

classification in reporting the study results, patients were retrospectively assigned to the category of relapsing-remitting MS if they were enrolled based on relapses in the preceding year (80% of patients) and to the category of secondary progressive MS if they were enrolled based on EDSS progression in the preceding year (20% of patients).

In conclusion, the two controlled trials show that mitoxantrone was effective in the treatment of patients with MS that could be classified as secondary progressive, progressive relapsing, or rapidly deteriorating relapsing-remitting MS.

5.0 Safety Results

This section summarizes the safety of mitoxantrone in the treatment of patients with MS. Data are available from two randomized multicenter trials (Studies 901 and 902) and one retrospective study (Study 903). This data is supplemented with safety information from the large experience with mitoxantrone in cancer patients.

5.1 Safety Results in Study 901

The study design of Study 901 is described in Section 4.1.1. Treatment toxicity was evaluated at each visit by the principal investigator (who was not masked to study drug) using standard clinical and laboratory evaluations. Adverse events were graded mild, moderate, or severe based on the WHO (World Health Organization) grading scale. Cardiac monitoring included an electrocardiogram (ECG) performed at each visit and evaluation of LVEF by echocardiogram at baseline, Month 12, and Month 24. Treatment was to be discontinued, regardless of any clinical sign or symptom, if the left ventricular ejection fraction (LVEF) decreased by 10% or more compared to baseline or if the LVEF was at or below 50%, or at or below the lower normal value for each site.

5.1.1 Extent of Exposure

The planned total mitoxantrone dose was 96 mg/m² for patients in the 12 mg/m² mitoxantrone group and 40 mg/m² for patients in the 5 mg/m² mitoxantrone group. Due to early drug discontinuation and dose reductions, the mean cumulative dose was

82.6 mg/m² (range, 12 - 96 mg/m²) for mitoxantrone 12 mg/m² and 37.2 mg/m² (range, 5 - 40 mg/m²) in the mitoxantrone 5 mg/m².

No patient in the placebo group had a dose adjustment. In the mitoxantrone 12 mg/m² group, there were 54 dose reductions per protocol-defined criteria among 27 patients (44%). Sixteen reductions were for hematologic toxicity, 35 were for Grade 2/3 nonhematologic toxicity (e.g., nausea, vomiting, diarrhea, alopecia, urinary tract infection, and other types of infections), two were for cardiac events (arrhythmia and pericardial effusion), and one was for an unknown cause. In the mitoxantrone 5 mg/m² group, there were 10 dose reductions among six patients (9%). Five were for Grade 2/3 nonhematologic toxicity (e.g., diarrhea, alopecia, enteritis, and constipation) and five were for cardiac events (arrhythmia, with four events occurring in a single patient). Dose escalation was not permitted in the study.

5.1.2 Deaths

No deaths occurred on study or within 30 days after completion of study drug treatment.

5.1.3 Withdrawals Due to Adverse Events

Treatment discontinuation due to an adverse event occurred in eight patients evaluable for safety. Six patients in the mitoxantrone 12 mg/m² group withdrew due to an adverse event, one for each of the following reasons: leukopenia, depression, asymptomatic decreased LVEF (per protocol requirement), bone pain and emesis, renal failure following urinary retention, and repeated urinary tract infections. Two patients withdrew due to an adverse event in the placebo group: one for hepatitis and one for myocardial infarction.

5.1.4 Adverse Events

Mitoxantrone given every 3 months at a dose of 12 or 5 mg/m² was generally well tolerated in this patient population. Most adverse events were of mild or moderate severity. There were more patients who reported a toxicity graded as "severe" in the

mitoxantrone 12 mg/m² group (19%, n = 12) compared to the mitoxantrone 5 mg/m² (6%, n = 4) or the placebo group (8%, n = 5). Adverse events graded as severe included nausea, stomatitis, arthritis, pulmonary embolism, renal cancer, fatigue, and depression.

The most common adverse events occurred in the gastrointestinal system, followed by the respiratory system, skin and appendages, urinary tract system, and female reproductive system. There was a significant difference (p < 0.05) between the placebo and the two mitoxantrone groups in the incidence of nausea, alopecia, urinary tract infections, menstrual disorder, and amenorrhea (alopecia was not significantly increased in the mitoxantrone 5 mg/m² group).

The following table lists adverse events that occurred in more than 5% of patients in the three groups ordered by decreasing frequency in the mitoxantrone 12 mg/m² group.

**Study 901 - Adverse Events in > 5% of Patients
 (By Decreasing Frequency in Mitoxantrone 12 mg/m² Group)**

Preferred term	Placebo (N = 64) %	Mitoxantrone	
		5 mg/m ² (N = 65) %	12 mg/m ² (N = 62) %
Nausea	20	55	76
Menstrual disorder *	26	51	61
Alopecia	31	38	61
Upper respiratory tract infection	52	51	53
Amenorrhea *	3	28	43
Urinary tract infection	13	29	32
Stomatitis	8	15	19
Leukopenia †	0	9	19
Arrhythmia	8	6	18
Diarrhea	11	25	16
Gamma GT increased †	3	3	15
ECG abnormal	3	5	11
Urine abnormal	6	5	11
Constipation	6	14	10
Rhinitis	14	11	8
Back pain	5	6	8
SGOT increased †	8	9	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

* Percentages reported for female patients only.

† Laboratory results reported as adverse events by the investigator.

5.1.5 Serious Adverse Events

Twenty-six patients (14%) experienced 29 serious adverse events (SAE) in Study 901 according to FDA-defined criteria: 10 patients in the mitoxantrone 12 mg/m² group experienced 11 SAEs, 10 patients in the mitoxantrone 5 mg/m² group experienced 10 SAEs, and six patients in the placebo group experienced eight SAEs. The table that follows lists the reported SAEs by treatment group and the relationship to study drug as determined by the investigator who was not blinded to study drug.

Study 901 - Serious Adverse Events

SAE	Relationship to study drug *
Mitoxantrone 12 mg/m² group	
Femoral head necrosis	Possible/remote
Pulmonary embolism	Remote
Renal insufficiency	Remote
Urinary tract infection	Remote
Kidney abnormalities, urinary retention	Remote
Acute endometritis	Remote
Cystitis hemorrhagic	Definitely not
Diarrhea	Definitely not
Pain due to femur head necrosis	Definitely not
Pregnancy	Definitely not **
Throat infection	Definitely not
Mitoxantrone 5 mg/m² group	
Urinary tract infection	Possible
Renal cell cancer	Possible
Anxiety	Remote
Mediastinal and hilar lymphadenopathy	Remote
Weakness	Remote
Rhinopharyngitis	Remote
Back pain	Definitely not
Vertebral fracture	Definitely not
Enteritis	Definitely not
Seborrheic dermatitis	Definitely not
Placebo group	
Depression	Remote
Sideropenic anemia	Remote
Pregnancy	Definitely not
Depression	Definitely not
Weakness	Definitely not
Back pain	Definitely not
Upper respiratory tract infection	Definitely not
Disease progression	Definitely not

* Investigator's evaluation.

** A pregnancy test was positive at the Month 9 evaluation. Patient had a normal delivery and gave birth to a healthy child.

Renal cell cancer was an unexpected SAE. Immunex considers its causal relationship to mitoxantrone to be unlikely since epithelial cancers are not usually reported to be related to the administration of cytotoxic antineoplastic agents. All other SAEs could be expected in patients with advanced MS.

5.1.6 Treatment Effects on the Heart

Based on clinical experience in patients with cancer, it was known that mitoxantrone has potential myocardial toxicity related to cumulative dose. Therefore, treatment effect on the heart was evaluated in an unblinded fashion using clinical, ECG, and echocardiographic criteria. Using WHO toxicity nomenclature, cardiac adverse events reported in the three treatment groups were as follows:

Study 901 - Cardiac Adverse Events in Each Treatment Group

Event	Placebo (N = 64) n (%)	Mitoxantrone	
		5 mg/m ² (N = 65) n (%)	12 mg/m ² (N = 62) n (%)
Arrhythmia	5 (8)	4 (6)	11 (18)
ECG abnormal	2 (3)	4 (6)	7 (11)
Heart valve disorder	1 (2)	2 (3)	1 (2)
Angina pectoris	1 (2)	1 (2)	1 (2)
Pericardial effusion	0	0	1 (2)
Cardiomyopathy	1 (2)*	0	0
Cardiac failure	0	1 (2)**	0
Hypotension	0	1 (2)	0

** Mild myocardial hypertrophy, LVEF within normal range.

* Asymptomatic decrease in LVEF, defined as $\geq 10\%$ decrease from baseline.

Arrhythmia events were more common in the mitoxantrone 12 mg/m² group; however, these events were reversible and did not lead to serious toxicity. ECG findings consisted mostly of supraventricular tachycardia and extrasystole.

Objective cardiac monitoring was also carried out using yearly echocardiograms to evaluate LVEF. Based on LVEF results, patients were categorized as having experienced a $\geq 10\%$ decrease in LVEF from baseline, a decrease of LVEF below the normal range determined by the site, or decrease in LVEF to $\leq 50\%$. As shown in the table that follows, there were no significant differences between the mitoxantrone and placebo

groups in LVEF decrease at the end of the second year of the study. No clinical sequelae occurred. One patient in the mitoxantrone 5 mg/m² group was coded as having experienced heart failure; however careful review of the records indicated that this was only an asymptomatic decrease of LVEF by > 10% from baseline.

Study 901 - Summary of LVEF Changes at End of Therapy (Year 2)

LVEF ≤ normal limit at center *	LVEF ≤ 50%	LVEF decrease ≥ 10% from baseline	Placebo (N = 64) n	Mitoxantrone	
				5 mg/m ² (N = 65) n	12 mg/m ² (N = 62) n
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
No LVEF examination after baseline			5	5	7

* Normal limits ranged from 40% to 65% across centers.

5.1.7 Clinical Laboratory Results

There were no significant differences among the three groups in the number of patients with results outside the normal range for mean hemoglobin and platelet counts. More patients in the mitoxantrone 5 mg/m² and 12 mg/m² groups had abnormal white blood cell counts (WBC) compared to patients in the placebo group, as shown in the table that follows.

Study 901 - Hematologic Results:

Number of Patients with Values Outside Normal Range

Laboratory value	Placebo (N = 64)		Mitoxantrone			
			5 mg/m ² (N = 65)		12 mg/m ² (N = 62)	
	Below NR	Above NR	Below NR	Above NR	Below NR	Above NR
Hemoglobin	14	2	15	1	14	1
Platelets	3	1	5	0	6	0
WBC	5	1	15	0	20	2

NR = normal range.

Overall, the hematologic toxicity reported in this trial was not associated with neutropenic fever or transfusions. The incidence of Grade 3-4 hematologic toxicity was rare and comparable in the 3 treatment groups, as shown in the following table.

**Study 901 – Percent of Patients with Grade 3-4 Hematologic Toxicity
 by WHO Criteria**

Laboratory value	Placebo (N = 64)	Mitoxantrone	
		5 mg/m ² (N = 65)	12 mg/m ² (N = 62)
ANC	1.6	0	0
WBC	1.6	0	0
Lymphocytes	0	3.1	0
Hemoglobin	0	0	0
Platelets	0	0	0

The next table shows the number of patients with abnormal blood chemistry results at any time during the study and shows that there were no clinically relevant differences between treatment groups. Similarly, there were no differences in Grade 3-4 chemistry toxicity between the three groups (data not presented).

**Study 901 - Blood Chemistry Results:
 Number of Patients with Results Outside Normal Range**

Laboratory value	Placebo (N = 64)		Mitoxantrone			
			5 mg/m ² (N = 65)		12 mg/m ² (N = 62)	
	Below NR	Above NR	Below NR	Above NR	Below NR	Above NR
Creatinine	0	7	0	6	0	7
Bilirubin	0	15	0	13	0	10
Gamma GT	0	20	0	19	0	19
SGOT	0	11	0	19	0	20
Alkaline phosphatase	2	8	1	8	1	5

NR = normal range.

5.1.8 Safety Data from Third-Year Follow-Up Evaluations

A total of 138 patients completed the third-year (Month 36) evaluation (1 year after completing treatment). The adverse event profile for the third year of the trial showed that patients who had been on mitoxantrone for 2 years did not have an increased incidence of delayed adverse events. No clinically significant differences were noted at Month 36 among the three treatment groups in the occurrence of adverse events, menstrual abnormalities, cardiotoxicity, infections, hospitalizations, and laboratory abnormalities. Most adverse events were of mild to moderate intensity and resolved

without incident. No deaths were reported to have occurred during the third year of the study.

No clinically relevant differences were noted in third-year ECG and LVEF results among the three treatment groups, and the results show there was no significant delayed cardiotoxicity. Third-year LVEF results are summarized in the table that follows.

Study 901 - LVEF Results at the End of Year 3

Parameter	Month 36 Results		
	Placebo (N = 35)	Mitox 5 mg/m ² (N = 44)	Mitox 12 mg/m ² (N = 36)
Mean LVEF (%)	67	66	68
Mean LVEF change from baseline to Month 36	1.37	-1.14	0.39
Pts with LVEF ≤ 50% [n (%)] †	0	1 (2)	1 (3)
Pts. with LVEF ≥ 10% below baseline [n (%)] †	4 (11)	13 (30)	8 (22)
Pts. with LVEF ≤ site limit [n (%)] †	0	4 (9)	1 (3)

Mitox = mitoxantrone.

† Some patients may have met criteria for more than one parameter.

5.2 Safety Results in Study 902

The study design of Study 902 is described in Section 4.2.1. Treatment toxicity was evaluated at each visit by the principal investigators (who were not masked to study drug) using standard clinical and laboratory evaluations. Adverse events were graded mild, moderate, or severe based on protocol-defined criteria. A cardiology evaluation (blood pressure, ECG, and echocardiogram) was performed at Months -2 and 6. If a lymphocyte count was < 900 cells/mm³, mitoxantrone administration was to be delayed until the count returned to ≥ 900 cells/mm³. For each patient, a general statement of treatment effectiveness and safety (clinical global impression [CGI]) was prepared at Month 6 by the principal investigators and recorded in the CRF.

5.2.1 Extent of Exposure

A total of 143 courses of mitoxantrone were administered. The average number of days between courses ranged from 27 to 37, with a mean of 30 days. The mean mitoxantrone

dose per course adjusted for body surface area was 11.9 mg/m² (range, 10.1 - 14.8) and the mean cumulative dose over the six courses was 81.2 mg/m² (range, 61.6 - 101.0).

5.2.2 Deaths

No deaths occurred on study or within 30 days after completion of study drug treatment.

5.2.3 Withdrawals Due to Adverse Events

Except for one patient in the mitoxantrone-plus-methylprednisolone group who discontinued treatment on Day 1 of the first course of study drug due to increased liver enzymes (considered unrelated to study drug and to be due to phenytoin), there were no other withdrawals due to adverse events.

5.2.4 Adverse Events

Six patients in the methylprednisolone-alone group and 18 patients in the mitoxantrone-plus-methylprednisolone group reported at least one adverse event. Of note, the investigators were not blinded to study drug when evaluating treatment toxicity. Only four events in three patients were graded as severe by the investigators: amenorrhea, depression and anorexia (in one patient), and intolerance to contact lenses.

The most common adverse events in the mitoxantrone-plus-methylprednisolone group involved the digestive system (nausea 29%), the genitourinary system (amenorrhea in 53% of female patients), the cutaneous system (alopecia 33%), and the respiratory system (throat infection and pharyngitis 24%). Events involving the respiratory system (throat infection, pharyngitis, rhinitis) were also reported, principally in the mitoxantrone-plus-methylprednisolone group. All the events reported in the mitoxantrone-plus-methylprednisolone group resolved rapidly except eight instances of amenorrhea, two of alopecia, two of mycosis, one of asthenia, and one of retrosternal burning, which were still present at the end of Month 6.

5.2.5 Treatment Effects on the Heart

No cardiotoxicity was detected in any patient. Three episodes of tachycardia occurred in one patient receiving mitoxantrone. These events resolved without incident and their relationship to study drug was deemed doubtful. There were no significant changes in blood pressure, heart rate, ECGs, or echocardiograms.

5.2.6 Clinical Laboratory Results

Hematologic evaluations were performed weekly from Month 0 to Month 6 in the mitoxantrone-plus-methylprednisolone group and only once a month in the methylprednisolone-alone group.

As shown in the table that follows, a decrease in WBC was reported in all patients within 2 weeks following mitoxantrone therapy. Except for two patients, WBC returned to Grade 1 or normal by the fourth week. No Grade 4 neutropenia was observed

**Study 902- Number (%) of Patients in Mitoxantrone + mP
 (N = 21) With Low WBC* at Any Time Over 6 Months**

Time	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)
Week 1	6 (29)	8 (38)	6 (29)	0	20 (95)
Week 2	2 (10)	11 (52)	8 (38)	0	21 (100)
Week 3	9 (43)	6 (29)	0	0	15 (71)
Week 4	7 (33)	2 (10)	0	0	9 (43)
Any time post dose	1 (5)	10 (48)	10 (48)	0	21 (100)

mP = methylprednisolone.

* Leukopenia graded using NCI common toxicity criteria (x 1000/mm³) as follows:

Grade 0 = ≥ 4.0, Grade 1 = 3.0-3.9, Grade 2 = 2.0-2.9, Grade 3 = 1.0-1.9, Grade 4 = < 1.0.

Ten patients in the mitoxantrone-plus-methylprednisolone group had platelet counts that were below the normal range, but counts were never less than 100,000/mm³. The platelet counts for all of these patients were normal at the end of the study. Grade 1 low hemoglobin (defined by NCI Common Toxicity Criteria as ≥ 10 g/dL but less than the lower limit of normal) was reported in five patients in the mitoxantrone-plus-methylprednisolone group and in ten patients in the methylprednisolone-alone group.

Overall, the hematologic abnormalities were reversible, did not lead to any clinical sequelae, and did not require transfusion of blood products. As with Study 901, there were no meaningful differences between the two groups with respect to blood chemistry results.

5.3 Retrospective Analysis (Study 903)

A retrospective analysis of the safety of mitoxantrone was conducted in 454 patients with MS treated in a single institution. The data collection was performed in 1999 at the Academic Hospital of Ulm University in Germany, under the direction of Prof. E. Mauch.

5.3.1 Study Objectives, Design, and Endpoints

The objectives of the study were to evaluate the safety of mitoxantrone in MS patients, including hematologic, cardiac, and infectious events, and to assess the activity of mitoxantrone in patients with various forms of MS.

This study consisted of a retrospective collection and analysis of up to 10 years of medical data from patients with MS treated at a single institution where mitoxantrone was their standard of care. All patients who received at least one dose of mitoxantrone were included; thus, the data represent an unbiased cohort of patients. These patients were not enrolled in a prospective clinical trial of mitoxantrone. All physicians at this center followed uniform treatment practices, providing consistent patient management. An attempt was made to obtain recent follow-up information on the patients not currently being treated at the center.

Safety assessments included the results of ECG and echocardiogram (if required) tests, as well as key adverse events categories and laboratory determinations. The efficacy results were assessed by EDSS, the number of relapses (severity and treatment status), the number of new Gd-enhancing MRI lesions, and T2 lesion load. In addition, the investigator provided a clinical global impression for each patient.

5.3.2 Demographic and Disease Characteristics

A total of 454 patients were identified and analyzed. These patients started treatment with mitoxantrone between November 1988 and September 1998. The table below summarizes demographic and disease characteristic data.

Study 903 - Mean Demographic and Disease Characteristics

Parameter	N = 454
Years since onset of MS (mean)	9.1
Gender (female/male)	276/178
At start of mitoxantrone treatment:	
Age (mean)	37.2
RR/SP/PP/unknown MS ratio (%)	63/22/13/1
No. patients with relapse in preceding 12 months	244
No. relapses in preceding 12 months (mean)	1.0
EDSS at baseline (mean)	5.11
EDSS deterioration in preceding 12 months (mean)	0.79
RR = relapsing-remitting MS.	
SP = secondary progressive MS.	
PP = primary progressive MS.	

Of note, a mean EDSS of 5.0 corresponds to a disability severe enough to impair full daily activities. Some patients had a near terminal disease with an EDSS of 8.0 or 9.0.

5.3.3 Extent of Exposure

Mitoxantrone was given at a dose of 12 mg/m² every 3 months, and the dose and schedule were adjusted as necessary in response to toxicity and disease activity. Data were not collected on mitoxantrone doses or other treatments administered outside the clinic.

The mean follow-up period after the last mitoxantrone dose administered in the clinic was 47 months. The table that follows summarizes mitoxantrone dosing. Eighty patients received 6, 7, or 8 doses (the range comparable to Studies 901 and 902).

Study 903 – Mitoxantrone Dosing Summary

Parameter	N = 454
Mean number of doses per patient (range)	4.44 (1-17)
No. (%) with ≥2 doses	387 (85%)
No. (%) with 6, 7, or 8 doses	80 (18%)
No. (%) with >8 doses	49 (11%)

5.3.4 Deaths

At the time of data collection, 20 of the 454 patients (4%) had died. Nine patients died due to infections, five due to respiratory failure, two due to cardiac events, and one due to cachexia. The causes of death for the remaining three patients are unknown. However, it is known that these three patients died at least 1, 2, and 5 years after their last dose of mitoxantrone administered in the clinic. Only three patients died within 17 months after receiving their last dose of mitoxantrone. The causes of death for these three patients were pneumonia, bladder dysfunction/infection, and respiratory failure. Eleven of the 20 patients (55%) died more than 3 years after receiving their last dose of mitoxantrone. No death was prospectively considered by the investigator to be temporally related to mitoxantrone administration.

5.3.5 Treatment Discontinuation Due to Adverse Events

Thirty-four patients (7%) discontinued treatment due to an adverse event. The most common adverse events leading to treatment discontinuation were infection (urinary tract infection, upper respiratory infection), leukopenia, lymphopenia, nausea, vomiting, and alopecia.

5.3.6 Adverse Events

Compared to the experiences with mitoxantrone in an oncology setting, there were no new or unusual adverse events in patients with MS.

5.3.6.1 Infections

A total of 171 patients (38%) had experienced at least one infectious episode. These episodes were not necessarily temporally related to mitoxantrone administration. The mean number of infections per patient was two. The most common type of infection was urinary tract infection (86% of infections), a clinical event frequently reported in patients

with advanced MS. Of the 171 patients who had infections, the majority (55%) had one infection, 22% had two infections, and 23% had three or more infections.

5.3.6.2 Cardiotoxicity

Clinical cardiotoxicity was reported by the investigator in seven patients (2%). The presence or absence of cardiotoxicity was unknown for two of the patients, and the remaining 445 patients (98%) had no evidence of cardiotoxicity. The following toxicities were reported: decreased LVEF (n = 5), arrhythmia (n = 1), and mitral valve insufficiency (n = 1). Arrhythmia and insufficiency of the mitral valve were not thought to be related to mitoxantrone based on experience in cancer patients. These data are summarized in the table below.

Study 903 - Cardiac Toxicity Reported in Seven Patients

Pt.	Type of Cardiac toxicity	Course	Cumulative dose (mg/m ²) *	Reason for discontinuation	Death/cause
122	Mitral valve insufficiency	4	41	Reduced LV function	No
246	Arrhythmia	1	11	Unknown AE	No
225	Decreased LVEF	11	130	Cardiotoxicity	No
233	Decreased LVEF	11	118	Cardiotoxicity	No
270	Decreased LVEF	12	119	Cardiotoxicity	No
281	Decreased LVEF	8	91†	Not reported in CRF	Yes: pulmonary infection and cardiomyopathy
369	Decreased LVEF	7	50	Decreased LVEF	Yes: respiratory failure

* Only data on doses given in the clinic were collected.

† This patient continued receiving mitoxantrone off site

Two of the seven patients with cardiotoxicity have died. The cause of death for one patient was reported as respiratory failure. The other patient died due to pulmonary infection and cardiomyopathy. This latter patient was known to have received additional mitoxantrone doses in another clinic (number of unknown courses).

5.3.6.3 Malignancies

Ovarian cancer was reported in one patient who had been treated with mitoxantrone. It is not considered to be associated with mitoxantrone.

5.3.6.4 Fertility and Effects on Menstrual Cycle

Thirty-three of the 276 women (12%) who took mitoxantrone reported amenorrhea. Eighty-two percent of the women reported that they had normal menses. It is not known whether the remaining 16 women experienced amenorrhea. None of the patients discontinued mitoxantrone due to amenorrhea.

Nine women were reported to have become pregnant after starting mitoxantrone therapy. Four pregnancies began during mitoxantrone treatment, while the remaining five patients became pregnant after requesting discontinuation of mitoxantrone treatment. Of these nine pregnancies, six resulted in the birth of normal children. At the time of data collection, one of the women had not yet given birth and the outcome of the remaining two pregnancies was unknown.

5.3.6.5 Clinical Laboratory Results

Twelve patients had Grade 4 neutropenia and 62 patients had Grade 3 neutropenia. Ten patients had Grade 3 lymphopenia. Twenty-eight patients had Grade 3 leukopenia. There were no reports of Grade 4 leukopenia.

5.3.7 Global Clinical Assessment

A clinical general impression (CGI) assessment of treatment effectiveness and safety was retrospectively assigned by the investigator for each patient. The CGI was considered “very good” in 13% of patients and “good” in 40% of patients. The CGI was “moderate” in 33% of patients and the remaining 14% were classified as either “poor” or “other”.

5.3.8 Safety Conclusions for Study 903

This retrospective analysis provides valuable information on the long-term safety of mitoxantrone in patients with MS treated in a single institution over a period of 10 years. Overall, mitoxantrone appeared to have a manageable safety profile in patients with MS. Decreased LVEF was reported in five patients (1%). There were no reports of secondary