11% for the $12mg/m^2$ group 10% for the $5mg/m^2$ group, and 7% for the placebo group). There were no subjects meeting the outlier criteria for creatinine in either treatment group in the phase II trial.

5.10 Musculoskeletal
There were no deaths attributable to musculoskeletal treatment emergent adverse events in either the phase II or phase III trial. In the phase III trial, two mitoxantrone subjects had serious AEs of osteonecrosis and one had a serious fracture. In the phase II trial there were no serious musculoskeletal AEs. In the phase III trial, back pain was the only musculoskeletal AE occurring in at least 5% and more commonly in the mitoxantrone subjects (8% in the $12mg/m^2$ group, 6% in the $5mg/m^2$ group) than in the placebo subjects (5%).

6.0 Discussion
The mitoxantrone MS NDA database is small and the quality safety data come from the Phase II and Phase III trial where 145 patients were exposed to mitoxantrone. Roughly 80 MS subjects were exposed to the proposed intended dose and 62 to the intended dose at the intended schedule. In these 2 studies, observers were not blinded to treatment and the effect of unblinded reporting on the adverse event rates is not known. No previously unidentified toxicities were recognized in these studies.

There are notable limitations to the value of the German cohort data. The approach taken in the chart abstraction process was to capture selected adverse events based on the known toxicities of the drug and therefore the data do not speak to potentially drug related, previously unrecognized toxicities. Even for the selected safety topics considered, I am uncertain about the sensitivity the review process for detecting the adverse events of interest. The clinic was an academic referral center for patients with MS. Patients apparently did not receive all of their medical care at this clinic and the sponsor indicated that there were patients who were treated and later discharged or left and were no longer followed by the clinic. Investigators made attempts to track down patients not being actively treated at the clinic. In some cases, follow up information for these patients came from referring physicians while in other cases it came from the patient or family members.

Experience in cancer patients and data from the controlled trials suggest that menstrual adverse events tend to occur near the beginning of therapy and these probably would be identified provided females were asked about this event. I am uncertain if the chart review would have

captured events that may have occurred months to years following last dose, particularly late occurring cardiotoxicity and leukemia. My uncertainty arises in part from data presented for deaths. In following up patients not actively treated at the clinic investigators documented late occurring deaths in previously treated patients. I noted above that several of the death narratives appear to rely on a family member's recollection for cause of death. This raises questions about ascertainment of other late occurring events that would depend on the memory or understanding of a family member.

Unfortunately, the review of infections in the German cohort provided little useful information. The sponsor's summary consisted of a listing of the site of infection and use of antibiotics. The MS population is at risk for infections, particularly UTIs and respiratory infections. Without a comparator group, enumeration of the infections is of uncertain value. More emphasis should have been placed on identifying and describing any infections occurring in the setting of low neutrophil counts. Since these types of events would not be generally expected in MS patients in the absence of treatment with an immunosuppressant, such an analysis could have provided useful risk information.

Since WBC counts generally were not generally performed at the time of the expected nadir in the German cohort, the identified cases of neutropenia or leukopenia are useful only for documenting the occurrence of this event but do not allow estimation of the risk in this population. In addition, echocardiographic data documenting decreases in LVEF are of limited value without detail about the magnitude of the decline or clinical information about the patient.

Upon completion of this review, the greatest safety concerns related to the use of mitoxantrone are marrow suppression, cardiac toxicity, and effects on fertility.

Mitoxantrone is a recognized bone marrow suppressant with most notable effect on white blood cells. In the Phase II trial, 90% of exposed subjects had a neutrophil count $<1.0 \times 10^9$/L and 43% had a neutrophil count $<0.5 \times 10^9$/L at any point during this study. The literature suggests that the nadir for WBC counts following treatment with mitoxantrone is expected at 10-14 days with recovery by day 21. Data from the phase II trial (the only MS NDA trial capable of assessing the course of marrow suppression) generally agree with time course described in the literature. In neither NDA controlled trial did the sponsor identify patients who were hospitalized for fever or infection associated with neutropenia, although the absence of such cases does not mean that this is not a potential risk for mitoxantrone treated patients. In fact, the labeling currently provides a risk of 10-11% for neutropenic fever among subjects treated with mitoxantrone in the prostate cancer trials. The MS study protocols had criteria for either decreasing or holding doses based on hematologic toxicity observed during the previous course. In the phase III trial, there were 15 dose adjustments in 9 subjects in the 12mg/m² group for hematologic toxicity. It is possible these maneuvers limited serious adverse sequelae. The current proposed labeling offers no specifics about monitoring for hematologic toxicity and includes no recommendations for adjusting dose when hematologic toxicity occurs.

Mitoxantrone treatment is associated with cardiac toxicity and the product labeling discusses this adverse event. Most of the available data for mitoxantrone associated cardiotoxicity are from use in cancer patients. In these populations, the cardiotoxicity risk appears to increase with increasing cumulative mitoxantrone dose. The risk for decrease in ejection fraction of at least 10% has been estimated in labeling at 13% and the risk for CHF has been estimated at 3% for those treated with cumulative doses of 140mg/m². There are factors that appear to increase the risk for cardiotoxicity including prior treatment with anthracyclines, prior mediastinal radiation therapy, and prior history of cardiac disease. For cancer patients treated with mitoxantrone who do not

have the above listed risk factors, data from the literature suggest that the risk for congestive heart failure ranges between 1 and 2% at a cumulative dose of 120mg/m^2. The risk appears to increase after 160mg/m^2 but there are few patients who received such high cumulative doses, limiting the accuracy of the risk estimate (see appendix for cumulative dose/CHF risk curves).

Available data suggest that mitoxantrone has the potential to cause myocardial damage in MS patients as well. A death in an MS patient identified from the spontaneous report database and a death from the German cohort illustrate associations of CHF and mitoxantrone in MS patients. Describing the risk of cardiotoxicity in MS patients in more detail is a difficult task. There have been fewer MS patients treated with mitoxantrone than cancer patients. The highest cumulative dose that any subject reached in the controlled NDA MS trials was 101mg/m^2 and there is little experience in the German cohort above 100mg/m^2 (n=30). In the phase III trial, there were no patients who developed CHF but one patient discontinued therapy for echocardiographic changes suggestive of cardiac toxicity. Additional patients experienced asymptomatic decreases in ejection fraction. In the phase II study there were no cases of CHF or treatment emergent echocardiographic changes following 6 courses of therapy.

An important point to note is that the MS controlled trial data above speak to risk of cardiotoxicity occurring in relatively close approximation to time of treatment. There are limited data speaking to risk for late occurring cardiotoxicity events in mitoxantrone treated patients in any population. Late occurring events are a potential concern because follow up studies in children treated with doxorubicin, a cardiotoxic anthracycline, suggest there may be a latency period of up to several years for cardiotoxicity manifestation[36,37]. The publication by Aviles[18] raises questions about the potential for late occurring cardiotoxicity events in cancer patients treated with mitoxantrone.

The MS studies incorporated inclusion criteria that required assessment of baseline cardiac function and screening of patients for history of heart disease or prior treatment with cardiotoxic drugs. Subjects were monitored at midpoint in the Phase III trial for cardiotoxicity. The current labeling includes no recommendations for baseline ejection fraction evaluation and has no recommendations for monitoring in the MS section of the labeling. The proposed labeling does not define a maximum cumulative dose or explain that subjects in controlled trials generally did not exceed cumulative doses of 100mg/m^2. MS is a chronic disease and patients could potentially require treatment in excess of the cumulative doses used in the NDA trials. Lack of baseline screening or ejection fraction monitoring, or use of cumulative doses in excess of those used in the controlled trials could lead to risks of cardiotoxicity that are higher than the risks observed during the controlled trials.

The information included in the NDA as well as the published literature, illustrate that mitoxantrone use is associated with amenorrhea. The sponsor has documented that menses resumed in some of the females after stopping treatment but that amenorrhea persisted in some subjects. It is unclear if this persistence was due to a permanent effect of the drug, inadequate follow up, or if some of these events represented menopause that would have occurred in the absence of treatment. Labeling should reflect that in those patients experiencing amenorrhea, menses may persist following discontinuation of mitoxantrone.

Further discussion is needed on the topic of logistics of drug administration (who, how, where?). The proposed labeling suggests that the drug should only be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy, a statement requiring some clarification. If the drug is to be administered by neurologists in outpatient settings, I feel that labeling would require additional information. Nomograms for calculating dose in mg/m^2 specific

recommendations about monitoring blood counts, specific advice about how to adjust dose based on hematologic toxicity should probably be included in labeling. Information about the cumulative dose studied in controlled trials and recommendations limiting maximal cumulative dose may be helpful in limiting cardiac toxicity around the time of treatment. Special concerns related to administration of the drug such as managing extravasation, or spills would also need to be addressed.

Conclusions

In the small number of individuals treated for MS in the NDA controlled trials, mitoxantrone was well tolerated with no deaths, few serious adverse events and few discontinuations of therapy. No previously unrecognized toxicities were observed in these studies. No serious cardiotoxiciy events were observed although these studies did not expose patients to cumulative doses above 100mg/m^2. Despite the occurrence of substantial decreases in neutrophil counts, there were no cases of persistent neutropenia and no identified cases of neutropenic fever.

Cardiotoxicity, neutropenia and its sequelae, amenorrhea, which in some cases may be permanent and the potential for late occurring leukemia are the major safety concerns associated with mitoxantrone use.

/S/

Gerard Boehm, MD, MPH

cc: NDA 21-120, Katz, Burkhart, Ruzer-Kammeyer, Boehm

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Appendicies

1. References
2. WHO Grade Toxicity Criteria
3. Cumulative v. cardiotoxicity risk, Crossely
4. Cumulative dose v. cardiotoxicity risk, Dukart and Barone
5. Cumulative dose v. cardiotoxicity risk, Posner
6. Cumulative dose v. cardiotoxicity risk, Mather et al.
7. AEs from leukemia trials, mitoxantrone labeling

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ON ORIGINAL**

Appendix 1 References

1 Cancer: Principles and Practice of Oncology, edited by Vincent DeVita, Samuel Hellman, Steven Rosenberg, 5th edition, copyright 1997 by Lippincott-Raven publishers.

2 Benjamin RS, Chawla SP, Ewer MS, Carrasco CH, Mackay B, Holmes F, Evaluation of Mitoxantrone cardiac toxicity by nuclear angiography and endomyocardial biopsy: an update, Investigational New Drugs 3, 117-121, 1985.

3Dukart G, Barone JS, An overview of Cardiac Episodes Following Mitoxantrone Administration, Cancer Treatment Symposia, vol. 3, 1984.

4 Crossley RJ, Clinical Safety and Tolerance of Mitoxantrone, Seminars in Oncology, vol. 11, Suppl 1 (September) 1984.

5 Posner LE, Dukart G, Goldberg G, Bernstein T, Cartwright K, Mitoxantrone: an Overview of Safety and Toxicity, Investigational New Drugs 3, 123-132, 1985.

6 Mather FJ, Simon RM, Clark GM, Von Hoff DD, Cardiotoxicity in Patients Treated with Mitoxantrone: Southwest Oncology Group Phase II Studies, Cancer Treatment Reports vol.71 No. 6, June 1987.

7 Foster BJ, Lev L, Bergemann C, Marsoni S, Cardiac Events in Phase II Trials with Mitoxantrone, Cancer Treatment Symposia, vol.3, pp. 43-63, 1984.

8 GamsRA, Wesler MJ, Mitoxantrone Cardiotoxicity: Results from Southeastern Cancer Study Group, Cancer Treatment Symposia vol. 3, pp. 31-33, 1984.

9 Cassidy J, Merrick MV, Smyth JF, Leonard RCF, Cardiotoxicity of Mitoxantrone Assessed by Stress and Resting Nuclear Ventriculography, Eur J Cancer Clin Oncol, vol.24, no. 5, pp. 935-938, 1988.

10 Vilani F, Galimberti M, Crippa F, Evaluation of Ventricular Function by Echocardiography and Radionuclide Angiography in Patients Treated with Mitoxantrone, Drugs Exptl Clin Res XV(10), pp. 501-506, 1989.

11 Fountzilas G, Afthonidis D, Geleris P, Salem N, Kottas G, Halkidis C, Apostolodis P, Beer M, Tourkantonis A, Cardiotoxicity Evaluation in Patients Treated with a Mitoxantrone Combination as Adjuvant Chemotherapy for Breast Cancer, Anticancer Research, 12: 231-234, 1992.

12 Aapro MS, Alberts DS, Woolfenden JM, Prospective Study of Left Ventricular Function Using Radionuclide Scans in Patients Receiving Mitoxantrone, Investigational New Drugs, 1,341-347, 1983.

13 Mouridsen HT, Cornbleet M, Stuart-Harris R, Mitoxantrone as First-Line Chemotherapy in Advanced Breast Cancer: Results of a Collaborative European Study, Investigational New Drugs, 3, 139-148 1985.

14 Shpall EJ, Jones RB, Holland JF, Intensive Single Agent Mitoxantrone for Metastatic Breast Cancer, J Natl Cancer Inst, vol. 80, #3, pp. 204-8, 4/6/1988.

15 Unverferth DV, Unverferth BJ, Balcerzak SP, Bashore TA, Neidhart JA, Cardiac Evaluation of Mitoxantrone, Cancer Treat Rep, vol. 67, #4, pp. 343-350, 4/83.

16 Vorobiof DA, Iturralde M, Falkson G, Assessment of Ventricular Function by Radionuclide Angiography in Patients Receiving 4'-epidoxorubicin and Mitoxantrone, Cancer Chemother Pharmacol, 15: pp. 253-257, 1985.

17 Coleman RE, Maisey MN, Knight RK, Mitoxantrone in Advanced Breast Cancer- A Phase II Study with Special Attention to Cardiotoxicity, Eur J Cancer Clin Oncol, vol. 20, no.6 pp. 771-776, 1984.

18 Aviles A, Arevila N, Diaz Maqueo JC, Gomez T, Garcia R, Nambo MJ, Late Cardiac Toxicity of Doxorubicin, Epirubicin, and Mitoxantrone Therapy for Hodgkin's Disease in Adults, Leukemia and Lymphoma vol. 11, pp. 275-279, 1993.

19 Noseworthy JH, Hopkins, MB, Vandervoort MK, Karlik SJ, Lee DH, Penman M, Rice GPA, Grinwich KD, Cauvier H, Harris BJ, Ebers GC, An Open Trial Evaluation of Mitoxantrone in the Treatment of Progressive MS, Neurology, 43:1401-1406, 1993.

20 Ruggero C, Marciano N, Mitoxantrone Therapy of Secondary Progressive Multiple Sclerosis: Pilot Study, Abstract, Neurology, 43:1993.

21 Mesaros S, Levic Z, Drulovic J, Stojsavljevic N, Dujmovic I, Abstract Treatment of Multiple Sclerosis with Mitoxantrone.

22 Gonsette RE, Mitoxantrone Immunotherapy in Multiple Sclerosis, Multiple Sclerosis, 1, 329-332, 1996.

23 Millefiorini E, Gasperini C, D'Andrea F, Bastianello S, Trojano M, Morino S, Brescia Morra V, Bozzao A, Calo A, Bernini ML, Gambi D, Prencipe M, Randomized Placebo Controlled Trial of Mitoxantrone in Relapsing-Remitting Multiple Sclerosis: 24-Month Clinical and MRI Outcome, J Neurol 244: pp. 153-159, 1997.

24 Faulds D, Balfour JA, Chrisp P, Langtry HD, Mitoxantrone. A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in the Chemotherapy of Cancer, Drugs vol. 41, pp. 400-449, 1991.

25 Poirier TI, Mitoxantrone, Drug Intelligence and Clinical Pharmacology, vol. 20, #2, pp. 97-105, 2/1986.

26 Kumpulainen EJ, Hirvikoski PP, Pukkala E, Johannson RT, Cancer Risk after Adjuvant Chemo- or Chemohormonal Therapy of Breast Cancer, Anti-Cancer Drugs, vol. 9, pp.131-134, 1998.

27 Mitchell PLR, Treleaven J, Swansbury GJ, Powles RL, Ashley S, Powles TJ, Secondary Acute Myeloid Leukemia (AML) and Myelodysplasia (MDS) Following Mitoxantrone Given as Adjuvant Therapy for Breast Cancer, Abstract, Proceedings of ASCO vol. 15, May 1996.

28 Philpott NJ, Bevan DH, Gordon-Smith EC, Secondary Leukemia after MMM combined Modality Therapy for Breast Carcinoma, The Lancet, vol. 341, p.1289, May 15, 1993.

29 Cremin P, Flattery M, McCann SR, Daly PA, Myelodysplasia and Acute Myeloid Leukemia Following Adjuvant Chemotherapy for Breast Cancer Using Mitoxantrone and Methotrexate with or without Mitomycin, Ann Oncol, vol. 7, p. 745-746, Sep 1996.

30 Sajeva MR, Musto P, Melillo L, Cascavilla N, Perla G, D'Arena G, Carotinuto M, Secondary Acute Myeloid Leukemia (s-AML) after 3-M (Mitoxantrone, Methotrexate, Mitomycin) Chemotherapy for Metastatic Breast Cancer: Report of Three Cases, Abstract, Proceedings of ASCO, vol. 16, 1997.

31 Melillo MLA, Sajeva MR, Musto P, Perla G, Cascavilla N, Minervini MM, D'Arena G, Carotenuto M, Acute Myeloid Leukemia Following 3M (Mitoxantrone, Mitomycin, and Methotrexate) Chemotherapy for Advanced Breast Cancer, Leukemia, vol. 11, #12, pp.181-183, Dec 1997.

32 Izumi T, Ohtsuki T, Ohya KI, Ogawa Y, Yoshida M, Muroi K, Imagawa S, Hatake K, Kuriki K, Saito K, Miura Y, Therapy Related Leukemia with a Novel 21q22 Rearrangement, Cancer Genet Cytogenet 90: pp. 44-48, 1996.

33 Vicari AM, Ciceri F, Folli F, Lanzi R, Colombo B, Comi G, Cambia L, Acute Promyelocytic Leukemia Following Mitoxantrone as Single Agent for the Treatment of Multiple Sclerosis, Leukemia, vol. 12, p.441, 1998.

34 Hagemeister F, Larremore D, Sellin R, Stovall M, Fuller L, Preservation of Ovarian Function Following Novantrone, Oncovin, Vinblastine, and Prednisone (NOVP) and Radiotherapy (XT) for Patients (PT) with Stage I-III Hodgkin's Disease (HD), Abstract, Proceedings of ASCO, vol. 13, March 1994.

35 Meistrick M, Wilson G, Mathur K, Fuller LM, Rodriquez MA, McLaughlin P, Romaguera JE, Cabanillas FF, Ha CS, Lipshultz LI, Hagemeister FB, Rapid Recovery of Spermatogenesis after Mitoxantrone, Vincristine, Vinblastine, and Prednisone Chemotherapy for Hodgkin's Disease, Journal of Clinical Oncology, vol.15, #12, pp. 3488-3496, Dec 1997.

36 Lipschultz SE, Colan SD, Gelber RD, Late Cardiac Effects of Doxorubicin Therapy foe Acute Lymphoblastic Leukemia in Childhood, New England Journal of Medicine, vol. 324, pp. 808-815, March 21, 1991.

37 Steinherz LJ, Steinherz PG, Tan C, Heller G, Murphy L, Cardiac Toxicity 4 to 20 Years after Completing Anthracycline Therapy, JAMA, vol 266, #12, Sep 25, 1991.