Pain Medicine

Pain Medicine 2010; 11: 180–194

Durability of Therapeutic Response to Milnacipran Treatment for Fibromyalgia. Results of a Randomized, Double-Blind, Monotherapy 6-Month Extension Study

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Abstract

Objective. To evaluate the durability of improvement and long-term efficacy of milnacipran treatment in fibromyalgia, to assess efficacy in patients re-randomized from placebo to milnacipran, and to collect additional information on the tolerability and efficacy of long-term treatment with milnacipran.

Design. A total of 449 patients who successfully completed a 6-month lead-in study enrolled in this 6-month extension study (87.7% of eligible subjects). Patients initially receiving milnacipran 200 mg/day during the lead-in study were maintained at 200 mg/day (n = 209); patients initially assigned to placebo or milnacipran 100 mg/day were re-randomized (1:4) to either 100 mg/day (n = 48) or 200 mg/day (n = 192) of milnacipran for an additional 6 months of treatment. Efficacy assessments included visual analog scale pain ratings, Fibromyalgia Impact Questionnaire (FIQ) total score, and Patient Global Impression of Change (PGIC).

Results. Patients continuing on milnacipran demonstrated a sustained reduction in pain over the full 12-month period. Additional beneficial effects were also maintained, as indicated by the PGIC and FIQ. Patients initially assigned to either placebo or milnacipran 100 mg/day in the lead-in study and subsequently re-randomized to milnacipran 200 mg/day in the extension study experienced further improvements in their mean pain scores, FIQ total scores, and PGIC ratings at 1 year. Milnacipran treatment was generally well tolerated. The most commonly reported newly emergent adverse event was nausea.

Conclusions. In addition to confirming that milnacipran safely and effectively improves the multiple symptoms of fibromyalgia, these data indicate that milnacipran provides 1-year durable efficacy in this patient population.

Key Words. Fibromyalgia; Milnacipran; Serotonin-Norepinephrine Reuptake Inhibitor; Pain; Analgesic; Long Term

Introduction

Fibromyalgia (FM) is a chronic pain disorder affecting 2–4% of the population and is more common in women than in men [1,2]. Recent biologic and neuroimaging studies support the hypothesis that aberrant pain processing in the central nervous system of FM patients may represent an important underlying defect [3,4]. In 1990, the American College of Rheumatology (ACR) established diagnostic criteria for FM, primarily to standardize clinical trial populations [5]. These criteria require an individual to possess chronic widespread pain involving all four quadrants of the body and axial skeleton in combination with tenderness in 11 of 18 standardized "tender points" on palpation. While the cardinal symptom of FM is chronic widespread pain, fatigue, sleep and cognitive disturbances, and decreased physical function also constitute important clinical domains of FM [5,6].

The symptoms associated with FM contribute to a significantly reduced quality of life and increased disability and health care costs [7–9]. Therefore, effective long-term treatment options with durable clinical benefits are important for treating FM patients. Although FM is considered a chronic, persistent illness, most published pharmacotherapy studies have focused on short-term (<3 months) results. However, long-term clinical trials are necessary to determine whether the efficacy and safety of a drug documented in short-term studies are maintained over longer periods of time [10].

Tricyclic antidepressants were the first medications found to be beneficial in FM during randomized clinical trials. Most of these trials were 6–12 weeks in duration and when carried out to 6 months, significant improvements over placebo were not observed [11]. Selective serotonin reuptake inhibitors have shown limited efficacy in FM trials [10,11]. Pregabalin, an antiseizure medication, was the first drug approved by the U.S. Food and Drug Administration (FDA) for the management of FM. Trials involving either pregabalin or gabapentin in treating FM have lasted from 2 to 6 months [12–16]. Duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, is also approved by the FDA for the management of FM. The efficacy and safety of duloxetine in FM patients has been investigated in clinical trials lasting 3 months [17,18] and 6 months [19,20], with 6-month extension studies [21] conducted on the two 6-month trials.

Milnacipran was approved by the U.S. FDA in January 2009 for the management of FM. It is a dual reuptake inhibitor of norepinephrine and serotonin that differs from other medications in this class by having low protein binding, minimal hepatic metabolism, and no significant effect on cytochrome P450 enzymes, indicating a low potential for pharmacokinetic drug interactions [22]. Additionally, milnacipran differs from other dual reuptake inhibitors by its approximate 3:1 preference for norepinephrine reuptake inhibition over that of serotonin [23]. Research suggests that norepinephrine and serotonin are among several neurotransmitter systems that may mediate endogenous analgesic mechanisms in the central nervous system [24,25]. It has also been postulated that norepinephrine reuptake inhibition may be more important than serotonin for the treatment of pain-related conditions [26–28]. However, the degree of NE to 5-HT reuptake inhibition may or may not be related to clinical efficacy.

The efficacy and safety of milnacipran has been previously established in three double-blind, placebo-controlled studies of 3 [29,30] and 6 months [31] in duration. Studies showed that compared with placebo, milnacipran significantly improved pain and multiple other symptoms of FM simultaneously, using a composite responder analysis [29,31]. These studies also demonstrated significant improvements with milnacipran versus placebo in core symptom domains, such as physical function, fatigue, and cognitive dysfunction. The 6-month study involving 888 FM patients randomized to placebo, 100 mg/day or 200 mg/day of milnacipran was the lead-in to this 6-month extension study [31]. The objectives of this long-term extension study were: 1) to determine whether the improvements in pain and other FM symptoms that were achieved at 6 months could be sustained through 1 year; 2) to further evaluate the efficacy of milnacipran in patients who were switched from placebo during the lead-in study to milnacipran in the extension study; and 3) to confirm the long-term safety and tolerability of milnacipran in the treatment of FM.

Materials and Methods

Study Design

This 6-month, randomized, multicenter, double-blind, extension study was conducted at 51 U.S. centers from May 20, 2004 to January 13, 2006. Patients completing the 6-month lead-in study [31] in which they received double-blind treatment with milnacipran 100 mg/day (n = 224), milnacipran 200 mg/day (n = 441), or placebo (n = 223), were eligible for enrollment. Of the 512 patients completing the 6-month lead-in study (placebo, n = 145; milnacipran 100 mg/day, n = 128; milnacipran 200 mg/day, n = 239), 449 (87.7%) patients elected to continue into this extension study. All participants in the present study received milnacipran 100 mg/day (50 mg twice daily [BID]) or 200 mg/day (100 mg BID) for a total of 28 weeks (2-week dose-escalation period, 26-week stable-dose period). The nature of the blinding was such that patients were not informed of their treatment assignments during the 6 months of the lead-in study. During the 6-month extension period (this study), patients were informed that they would receive milnacipran but remained blinded to the dose they would receive.

Patients initially randomized to the milnacipran 200 mg/day group in the lead-in study underwent a sham dose escalation (i.e., no change in dosing) prior to stable-dose maintenance at 200 mg/day (n = 209); those patients previously in the 100 mg/day group were re-randomized at a 1:4 ratio to continue at 100 mg/day (n = 19) or to escalate to 200 mg/day (n = 92) for the extension study. Patients initially randomized to the placebo group in the lead-in study were re-randomized at a 1:4 ratio and escalated to 100 mg/day (n = 29) or 200 mg/day (n = 100) for the extension study (Figure 1).

Participants

Patients 18–71 years of age with a diagnosis of FM, as defined by the 1990 ACR [5], met all of the entry criteria for the lead-in study, including: willingness to withdraw from all centrally acting therapies commonly used for FM (including antidepressants, sedative-hypnotic agents, anticonvulsants, muscle relaxants, and mood stabilizers); and for females of childbearing potential, a negative urine pregnancy test prior to randomization and use of an approved form of contraception. Patients with the following criteria were excluded from the lead-in and the extension studies: severe psychiatric illness (assessed by the Mini International Neuropsychiatric Interview [MINI] [32] in

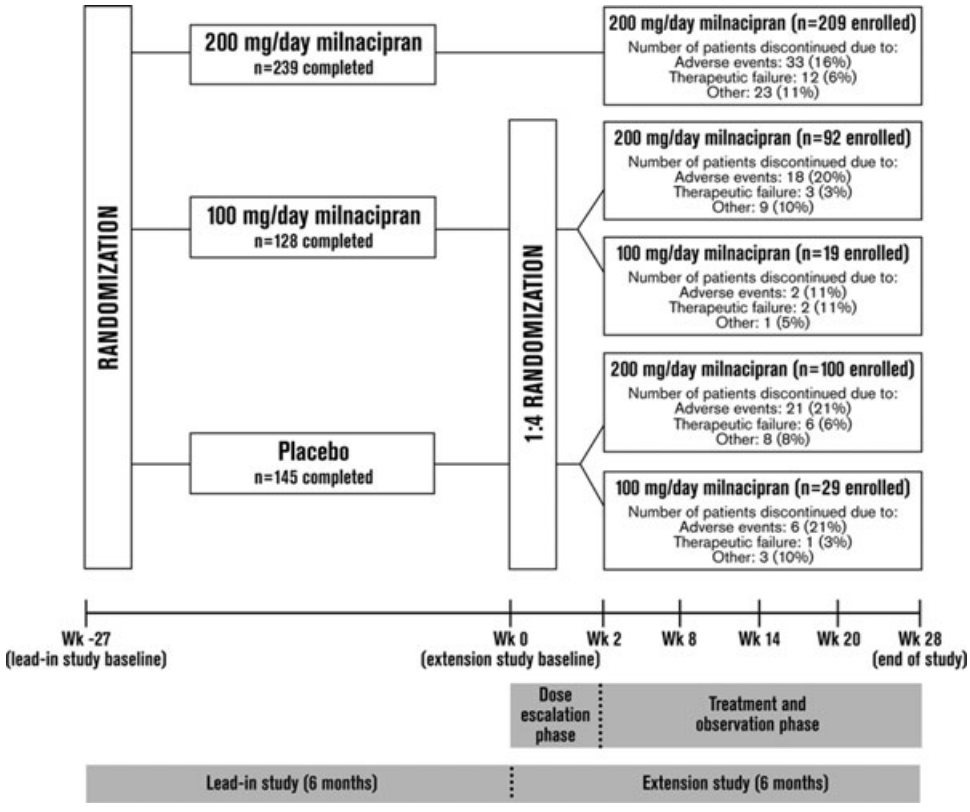

Figure 1 Study design and patient disposition.

the lead-in study and by self-report or investigator judgment in the extension study), including current major depressive episode; significant risk for suicide (assessed by investigator judgment); abuse of alcohol, benzodiazepines, or other drugs (assessed by drug screening in the lead-in study and repeated in the extension study at the discretion of the investigator); any history of behavior that would prohibit compliance for the duration of the study; active cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, or autoimmune disease; current systemic infection; active cancer (except basal cell carcinoma); pregnancy or breastfeeding; and genitourinary disorders. Clinical investigator meetings were conducted to uniformly train all interviewers (experienced psychiatrists, psychologists, or other clinically trained professionals) in the administration of the MINI.

Permissible concomitant therapies included NSAIDs; herbal-based therapies except S-adenosylmethionine and St John's Wort; stable doses of corticosteroids equivalent to ≤10 mg/day prednisone; ≤60 mg/day hydrocodone (administered and analyzed as analgesic rescue therapy and not allowed during the 48 hours prior to study visits); zolpidem (Ambien), chloral hydrate, or over-the-counter sleep remedies for insomnia; and the lowest possible effective dose of the 5-$HT_{1B/1D}$ agonist rizatriptan (Maxalt) to treat migraine headaches. Nonpermissible concomitant medications were benzodiazepines, centrally acting analgesics, anesthetic patches, antidepressants, and digoxin.

The study was approved by the Institutional Review Board at each study center and was conducted in accordance with the *Guidelines for Good Clinical Practice* [33]. All patients gave written, informed consent.

Efficacy and Safety Outcome Measures

Consistent with the originally planned primary efficacy parameters used in the lead-in study, the efficacy parameters included: patient-reported pain recalled over the past 24 hours or past 7 days based on a 0–100 paper visual analog scale (VAS) with anchors of "no pain" and "worst possible pain"; the Patient Global Impression of Change (PGIC) where patients rated their impression of overall change in their FM since entering the extension study using a 7-point scale (1 = "very much improved," 7 = "very much worse"); and Fibromyalgia Impact Questionnaire (FIQ) total score and Physical Function subscale score [34]. Additional efficacy measures were the Beck Depression Inventory (BDI) [35], the Medical Outcome Study (MOS)-Sleep Problems Index [36,37], Patient Global Disease Status (PGDS), the Multidimensional Fatigue Inventory (MFI) [38], and the Multiple Ability Self-Report Questionnaire (MASQ) [39].

Baseline safety measurements were the last observed value prior to the first dose of the double-blind study medication in the lead-in study. Information on concomitant medications and adverse events (AEs) was collected

at extension study weeks 1, 2, 8, 14, 20, and 28. Vital signs were measured at extension study weeks 2, 8, 14, 20, and 28. Baseline efficacy measurements for the lead-in study were the last assessments obtained prior to randomization; baseline efficacy measurements for the extension study were taken at the first extension study visit (week 0, i.e., week 27 of the lead-in study). Efficacy assessments were collected at extension study weeks 0, 8, 14, 20, and 28. BDI was assessed at extension study weeks 0, 14, and 28. Patients who discontinued the study prior to week 28 completed end-of-study assessments at their last visit.

Tolerability and safety evaluations were based on vital signs and spontaneously reported AEs recorded at study visits. Both treatment-emergent AEs (TEAEs) as well as newly-emergent AEs (NEAEs) were analyzed. TEAEs were defined as AEs reported during the lead-in study (lead-in study TEAEs) or extension study (extension-study TEAEs) that either occurred after the first dose of medication in the lead-in study (i.e., week 0) or increased in severity after week 0. NEAEs were defined as the subset of TEAEs reported during the extension study that were not present prior to (or worsened after) the first dose of extension study medication. Blood and urine samples for hematology and clinical chemistry assessments were obtained at weeks 14 and 28 (end of study) or upon study termination. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA; Maintenance and Support Services Organization, Chantilly, VA) Version 8.1.

Statistical Analyses

All efficacy analyses were based on the intent-to-treat population. Descriptive statistics (number of patients, mean, standard error of the mean) and 95% confidence intervals (95% CIs) were presented by the sequence of treatment received in the lead-in study and the current study. Analyses of VAS pain recall, FIQ, and PGIC scores were based on patients with assessments at each study visit where patient's early termination assessment (if applicable) was assigned to the next study visit, and included changes from lead-in study and extension study baseline values. Analyses of other efficacy parameters were based on lead-in study baseline and end-of-study values, which included week 28 (55 weeks of total treatment) assessments from patients who completed treatment, as well as assessments from patients who discontinued the study early.

Results

Patient Demographics and Disposition

A total of 449 of the 512 patients (87.7%) who completed the lead-in study [31] enrolled in this 6-month extension study (Figure 1). There were no clinically relevant differences in demographic and baseline characteristics between treatment groups (Table 1). The mean age of all patients was 49.7 years, and most patients were female (96.9%) and white (93.8%). The mean duration of FM was 5.3 years, and the mean lead-in study baseline paper VAS 24-hour recall pain scores (i.e., pain scores prior to randomization in the lead-in study) could be described as severe (73 out of 100) [40,41].

A total of 301 (67.0%) randomized patients completed the 28-week extension study (Figure 1). Of the randomized patients, 17.8% discontinued due to AEs, 5.8% due to withdrawal of consent, and 5.3% due to therapeutic failure. The percentages of patients who discontinued from the study because of AEs were slightly higher for patients who switched from placebo to milnacipran or from milnacipran 100 to 200 mg/day than for those who remained at a fixed dose of milnacipran throughout both studies. Rates of discontinuation were lowest for patients with long-term exposure to milnacipran (i.e., continuation of milnacipran at the same dose in the lead-in and extension studies [100 or 200 mg/day for 12 months]). Among patients receiving milnacipran 200 mg/day in both the lead-in and extension studies (n = 209), 141 (67.5%) completed the extension study and thus had 12 months of continuous exposure to the highest dose used in these studies. Among extension study patients who received milnacipran 100 mg/day in the lead-in study (n = 111) and were randomized to either 100 or 200 mg/day in the extension study, a total of 76 (68.5%) patients completed an additional 6 months, representing another group of patients who received a total of 12 months of continuous treatment with milnacipran. Overall, study drug compliance (i.e., percentage of study drug capsules taken relative to the number prescribed) was 92%.

It should be pointed out that due to the randomization ratios in the lead-in (1:1:2, placebo: milnacipran 100 mg/day: milnacipran 200 mg/day) and extension studies (1:4, milnacipran 100 mg/day: milnacipran 200 mg/day), relatively few patients were treated with milnacipran 100 mg/day in the extension study. Only 19 patients were randomized to receive milnacipran 100 mg/day for the entire 1-year treatment period, while 29 patients were re-randomized from placebo to the 100 mg/day dose (Figure 1). Therefore, the most robust information comes from the patients treated with milnacipran 200 mg/day in the extension study. The limited data for patients treated with 100 mg/day in the extension study are summarized in Tables 2 and 3.

Efficacy Outcomes

At the end of 1 year, patients treated with milnacipran showed a marked improvement in pain, regardless of whether they were maintained on milnacipran for the entire 1-year period or re-randomized from placebo to milnacipran for the extension study. Patients maintained on milnacipran 200 mg/day for 1 year had a mean decrease from lead-in study baseline in 7-day recall pain scores of –35.1 points (95% CI –39.9 to –30.4) (Figure 2A), while patients re-randomized from placebo to milnacipran 200 mg/day had a mean decrease of –35.8 points (95% CI –42.6 to –29.0) (Figure 2B). Respectively, these results represent 46.7% and 47.2% improvements in pain. Similar

Table 1 Key patient demographic and baseline* values

Extension study treatment	Milnacipran 100 mg/day			Milnacipran 200 mg/day			
Lead-in study treatment	Placebo (N = 29)	Milnacipran 100 mg/day (N = 19)	Total (N = 48)	Placebo (N = 100)	Milnacipran 100 mg/day (N = 92)	Milnacipran 200 mg/day (N = 209)	Total (N = 401)
Age, mean (SEM), years	50.4 (2.0)	50.3 (1.8)	50.3 (1.4)	49.3 (0.9)	50.4 (1.1)	49.4 (0.7)	49.6 (0.5)
Sex, N (%)							
Female	27 (93.1)	19 (100)	46 (95.8)	95 (95.0)	89 (96.7)	205 (98.1)	389 (97.0)
Male	2 (6.9)	0	2 (4.2)	5 (5.0)	3 (3.3)	4 (1.9)	12 (3.0)
Race, N (%)							
White	28 (96.6)	19 (100)	47 (97.9)	94 (94.0)	85 (92.4)	195 (93.3)	374 (93.3)
Nonwhite	1 (3.4)	0	1 (2.1)	6 (6.0)	7 (7.6)	14 (6.7)	27 (6.7)
Weight, mean (SEM), kg	85.9 (3.1)	83.7 (3.4)	85.0 (2.3)	82.9 (1.9)	83.2 (2.1)	82.2 (1.4)	82.6 (1.0)
BMI, mean (SEM)	30.9 (1.0)	31.0 (1.2)	30.9 (0.8)	30.8 (0.7)	30.8 (0.7)	30.7 (0.5)	30.8 (0.4)
FM duration, mean (SEM), years	5.4 (1.0)	5.7 (1.3)	5.5 (0.8)	5.9 (0.6)	4.9 (0.5)	5.2 (0.3)	5.3 (0.3)
Efficacy measure [range], mean (SEM)							
Pain VAS 24-hour recall [0–100]	71.1 (2.3)	75.5 (4.1)	72.9 (2.2)	73.8 (1.6)	71.6 (1.7)	73.3 (1.1)	73.0 (0.8)
Pain VAS 7-day recall [0–100]	74.6 (2.0)	79.1 (2.5)	76.4 (1.6)	75.8 (1.5)	76.4 (1.4)	76.2 (1.0)	76.1 (0.7)
FIQ total [0–100]	64.5 (2.2)	63.5 (2.3)	64.1 (1.6)	63.6 (1.5)	64.1 (1.5)	63.8 (1.0)	63.8 (0.7)
FIQ Physical Function [0–10]	1.4 (0.1)	1.2 (0.2)	1.3 (0.1)	1.3 (0.1)	1.4 (0.1)	1.5 (0.04)	1.4 (0.03)
BDI [0–63]	13.5 (1.8)	12.3 (1.5)	13.0 (1.2)	12.8 (0.9)	13.9 (0.9)	14.0 (0.6)	13.7 (0.4)
MFI total [20–100]	69.5 (1.7)	68.8 (2.8)	69.3 (1.5)	65.1 (1.4)	66.9 (1.4)	67.7 (0.9)	66.8 (0.7)
MOS-Sleep Problems Index I [0–100]	56.7 (3.8)	61.4 (3.3)	58.6 (2.6)	52.3 (1.6)	56.9 (1.8)	57.5 (1.1)	56.1 (0.8)
MOS-Sleep Problems Index II [0–100]	57.6 (3.7)	63.3 (3.3)	59.9 (2.6)	53.4 (1.6)	58.2 (1.7)	58.3 (1.1)	57.1 (0.8)
MASQ total [38–190]	89.4 (3.4)	91.7 (3.0)	90.3 (2.4)	86.6 (1.9)	88.8 (2.1)	88.2 (1.2)	87.9 (0.9)

* Baseline at the beginning of lead-in study.

BDI = Beck Depression Inventory; BMI = body mass index; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; MASQ = Multiple Ability Self-Report Questionnaire; MFI = Multidimensional Fatigue Inventory; MOS = Medical Outcomes Study; PGDS = Patient Global Disease Status; SEM = standard error of the mean; VAS = visual analog scale.

Table 2 Mean change from baseline* in pain VAS 7-day recall and FIQ total scores in extension study patients receiving milnacipran 100 mg/day

Efficacy measure	Pain VAS 7-Day Recall Score						FIQ Total Score					
Extension study treatment	Milnacipran 100 mg/day						Milnacipran 100 mg/day					
Lead-in study treatment	Placebo (N = 29)			Milnacipran 100 mg/day (N = 19)			Placebo (N = 29)			Milnacipran 100 mg/day (N = 19)		
Visit	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI
Week 0	28	–26.9 (4.3)	–35.8, –18.1	19	–37.3 (6.4)	–50.6, –23.9	29	–25.0 (2.4)	–29.9, –20.0	19	–26.1 (4.4)	–35.3, –16.9
Week 8	26	–33.1 (4.6)	–42.5, –23.6	17	–35.1 (5.3)	–46.3, –23.9	27	–26.2 (3.8)	–34.1, –18.4	17	–24.7 (3.9)	–33.0, –16.3
Week 14	20	–25.8 (5.7)	–37.6, –13.9	16	–46.6 (5.0)	–57.3, –35.9	21	–22.1 (5.1)	–32.7, –11.4	16	–28.7 (4.4)	–38.0, –19.3
Week 20	18	–31.7 (5.5)	–43.2, –20.1	15	–38.5 (5.1)	–49.4, –27.5	19	–27.9 (4.8)	–38.0, –17.8	15	–24.8 (4.1)	–33.6, –16.0
Week 28	18	–25.3 (8.3)	–42.8, –7.7	14	–33.2 (5.8)	–45.8, –20.6	19	–23.8 (5.6)	–35.6, –12.0	14	–23.1 (4.3)	–32.5, –13.7

* Baseline at the beginning of lead-in study.
95% CI = 95% confidence interval; FIQ = Fibromyalgia Impact Questionnaire; SEM = standard error of the mean; VAS = visual analog scale.

Table 3 Efficacy measures (mean changes in scores from lead-in study baseline at end of study)

Lead-in study treatment	Placebo				Milnacipran 100 mg/day				Milnacipran 200 mg/day	
Extension study treatment	Milnacipran 100 mg/day (N = 29)		Milnacipran 200 mg/day (N = 100)		Milnacipran 100 mg/day (N = 19)		Milnacipran 200 mg/day (N = 92)		Milnacipran 200 mg/day (N = 209)	
	n	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)
Pain VAS 24-hour recall	28	–25.7 (5.6)	100	–29.1 (2.7)	19	–33.0 (5.1)	92	–30.1 (3.3)	209	–30.2 (2.1)
FIQ-PF	29	–0.4 (0.1)	97	–0.4 (0.1)	19	–0.4 (0.2)	90	–0.5 (0.1)	209	–0.6 (0.1)
PGDS	28	–23.1 (4.8)	100	–25.2 (2.9)	19	–27.7 (5.3)	92	–26.9 (3.3)	209	–28.2 (2.1)
BDI	29	–4.7 (1.4)	100	–4.7 (1.0)	19	–3.5 (1.1)	92	–5.3 (0.9)	209	–5.6 (0.6)
MFI total	29	–9.9 (2.3)	100	–5.3 (1.4)	19	–9.1 (2.9)	92	–7.7 (1.6)	209	–8.8 (1.0)
MOS-Sleep Problems Index I	29	–8.9 (3.2)	100	–7.1 (1.9)	19	–10.2 (2.9)	92	–10.1 (2.4)	209	–11.0 (1.3)
MOS-Sleep Problems Index II	29	–9.6 (3.2)	100	–8.4 (1.9)	19	–11.8 (2.5)	92	–11.1 (2.3)	209	–12.0 (1.3)
MASQ total	29	–1.9 (3.3)	100	–1.1 (1.4)	19	–1.2 (3.0)	92	–2.8 (1.4)	209	–3.5 (1.0)

BDI = Beck Depression Index; FIQ-PF = Fibromyalgia Impact Questionnaire-Physical Function; MASQ = Multiple Ability Self-Report Questionnaire; MFI = Multidimensional Fatigue Inventory; MOS = Medical Outcomes Study; PGDS = Patient Global Disease Status; SEM = standard error of the mean; VAS = visual analog scale.

results were observed in the 24-hour recall pain scores (Table 3). For those patients maintained on milnacipran 200 mg/day for 1 year, improvements in pain (7-day recall pain scores) at the end of the lead-in study (–32.5 points, 95% CI –36.7 to –28.3) were approximately the same as improvements observed at the end of the extension study (–35.1, 95% CI –39.9 to –30.4) (Figure 2A). These results indicate that the pain improvements obtained in the first 6 months during the lead-in study were maintained during the second 6 months of the extension study.

For patients re-randomized from placebo to milnacipran 200 mg/day, a decrease from extension study baseline in 7-day recall pain scores (–12.4 points) was evident by the first assessment (week 8 of the extension study), representing a 22.8% improvement in pain. This improvement was maintained at each of the visits in the extension study, with mean changes from extension study baseline in 7-day recall pain scores ranging from –11.0 to –14.1 points. These results represent additional improvements in pain over those observed during placebo treatment in the lead-in study.

Similar to improvements seen in patients re-randomized from placebo to milnacipran 200 mg/day, additional improvements in pain perception during the extension study were found in patients re-randomized from milnacipran 100 mg/day to 200 mg/day. At week 28 in this group, the mean change from extension-study baseline in 7-day recall pain score was –2.8 points, representing an additional 7.1% improvement in pain (Figure 2). Similar improvements from extension study baseline to week 28 in 24-hour recall pain were noted (data on file). Additionally, of the 92 patients re-randomized from milnacipran 100 mg/day to 200 mg/day, 36 were classified as pain nonresponders at the end of the lead-in study (i.e., those patients who did not achieve ≥30% improvement from baseline in 24-hour recall pain VAS scores). Of these lead-in study nonresponders, 45.7% (16 of 35) reported a ≥30% improvement in pain from extension study baseline at the first visit following re-randomization to the higher dose of milnacipran. At the final visit of the extension study, 39.1% (9 of 23) of patients reported a ≥30% improvement in pain from extension study baseline, indicating that some patients benefited from the higher milnacipran dose.

The primary outcome of the lead-in study was a 2-measure composite responder analysis that required individual patients to achieve a simultaneous improvement of ≥30% from baseline in 24-hour recall pain VAS scores based on an electronic diary *and* a PGIC score of 1 ("very much improved" or 2 ("much improved"). In the lead-in study, there were 104 patients who were randomized to milnacipran 200 mg/day who met this rigorous response criterion at the end of the week 15 landmark visit and subsequently entered this extension study. The pain data for this cohort are shown in Figure 3, illustrating the durable pain relief throughout the full year of treatment experienced by this group.

In addition to the pain improvements described above, patients demonstrated similar responses in other domains

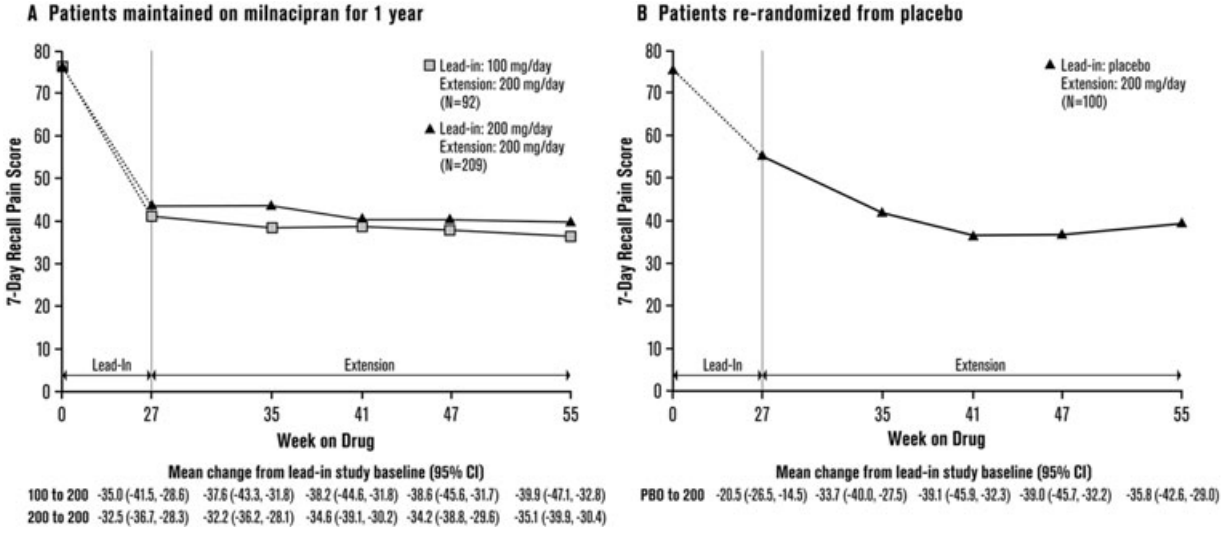

Figure 2 Treatment effect of milnacipran 200 mg/day on 7-day recall pain scores for 1 year. Mean 7-day recall pain scores in (A) patients re-randomized from milnacipran 100 mg/day to 200 mg/day or maintained on milnacipran 200 mg/day, and (B) patients re-randomized from placebo to milnacipran 200 mg/day. Values represent observed cases at each study visit. 100 to 200 = milnacipran 100 mg/day to milnacipran 200 mg/day; 200 to 200 = milnacipran 200 mg/day to milnacipran 200 mg/day; PBO to 200 = placebo to milnacipran 200 mg/day; 95% CI = 95% confidence interval.

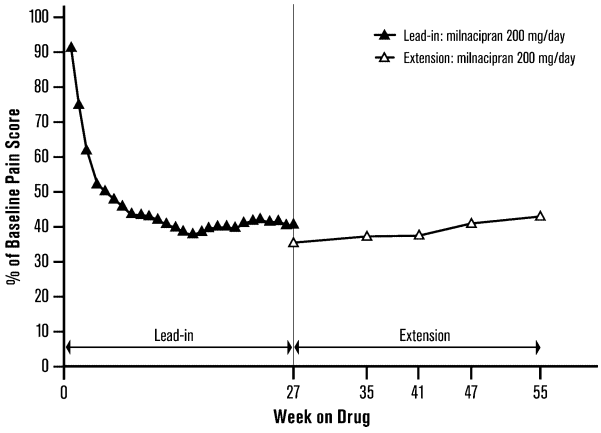

Figure 3 One year pain relief in milnacipran 200 mg/day-treated patients who met 2-measure composite responder criteria at week 15 of lead-in study and continued in extension study. Values represent reported percent pain (24-hour recall score) relative to the lead-in study baseline using last observation carried forward. Pain data from the lead-in study were collected using an electronic visual analog scale (VAS) measure and data from the extension study were recorded using a paper VAS measure. Data were collected from responders at week 15 (primary endpoint) of the lead-in study who received milnacipran 200 mg/day during both the lead-in and extension studies (n = 104). In the lead-in study, 2-measure composite responders were defined as patients reporting ≥30% reduction in pain scores and a rating of "much improved" or "very much improved" on the Patient Global Impression of Change.

important for fibromyalgia patients. Patients maintained on milnacipran for 1 year or re-randomized from placebo to milnacipran also showed marked and generally comparable improvements in FIQ total scores relative to the baseline of the lead-in study. In patients receiving milnacipran 200 mg/day for 1 year, improvements in FIQ total scores during the lead-in study were maintained for an additional 6 months. Similar improvements from lead-in study baseline were seen at end of the lead-in study (–25.4, 95% CI –28.6 to –22.3) and at week 28 of the extension study (–26.0, 95% CI –29.5 to –22.5) (Figure 4A).

In patients re-randomized from placebo to milnacipran 200 mg/day, improvements in FIQ total score were observed at all visits and were similar to improvements seen in patients receiving continuous milnacipran treatment (Figure 4B). Patients treated with milnacipran 100 mg/day in the lead-in study and subsequently re-randomized to milnacipran 200 mg/day in the extension study showed further improvements in FIQ total score at all extension study visits (Figure 4A).

In the lead-in study, significant differences favoring milnacipran over placebo were observed for PGIC [31]. During the extension study, patients in all milnacipran treatment groups continued to show improvement in PGIC scores relative to entry into the extension study (Table 4). At week 28, the mean PGIC scores were the same for patients receiving 1 year of milnacipran 200 mg/day (2.2, 95% CI 2.0–2.4) and those re-randomized from placebo to milnacipran 200 mg/day (2.2, 95% CI 1.9–2.5).

Of the patients re-randomized from milnacipran 100 mg/day to 200 mg/day (n = 92), 40 were classified as PGIC nonresponders at the end of the lead-in study (i.e., those patients who achieved a PGIC score >2). Among PGIC nonresponders to milnacipran 100 mg/day during the lead-in study, 12/25 (48.0%) were responders at the end of the extension study (i.e., rated themselves as "much improved" or "very much improved" on the PGIC).

Finally, patients treated with milnacipran showed improvement at the end of the extension study (relative lead-in study baseline) in other parameters important in FM (Table 3).

Safety and Tolerability

Milnacipran was well tolerated at doses of 100 and 200 mg/day for up to 1 year. The overall incidence of TEAEs during the extension study was 77.1% and 78.6% among the milnacipran 100 mg/day and 200 mg/day groups, respectively (Table 5). The most commonly reported TEAE in the extension study was nausea (milnacipran 100 mg/day, 22.9%; 200 mg/day, 23.9%). Other TEAEs reported in at least 5% of total patients were sinusitis, headache, constipation, hypertension, hyperhidrosis, and dizziness.

The overall incidence of NEAEs was 68.8% and 74.3% for milnacipran 100 mg/day and 200 mg/day, respectively (Table 5). The overall incidence of NEAEs was similar among patients re-randomized from placebo to milnacipran 100 mg/day or 200 mg/day and those maintained on milnacipran 200 mg/day. However, individual NEAEs such as nausea, headache, hyperhidrosis, and constipation were more common in patients re-randomized from placebo to milnacipran 200 mg/day than in those continuing on milnacipran. Patients re-randomized from milnacipran 100 mg/day to 200 mg/day had a slightly greater incidence of NEAEs compared with those re-randomized from placebo to milnacipran 200 mg/day or those maintained on 200 mg/day. The incidence of NEAEs occurring in the extension study was similar to that of TEAEs, with the exception of nausea, which occurred at a lower rate as an NEAE (milnacipran 100 mg/day, 18.8%; 200 mg/day, 17.5%).

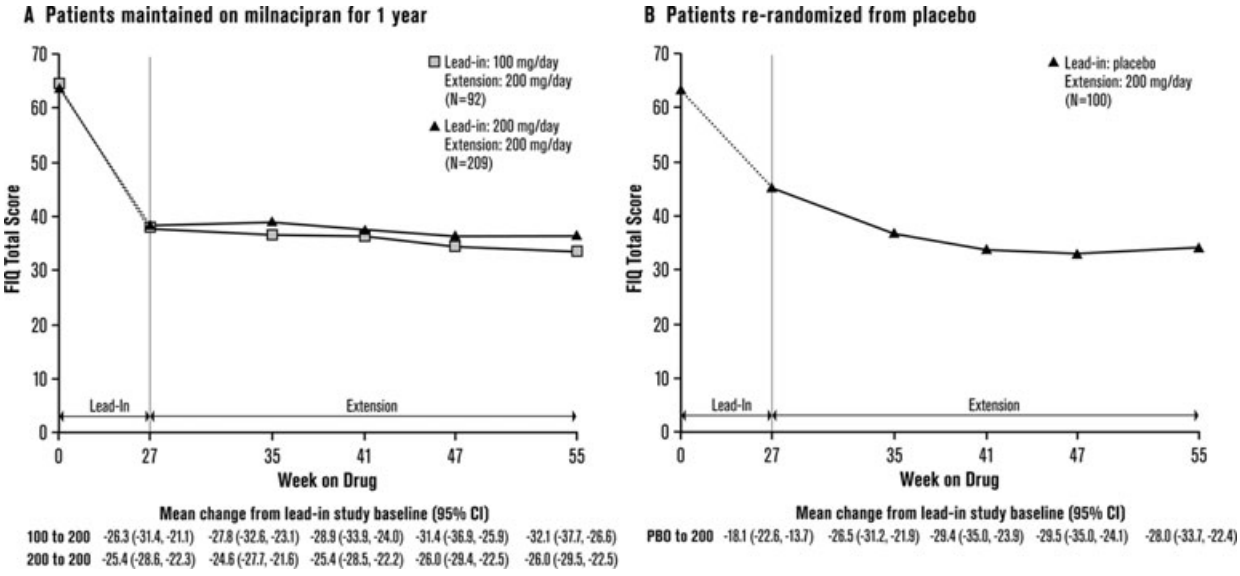

Figure 4 Treatment effect of milnacipran 200 mg/day on Fibromyalgia Impact Questionnaire (FIQ) total scores for 1 year. Mean FIQ total scores in (A) patients re-randomized from milnacipran 100 mg/day to 200 mg/day or maintained on milnacipran 200 mg/day, and (B) patients re-randomized from placebo to milnacipran 200 mg/day. Values represent observed cases at each study visit. 100 to 200 = milnacipran 100 mg/day to milnacipran 200 mg/day; 200 to 200 = milnacipran 200 mg/day to milnacipran 200 mg/day; PBO to 200 = placebo to milnacipran 200 mg/day; 95% CI = 95% confidence interval.

The profile of NEAEs occurring in the extension study was similar to that of TEAEs in the 27-week lead-in study (Figure 5). Prolonged exposure to milnacipran did not result in any new safety concerns or findings. No new AEs of concern emerged during the extension study that had not already been reported during the lead-in study. The most commonly reported AEs during the lead-in study (i.e., nausea, headache, and constipation) occurred with lower frequency during the extension study. The only two AEs with a higher incidence in the extension study than in the lead-in study were sinusitis (lead-in study, 6.5%; extension study, 9.1%) and hypertension (lead-in study, 4.5%; extension study, 6.6%). AEs resulted in premature discontinuation in 16.7% of milnacipran 100 mg/day patients and 16.0% of milnacipran 200 mg/day patients. The only AE resulting in premature discontinuation of greater than 2% of patients was nausea (100 mg/day, 6.3%; 200 mg/day, 4.7%). Serious AEs were reported in 16 of 449 patients (3.6%) during the 6-month extension study period, with five events (two patients with chest pain, one patient with heart rate increased and heart rate irregular, and one patient with migraine) judged as possibly or probably related to study medication. There were no deaths reported during the study. There were no clinically relevant mean changes from baseline for any of the laboratory parameters tested.

Some patients in the extension study experienced changes in supine heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) (Table 6). As expected, patients who were re-randomized from placebo to milnacipran had greater increases in heart rate and blood pressure during the extension study as compared with the lead-in study. These increases were similar to the mean changes observed in the milnacipran pivotal trials [29,31]. In patients receiving milnacipran for 1 year, mean changes in vital signs during the lead-in study were generally similar to changes observed at the end of the extension study. These results suggest that for patients with continuous milnacipran treatment, vital sign increases mostly occurred during the lead-in study. Mean changes in supine SBP and DBP in patients receiving milnacipran 100 mg/day group for 1 year were slightly higher during the extension study than in the lead-in study; however, the size of this treatment group was very small (n = 19). For patients maintained on milnacipran 200 mg/day for 1 year, mean supine DBP was lower at the end of the extension study than at the end of the lead-in study. Similar results were observed in mean supine DBP and heart rate in patients who were escalated from milnacipran 100 mg/day to 200 mg/day.

Potentially clinically significant (PCS) increases in supine heart rate (≥120 bpm with an increase of ≥20 bpm from baseline) and SBP (≥180 mm Hg with an increase of ≥20 mm Hg from baseline) were infrequent at both dosages of milnacipran (<1%). The incidence of PCS changes in supine SBP or heart rate did not increase with long-term milnacipran treatment. In patients maintained on milnacipran 100 mg/day in both studies (n = 19), PCS

Table 4 Patient Global Impression of Change (PGIC) score, by visit*

Lead-in study treatment	Placebo						Milnacipran 100 mg/day						Milnacipran 200 mg/day		
Extension study treatment	Milnacipran 100 mg/day (N = 29)			Milnacipran 200 mg/day (N = 100)			Milnacipran 100 mg/day (N = 19)			Milnacipran 200 mg/day (N = 92)			Milnacipran 200 mg/day (N = 209)		
Visit	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI	n	Mean (SEM)	95% CI
Week 0†	29	2.9 (0.2)	2.5, 3.4	100	3.1 (0.1)	2.8, 3.3	19	2.4 (0.2)	1.9, 2.9	92	2.6 (0.1)	2.4, 2.9	209	2.5 (0.1)	2.3, 2.7
Week 8‡	27	2.6 (0.2)	2.1, 3.1	97	2.6 (0.1)	2.4, 2.9	17	2.8 (0.4)	2.1, 3.6	89	2.5 (0.1)	2.3, 2.7	202	2.5 (0.1)	2.4, 2.7
Week 14‡	21	2.5 (0.2)	2.1, 2.8	75	2.2 (0.1)	2.0, 2.5	16	2.1 (0.2)	1.6, 2.6	81	2.2 (0.1)	2.0, 2.4	175	2.4 (0.1)	2.2, 2.6
Week 20‡	19	2.3 (0.2)	1.9, 2.7	70	2.1 (0.1)	1.9, 2.4	15	2.5 (0.3)	1.8, 3.3	67	2.0 (0.1)	1.8, 2.2	157	2.3 (0.1)	2.1, 2.5
Week 28‡	19	2.3 (0.2)	1.9, 2.7	65	2.2 (0.1)	1.9, 2.5	14	2.1 (0.2)	1.6, 2.6	64	1.9 (0.1)	1.7, 2.1	147	2.2 (0.1)	2.0, 2.4

* Decrease in score indicates improvement.
† Values for Week 0 are from Week 27 of the lead-in study and represent improvement from the start of the lead-in study.
‡ Values represent improvement from the start of the extension study.
95% CI = 95% confidence interval; SEM = standard error of the mean.

increases in supine DBP (≥110 mm Hg with an increase of ≥15 mm Hg from baseline) occurred in 5.6% of patients. In patients receiving milnacipran 200 mg/day for 1 year, PCS increases in supine DBP occurred in 1.5% of patients.

A more clinically relevant measure of the effect on blood pressure may be the incidence of sustained hypertension. Sustained increases in supine DBP (i.e., ≥90 mm Hg and an increase of ≥10 mm Hg from baseline on three consecutive visits) occurred in 3.2% of patients receiving milnacipran 200 mg/day. Sustained increases in supine SBP values (i.e., ≥140 mm Hg and an increase of ≥20 mm Hg from baseline on three consecutive visits) occurred in less than 1% of patients receiving milnacipran 200 mg/day. No sustained increases in supine DBP or SBP were observed in patients treated with milnacipran 100 mg/day, although this group was too small to allow meaningful conclusions.

The mean baseline body mass index (BMI) was 30.8 in the extension study, indicating that many of the patients were either overweight or obese (Table 1). Depending on the treatment received during the lead-in study, patients could have been exposed to milnacipran for 6 or 12 months. In those patients treated with milnacipran 200 mg/day for 12 months, mean weight changes were –3.1 lbs at the end of lead-in study (n = 209) and –1.4 lbs at the end of extension study (n = 141). Similarly, patients treated with milnacipran 100 mg/day for 6 months and 200 mg/day for 6 months demonstrated mean weight changes of –3.1 lbs at the end of lead-in study (n = 92) and –2.3 lbs at the end of extension study (n = 61). In patients re-randomized from placebo to milnacipran 200 mg/day, mean weight changes were +0.1 lbs at the end of lead-in study (n = 100) and –1.4 lbs at the end of extension study (n = 65).

Discussion

The current study demonstrates that milnacipran is effective and well tolerated during continuous long-term treatment for 1 year in FM patients. Data presented here support and extend the findings of a 6-month double-blind, placebo-controlled lead-in trial of milnacipran in the treatment of FM [31]. Improvements in pain, global status, physical function, and other FM-associated symptoms that were observed after 6 months of treatment in the placebo-controlled lead-in study were maintained for an additional 6 months with continued milnacipran treatment.

Patients who received continuous treatment with milnacipran 100 or 200 mg/day demonstrated persistent efficacy over 1 year, with an improvement of 41% and 47%, respectively, from lead-in study baseline in mean 7-day recall pain scores at week 28. These changes represent clinically meaningful improvements in pain (≥30% change from baseline [42]), as well as a shift from severe pain scores before treatment (mean pain scores >70) to moderate pain scores after 6 to 12 months of milnacipran treatment (mean pain scores between 30 and 50) [40,41].

Table 5 Treatment-emergent adverse events (TEAEs) and newly emergent adverse events (NEAEs) with an incidence of >5% in total population during extension study treatment

Extension study treatment	Milnacipran 100 mg/day (N = 48)*	Milnacipran 200 mg/day (N = 401)†	Total (N = 449)
Any TEAE, n (%)	37 (77.1)	315 (78.6)	352 (78.4)
Nausea	11 (22.9)	96 (23.9)	107 (23.8)
Sinusitis	3 (6.3)	38 (9.5)	41 (9.1)
Headache	2 (4.2)	37 (9.2)	39 (8.7)
Constipation	4 (8.3)	29 (7.2)	33 (7.3)
Hypertension	2 (4.2)	30 (7.5)	32 (7.1)
Hyperhidrosis	4 (8.3)	27 (6.7)	31 (6.9)
Dizziness	3 (6.3)	23 (5.7)	26 (5.8)
Any NEAE, n (%)	33 (68.8)	298 (74.3)	331 (73.7)
Nausea	9 (18.8)	70 (17.5)	79 (17.6)
Sinusitis	3 (6.3)	33 (8.2)	36 (8.0)
Headache	2 (4.2)	30 (7.5)	32 (7.1)
Hyperhidrosis	4 (8.3)	25 (6.2)	29 (6.5)
Hypertension	2 (4.2)	27 (6.7)	29 (6.5)
Constipation	3 (6.3)	23 (5.7)	26 (5.8)
Dizziness	2 (4.2)	21 (5.2)	23 (5.1)

* Patients who received placebo (n = 29) or milnacipran 100 mg/day (n = 19) during the lead-in study.
† Patients who received placebo (n = 100), milnacipran 100 mg/day (n = 92), or milnacipran 200 mg/day (n = 209) during the lead-in study.

In patients maintained on milnacipran 100 or 200 mg/day for 12 months, the final observed 7-day recall pain scores remained within 2% of extension study baseline scores. In patients re-randomized from milnacipran 100 mg/day to 200 mg/day, the final observed weekly pain scores represented an additional 7.1% improvement from extension study baseline. Furthermore, patients responding to milnacipran treatment in the lead-in study showed durable pain relief for at least 1 year. This trial also included efficacy measures assessing the multiple symptoms associated with FM, which included fatigue (MFI), cognitive dysfunction (MASQ), decreased functioning (FIQ), and sleep disturbances (MOS-Sleep Problems Indices). Analyses of these data demonstrated that after 1 year of milnacipran treatment, patients showed improvements in fatigue, functioning, and no worsening in sleep parameters.

This extension trial also demonstrated that patients switched from milnacipran 100–200 mg/day had further improvements in pain, PGIC, and FIQ. Approximately 40–50% of milnacipran 100 mg/day patients classified as pain or PGIC nonresponders at the end of the lead-in study became responders when switched to milnacipran 200 mg/day in the extension study. These results suggest that some patients may achieve additional benefits from the higher dose of milnacipran. Patients switched from placebo to milnacipran 200 mg/day improved in pain, FIQ, and PGIC scores, which is consistent with findings from previous milnacipran clinical trials that showed improvements in these measures in milnacipran-treated patients compared with placebo [29–31]. In these patients, improvements in pain from lead-in study baseline were similar to those found in patients who were maintained on continuous milnacipran treatment. Smaller changes in pain and FIQ scores were observed in patients re-randomized from placebo to milnacipran 100 mg/day compared with other treatment arms, but the size of this group was very small (n = 29) and included placebo responders from the lead-in study.

Findings from the extension study demonstrate that the majority of patients (88%) completing the lead-in study elected to enroll in the extension study, and more than half of these patients (67%) completed the additional 6 months of dose-blinded monotherapy. Additionally, 217 of the 320 patients continuing on milnacipran in the extension study completed the study and thus were exposed to 1 year of continuous treatment. Of these 217 patients, 141 were on milnacipran 200 mg/day for the entire period. Long-term treatment with milnacipran did not result in any new safety concerns. In the 449 patients who chose to enter this extension study, no new AEs of concern arose during the extension trial that had not been observed in the lead-in study. In these patients, milnacipran was generally well tolerated, with at least 90% of TEAEs rated as mild to moderate in severity. Similar to other milnacipran FM studies, the most commonly reported adverse event in the extension study was nausea. Patients switched from placebo or milnacipran 100 mg/day in the lead-in study to 200 mg/day in the extension study experienced slightly higher incidences of AEs. Some patients in this study experienced increases in heart rate and blood pressure;

Figure 5 Adverse events in patients continuing milnacipran treatment. Adverse events shown are treatment-emergent adverse events (TEAEs) or newly emergent adverse events (NEAEs) occurring in ≥5% of patients in the lead-in or extension studies, respectively. *Lead-in study population*: patients receiving milnacipran 100 mg/day (N = 224) or 200 mg/day (N = 441) for 6 months. *Extension study population*: patients maintained on milnacipran 100 mg/day (N = 19), 200 mg/day (N = 209), or re-randomized from 100 to 200 mg/day (N = 92) for a total treatment duration of 1 year. URT = upper respiratory tract.

regular monitoring of heart rate and blood pressure is advisable in patients receiving milnacipran treatment.

Several limitations should be noted to the current study. By study design, this was a continuation study of "completers" to the initial 6-month blinded, placebo-controlled study. Patients were aware that they were taking the active medication in this continuation trial, although they remained blinded to the dose. The inclusion of placebo-treated patients for another 6 months would have been instructive but was not considered practical. The randomization scheme for both the lead-in, randomized trial, and this extension report ensured that a large number of patients were exposed to the 200 mg/day dose as it was of interest to expand the pool of patients exposed to the higher dose. However, this limited the number of patients assigned to the 100 mg/day dose. Because of the limited power to evaluate the efficacy and safety of the 100 mg/day dose, no comments can be made as to the comparable efficacy and tolerability of the two doses. However, the slightly improved outcome when patients were switched from the 100 to 200 mg/day dose without tolerability issues was important. In the United States, milnacipran is approved at the 100 mg/day dose with instructions that based on individual patient response, the dose may be increased to 200 mg/day.

Table 6 Mean changes in vital signs during lead-in study and extension study*

Lead-in study treatment	Placebo		Milnacipran 100 mg/day		Milnacipran 200 mg/day
Extension study treatment	Milnacipran 100 mg/day (N = 29)	Milnacipran 200 mg/day (N = 100)	Milnacipran 100 mg/day (N = 19)	Milnacipran 200 mg/day (N = 92)	Milnacipran 200 mg/day (N = 209)
Vital sign changes	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
Supine heart rate, bpm					
During lead-in study	–1.6 (1.7)	–0.1 (1.1)	7.3 (3.0)	7.8 (1.3)	9.3 (0.8)
During extension study	7.3 (2.4)	7.6 (1.1)	–1.0 (2.5)	–0.2 (1.1)	1.0 (0.8)
Supine SBP, mm Hg					
During lead-in study	0.2 (2.9)	0.6 (1.4)	–2.4 (3.9)	3.3 (1.4)	2.7 (1.0)
During extension study	1.1 (2.6)	4.2 (1.4)	2.1 (2.4)	0.6 (1.5)	0.4 (1.0)
Supine DBP, mm Hg					
During lead-in study	–1.9 (2.0)	1.5 (1.0)	–1.2 (2.5)	3.1 (1.0)	2.3 (0.7)
During extension study	1.4 (1.8)	2.8 (0.9)	0.4 (2.2)	–0.6 (1.0)	–0.8 (0.7)

* Based on end-of-study values (includes all patients who completed extension study treatments or who discontinued early from extension study).
bpm = beats per minute; DPB = diastolic blood pressure; SBP = systolic blood pressure; SEM = standard error of the mean.

Patients with medical and psychiatric conditions were excluded from the study. Additionally, patients discontinued medications commonly used to treat FM as this was a monotherapy design. Therefore, these findings may not be generalizable to some FM patients seen in clinical practice. Even though all patients, study site investigators, and staff remained blinded to the dose of milnacipran received in both the lead-in and extension studies, all patients knew they were receiving some dose of milnacipran during the extension study. Given the lack of placebo comparator groups, limitations may exist in interpreting the data. Furthermore, this study represents a select group of patients. Of the 888 patients who were randomized in the lead-in study, 42% discontinued the study; 88% of the remaining and eligible patients chose to enroll in the extension study. Thus, the extension study sample represents the two following sets of patients: those who tolerated milnacipran well and successfully adhered to their medication for 6 months, and those who were diligent and motivated enough to remain on placebo for 6 months.

In conclusion, these findings confirm the results of other studies showing that milnacipran is well tolerated and effective in the treatment of FM, improving both the pain and multidimensional symptoms of FM. The effects of milnacipran in the treatment of FM are durable and sustained for at least 1 year in this patient population.

Acknowledgments

Supported by Forest Laboratories, Inc., New York, New York and Cypress Bioscience, Inc., San Diego, California. Dr. Goldenberg has no financial relationships with a cumulative value of more than $10,000 per year in the past 3 years with any company whose products may be related to the topic of this manuscript. Dr. Clauw has served as a consultant and/or received grant support from Forest Laboratories, Inc., Cypress Bioscience, Inc., Pierre Fabre Médicament, Eli Lilly and Company, and Pfizer Inc. Dr. Mease has served as a consultant and/or received grant support from Forest Laboratories, Inc., Cypress Bioscience, Inc., Eli Lilly and Company, and Pfizer Inc. Drs. Palmer and Chen are employees of Forest Research Institute. Dr. Gendreau is an employee of Cypress Bioscience, Inc. Investigators: Christopher D. Alftine, MD; Floyd N. Andersen, MD; Lesley M. Arnold, MD; Andrew R. Baldassare, MD; Mira Baron, MD; Scott W. Baumgartner, MD; Margaret E. Blanton, MD; David G. Borenstein, MD; Patricia P. Buchanan, MD; Francis X. Burch, MD; Stephen Burnstein, DO; David Carfagno, DO; Sylvia L. Cerel, MD; Vishala L. Chindalore, MD; John J. Condemi, MD; Jeffrey C. Davis, MD; Michael P. DeMicco, MD; Emma Dilorio, MD, FACR; Daniel J. Dionne, MD; John E. Ervin, MD, FACP, FACR; Robert E. Ettlinger, MD; Justus J. Fiechtner, MD, MPH; Joseph Z. Forstot, MD; Jeffrey Gitt, DO; Don L. Goldenberg, MD, FACP; Jerry Green, MD; Robert M. Griffin Jr, DO; Wayne L. Harper, MD; E. Robert Harris, MD; Imran Iqbal, MD; Anita S. Kablinger, MD; Robert Katz, MD; Paul L. Katzenstein, MD; Elliot J. Kopp, MD; John LaFata, MD; Robert W. Levin, MD; Jeffrey D. Lieberman, MD; David R. Mandel, MD; Harris H. McIlwain, MD; Philip Mease, MD; Kenneth M. Nies, MD; John E. Pappas, MD; Richard G. Pellegrino, MD, PhD; Joachim D. Raese, MD; Constantine Saadeh, MD; Philippe A. Saxe, MD; Anthony I. Sebba, MD; Richard P. Singer, MD; John Tesser, MD; Dana R. Trotter, MD; Bridget Walsh, DO; Nathan Wei, MD; Richard L. Weinstein, MD; Craig W. Wiesenhutter, MD; Hayes T. Williams, MD, PhD; Patrick B. Wood, MD. Editorial assistance was provided by Prescott Medical Communications Group, Chicago, Illinois.

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