

addition, animal models of collagen-induced arthritis and orthotopic heart transplants have confirmed the immunosuppressive effects of mitoxantrone.

3.0 Clinical Development Program of Mitoxantrone in Multiple Sclerosis

3.1 Published Open-Label Studies

Following publication of preclinical studies demonstrating the activity of mitoxantrone in EAE models, open-label studies of mitoxantrone in MS were conducted in the late 1980s in Europe and Canada. The data from five studies involving 73 patients were published in English language journals: two in peer-reviewed journals (Mauch 1992, Noseworthy 1993) and three in meeting abstracts (Gonsette 1990, Kappos 1990, Ruggiero 1993). Mitoxantrone was administered at doses ranging from 8 to 14 mg/m², with intervals between courses ranging from 3 weeks to 3 months. The essential study design elements and patient demographics of these five studies are presented in the table that follows.

Design of Open-Label Single-Arm Studies Published in English Language Journals

Author	RE Gonsette (1990)	L Kappos (1990)	E Mauch (1992), H Krapf (1995)*	J Noseworthy (1993)	C Ruggiero (1993)
Mitoxantrone dose & schedule	14 mg/m ² IV over 30 min. every 3 weeks, for 2 to 8 courses (median 3), until lymphocytes ≤ 1000/mm ³	10 mg/m ² IV every 3 weeks, for 3 to 5 courses, depending on leukocyte counts and/or disease activity	12 mg/m ² IV every 3 months	8 mg/m ² IV every 3 weeks, for 7 courses; subsequent doses increased or decreased as needed based on hematologic results. Maximum dose 10 mg/m ² IV	10 mg/m ² IV every 3 months (8 mg/m ² IV for immunosuppressed patients)
Study duration	Median 12 months (range 6 to 23 months)	Not available	12 months (MRI follow-up, 24 months)	21 weeks (follow-up, 18 months)	Mean 14 months (range 5 to 21 months)
Patients treated	22	14	10	13	14
Disease status	Remittent-progressive (n = 16) Progressive (n = 6)	“Clinically definite rapidly progressive” (n = 14)	Relapsing-remitting (n = 6) Secondary progressive (n = 4)	Progressive (n = 13)	Secondary progressive (n = 14)
Publication	Neurology 1990;40:261 (Abstract 537P).	Neurology 1990;40:261 (Abstract 539P).	Eur Arch Psychiatry Clin Neurosci 1992;242:96-102. * Neurology 1995;37:113-9. MRI data for patients reported by Mauch et al.	Neurology 1993;43:1401-6.	Neurology 1993;43:A281 (Abstract 494S).

These open-label studies in MS showed that mitoxantrone was usually well tolerated and that the adverse effects, most of which were of short-term duration, were less frequent when longer intervals between courses were allowed. Furthermore, some of these studies suggested that patients might benefit from this form of therapy. It was concluded that further controlled studies at the dose of 12 mg/m² were indicated.

3.2 Phase II and III Randomized Trials

Based on these promising results, Lederle-Europe, Immunex's corporate partner for mitoxantrone outside the U.S., sponsored two randomized trials of mitoxantrone in MS in the early 1990s. A multicenter Phase II corticosteroid-controlled study was sponsored in France and a multicenter Phase III placebo-controlled study was sponsored in four other European countries.

The Immunex filing with FDA consists of three studies. The two Lederle-sponsored randomized controlled studies were the basis for demonstrating mitoxantrone efficacy and safety in MS. Results of a third study, consisting of a retrospective analysis of data collected from a single institution in Germany, were included in the filing to provide additional long-term safety information on mitoxantrone in MS.

An investigator-sponsored, Phase II randomized, placebo-controlled, multicenter study was also conducted in Italy. This study enrolled 51 patients with relapsing-remitting MS who were randomized to receive either placebo (n = 24) or mitoxantrone (n = 27) at a dose of 8 mg/m² IV once a month for 1 year. The results from this study were published in peer-reviewed journals and showed that mitoxantrone significantly slowed disease progression and decreased the number of relapses (Millefiorini 1997; see Appendix G, Published Papers), and reduced the number of Gd-enhancing lesions on MRI scans (Bastianello 1994; see Appendix G, Published Papers). In addition, the investigators reported that the treatment had no cardiac toxicity (De Castro 1995, see Appendix G). This study was not included in the Immunex filing because it was not monitored by Lederle-Europe and the case report forms were not retrievable by Immunex.