The Efficacy and Safety of Milnacipran for Treatment of Fibromyalgia. A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT. ***Objective.*** To evaluate the safety and efficacy of milnacipran, a dual norepinephrine and serotonin reuptake inhibitor, in the treatment of fibromyalgia (FM).

Methods. A 27-week, randomized, double-blind, multicenter study compared milnacipran 100 and 200 mg/day with placebo in the treatment of 888 patients with FM. Two composite responder definitions were used to classify each patient's individual response to therapy. "FM responders" concurrently satisfied response criteria for improvements in pain (visual analog scale 24-h morning recall), patient global impression of change (PGIC), and physical functioning (SF-36 Physical Component Summary); while "FM pain responders" concurrently satisfied response criteria for improvements in pain and PGIC.

Results. At the primary endpoint, after 3-month stable dose treatment, a significantly higher percentage of milnacipran-treated patients met criteria as FM responders versus placebo (milnacipran 200 mg/day, $p = 0.017$; milnacipran 100 mg/day, $p = 0.028$). A significantly higher percentage of patients treated with milnacipran 200 mg/day also met criteria as FM pain responders versus placebo ($p = 0.032$). Significant pain reductions were observed after Week 1 with both milnacipran doses. At 15 weeks, milnacipran 200 mg/day led to significant improvements over placebo in pain (real-time, daily and weekly recall; all measures, $p < 0.05$), PGIC ($p < 0.001$), fatigue ($p = 0.016$), cognition ($p = 0.025$), and multiple SF-36 domains. Milnacipran was safe and well tolerated by the majority of patients during 27 weeks of treatment; nausea and headache were the most common adverse events.

Conclusion. Milnacipran is safe and effective for the treatment of multiple symptoms of FM. (First Release Dec 15 2008; J Rheumatol 2009;36:398–409; doi:10.3899/jrheum.080734)

Key Indexing Terms:

FIBROMYALGIA	PAIN	MILNACIPRAN
PHYSICAL FUNCTION	FATIGUE	RHEUMATOLOGY

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Fibromyalgia (FM) is a common systemic disorder characterized by widespread musculoskeletal pain and a generalized reduced threshold for pain sensation. Patients with FM typically experience a variety of other symptoms, including sleep disturbance, fatigue, stiffness, cognitive dysfunction, and depressive symptoms[1-3]. The chronicity and severity of pain and other symptoms of FM can lead to functional impairments that negatively affect a patient's quality of life[4]. FM is estimated to affect about 2% to 4% of the population in the United States and is much more common in women than in men[3,5].

Diagnostic criteria were established in 1990 by the American College of Rheumatology (ACR), primarily for the purpose of standardizing clinical trial populations[2]. These criteria require that an individual have chronic widespread pain involving all 4 quadrants of the body and the axial skeleton, as well as the presence of pain in 11 of 18 standardized "tender points" on palpation. The etiology and pathogenesis of FM is not well understood, but increasing evidence suggests that a dysregulation of pain processing

within the central nervous system leads to a heightened perception of pain and other sensory stimuli, a phenomenon known as central augmentation or sensitization[3,6-8].

The treatment of FM has traditionally included nonpharmacologic therapies, such as exercise and cognitive behavioral therapy, as well as neuromodulatory medications that have not been specifically approved for use in FM, including tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI)[3,9]. Historically, a number of clinical trials have been conducted to assess the safety and efficacy of a range of pharmacotherapies in FM, generally with mixed results[10]. For example, results from such studies indicate that opioids have not generally proven effective in treating pain intensity or symptoms, and new evidence suggests that use of opioids may eventually lead to worsening of certain types of chronic pain[10]. Further, results from clinical trials with SSRI in FM have been mixed[9]. In June 2007, the US Food and Drug Administration (FDA) approved pregabalin, an α_2-δ ligand with anticonvulsant and analgesic-like activity, and in June 2008, duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), for the management of FM.

Milnacipran has been evaluated in a Phase 2[11] and 2 other large Phase 3 trials[12,13] as a potential treatment for FM. The present publication reports results from the first of the Phase 3 trials to be conducted and completed. Milnacipran is a dual reuptake inhibitor of norepinephrine and serotonin, which is distinguished by a 3-fold greater efficacy in inhibiting norepinephrine reuptake *in vitro* compared to serotonin reuptake[14]. These 2 neurotransmitters have been shown to exert significant modulatory effects on peripheral and central pain processing[15]. Animal models of pain suggest that norepinephrine and serotonin have direct pain-relieving benefit, and that dual reuptake agents yield greater analgesic effects than compounds that selectively raise serotonin[16,17]. Because primary metabolites of norepinephrine and serotonin are reduced in the cerebrospinal fluid (CSF) of patients with FM[18], it has been suggested that medications that enhance both serotonin and norepinephrine neurotransmission could reduce pain in FM patients[3]. Additionally, reductions in norepinephrine and dopamine CSF levels could be responsible for common FM symptoms such as fatigue, memory difficulties, low energy, and lack of motivation[19,20].

Pharmacologically, milnacipran can be distinguished *in vitro* from other dual reuptake inhibitors, including duloxetine and venlafaxine, by its selectivity for norepinephrine over serotonin[21]; both duloxetine and venlafaxine are more selective for serotonin reuptake inhibition[14]. It has been postulated that noradrenergic actions may be more important for the treatment of pain-related conditions as compared to serotonergic actions[22-24]. Milnacipran is pharmacologically similar to some TCA in its ability to inhibit the reuptake of both serotonin and norepinephrine; however, unlike TCA, milnacipran lacks significant anticholinergic, antihistaminergic, and α-adrenergic receptor blockade activity, which may account for its favorable safety profile relative to TCA[14,25]. The weak protein binding (13%) of milnacipran, a low degree of hepatic metabolism, and its lack of effect on the cytochrome P450 system significantly reduces its potential for drug-drug interactions[26].

Previous clinical experience with milnacipran in the treatment of FM includes a randomized, double-blind, controlled, 12-week trial in 125 patients[11,27]. Compared to patients receiving placebo, those assigned to once- or twice-daily milnacipran (maximum total daily dose: 200 mg) had statistically significant pain relief, as well as improvements in a range of other FM symptoms, including decreased physical functioning and fatigue. Twice-daily dosing had significantly better analgesic properties and a better tolerability profile than once-daily dosing. The benefits of milnacipran on pain and other symptoms were independent of depression severity, as measured by the Beck Depression Inventory (BDI), suggesting that these positive therapeutic effects were independent of any effects on depressive symptoms. Milnacipran was well tolerated in this study, with patients reporting transient adverse events that were predominantly mild to moderate in intensity.

Based on the evidence cited above that milnacipran 200 mg/day is safe and efficacious in the treatment of FM, a Phase 3 clinical trial was conducted. This study was a 27-week, randomized, double-blind, placebo-controlled, multicenter, parallel group study designed to assess the safety and efficacy of milnacipran in the treatment of FM. In light of various clinical experiences reporting the analgesic effects of this drug at lower doses[28-31], the safety and efficacy of milnacipran 100 mg/day in the treatment of FM were also investigated.

MATERIALS AND METHODS

Study overview. The study was conducted in 59 outpatient clinical/research centers in the United States. Enrollment began October 21, 2003, and the study was completed July 1, 2005. The outpatient study protocol and patient informed consent forms were approved by the relevant institutional review boards at each site. Screening assessments included a medical and psychological history, physical and laboratory examinations, and the Mini International Neuropsychiatric Interview (MINI)[32].

Entry criteria. Female and male subjects were eligible for inclusion if they were 18 to 70 years of age and met the ACR criteria for FM[2]. Patients had to be willing to use a contraceptive (if female), and to withdraw from all centrally-acting therapies commonly used for FM, including antidepressants, sedative-hypnotic agents, muscle relaxants, and centrally-acting analgesics, as well as transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anesthetic or narcotic patches. All analgesic medications were prohibited during the study, except for acetaminophen, aspirin, and stable doses of nonsteroidal antiinflammatory agents (NSAID). Patients requiring additional analgesic therapy were allowed hydrocodone as a rescue medication; however, doses were not to exceed 60 mg/day and were not allowed during each 2-week period of data collection preceding the primary endpoints (Weeks 14-15 and Weeks 26-27) or during the 48-hour period immediately prior to study visits. Additionally, subjects had to fulfill criteria related to the recording of

daily FM symptoms on an electronic patient experience diary (PED), including: (1) ability to read the PED screen text and understand English; (2) ability to hear and respond to PED audible prompts; (3) willingness to use the PED device daily for a minimum of 29 weeks; (4) completion of at least 70% of the random prompts during relevant days in the baseline period; (5) missing no more than 2 morning reports during relevant days in the baseline period; and (6) having a visual analog scale (VAS) pain intensity rating (based on PED 24-h morning recall pain) of ≥ 50 on a 0 to 100 scale at the end of the second week of the baseline period.

Key exclusion criteria included: severe psychiatric illness; current major depressive episode (as assessed by the MINI); significant risk of suicide according to the investigator's judgment; alcohol or other drug abuse; a history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease; autoimmune disease; systemic infection; cancer or current chemotherapy; significant sleep apnea; active peptic ulcer or inflammatory bowel disease.

Study design. This study was a 27-week, randomized, double-blind, placebo-controlled comparison of 2 doses of milnacipran, 100 and 200 mg/day, to placebo. The study design involved 4 phases: screening and washout, baseline assessment, dose escalation, and stable-dose phase. After completing a washout period (Weeks 1 to 4) for centrally-acting therapies often used for FM, patients entered a 2-week baseline period. During this period, patients were trained in the use of the PED (invivodata, inc.; Pittsburgh, PA, USA), and baseline safety and efficacy data were recorded. Per study guidelines, data collection began at the start of the baseline phase. At the end of the 2-week baseline assessment period, patients were randomized using a 1:1:2 ratio to receive placebo, milnacipran 100 mg/day, or milnacipran 200 mg/day, respectively. The greater allocation of subjects to the 200 mg/day arm was to allow additional patients to be exposed to the higher dose of milnacipran for longterm safety data collection. All randomized medications were administered orally twice daily in divided doses. The dose-escalation period lasted 3 weeks, during which patients reached their assigned dose level; sham dosing was implemented in the placebo group (Weeks 1 to 3) and milnacipran 100 mg/day group (Week 3) to maintain blinding. All patients were scheduled to receive a total of 24 weeks of stable dose treatment after the 3-week dose-escalation period for a total of 27 weeks of drug exposure.

The efficacy and safety assessments (listed below) were conducted at the screening visit, beginning of the baseline period, randomization visit, end of dose-escalation at treatment Week 3, and at Weeks 7, 11, 15, 19, 23, and 27 after randomization (i.e., at the end of the 4th, 8th, 12th, 16th, 20th, and 24th week of the stable dose period, respectively).

Primary efficacy variables. Patient-reported outcome measures were combined to define 2 composite responder definitions. The primary efficacy measure for "treatment of FM" was a composite responder rate assessed at Weeks 15 and 27, defined as the percentage of patients who concurrently met all of the following 3 criteria: (1) ≥ 30% pain improvement, as assessed by the change from baseline in 24-h morning recall pain collected from daily PED morning reports and averaged for the 14 days immediately preceding and including study visit days; (2) a rating of "very much improved" (score = 1) or "much improved" (score = 2) on the Patient Global Impression of Change (PGIC); and (3) ≥ 6-point improvement from baseline in physical function as measured by the Medical Outcome Study Short-Form 36 (SF-36) Physical Component Summary (PCS) score[33]. The primary efficacy measure for "treatment of the pain of FM" was a composite responder rate assessed at Weeks 15 and 27 based on the pain improvement and PGIC thresholds listed above.

The response definitions used in this program were developed in consultation with the FDA and in accord with their recommendations for the development of FM therapies. During the course of the milnacipran clinical development program, 2 changes in responder criteria were made relative to the original protocol definition: first, a more stringent definition of improvement for the global domain [eliminating "minimally improved" (PGIC score = 3) as defining responders], and second, the use of the better validated SF-36 PCS rather than the Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) subscore to assess improved physical functioning.

Patients reported their pain intensity by responding to prompts from the electronic diaries several times each day (morning, evening, and at random times), and on a weekly basis. Patients were asked to record current pain levels ("real-time pain") and recalled pain (24-h morning recall and weekly recall) using a VAS pain scale (range 0 to 100 with anchors of "no pain" and "worst possible pain"). Patients also reported their pain intensity using paper VAS assessments during study visits. For the PGIC measure, patients rated their FM relative to the start of the study using a 7-point scale (1 = "very much improved"; 7 = "very much worse"). The SF-36 Health Survey was used to measure 8 domains of health status: physical functioning, bodily pain, role limitation due to physical problems, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36 PCS and the SF-36 Mental Component Summary (SF-36 MCS) subscores were calculated by combining and weighting the various individual domains[33].

Secondary efficacy measures examined the influence of milnacipran on the following domains: pain severity (PED and paper-based VAS assessments of 24-h recall pain, real-time pain, and weekly recall pain); patient global impression of change (PGIC); physical function (SF-36 PCS); mental function (SF-36 MCS); impact of disease [Fibromyalgia Impact Questionnaire (FIQ)]; fatigue [Multidimensional Fatigue Inventory (MFI)]; severity of depressive symptoms (BDI); sleep quality [Medical Outcomes Study (MOS)-Sleep Problems Index scale]; general health-related quality of life (SF-36 domain scores, FIQ, Multidimensional Health Assessment Questionnaire); self-reported cognitive impairments [Multiple Ability Self-report Questionnaire (MASQ)]; and quality of sexual experiences (Arizona Sexual Experiences Scale)[34-41].

Tolerability and safety assessments. Adverse events spontaneously reported by patient self-report and investigator-observed treatment-emergent adverse events were recorded at each study visit along with the dates of onset and resolution. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 8.0. Clinical laboratory tests (hematology, serum chemistries, and urinalysis) were performed by the investigator at screening and at Weeks 15 and 27. Vital signs (standing and supine heart rate, blood pressure) and weight were measured by the investigator at the screening visit and at all subsequent clinic visits.

Measurement of medication compliance. Study medication compliance was measured by a count of capsules returned at each visit during the entire treatment period (i.e., dose-escalation and stable-dose periods combined).

Statistical analyses. Primary endpoint statistical analyses were originally based on the last observation carried forward (LOCF) at landmark visits (Weeks 15 and 27). Subsequently, and in accord with FDA recommendations, the more conservative baseline observation carried forward (BOCF) method for imputing missing efficacy data related to the primary FM and FM pain responder analyses at Week 15 was utilized. For the primary composite responder analyses at Week 27, a modified BOCF (BOCF for patients prematurely discontinuing the study before Week 15, LOCF for patients completing Week 15 but prematurely discontinuing before Week 27) was adopted. Primary and secondary analyses were also performed using observed case (OC) analysis at Weeks 15 and 27. In OC analysis, only patients completing these 2 endpoints at 15 and 27 weeks were assessed.

All statistical tests were 2-sided hypothesis tests performed at a significance level of 0.05, and all confidence intervals were 2-sided 95% confidence intervals. In all logistic regression and analysis of variance (ANOVA) or analysis of covariance (ANCOVA) analyses, only patients with complete data for the specific treatment comparison were included. Any patient who took narcotic/opioid medication within 48 h of the primary endpoint visit, or on 3 or more days during the 14 days preceding the visit, was automatically considered a nonresponder, even if the analgesic was used for a reason other than FM. The proportion of responders for the FM pain composite was analyzed using a logistic regression model with treatment group, baseline pain score, and baseline pain-by-treatment group interaction as explanatory variables. The proportion of responders for the FM composite

was analyzed using the same model, but included the baseline SF-36 PCS and baseline SF-36 PCS-by-treatment group interaction as explanatory variables. All patients who received at least 1 dose of study medication were included in the intent-to-treat (ITT) analysis. A multiple comparison procedure was used to control the overall type I error for the primary analysis (LOCF) of responders.

Changes from baseline in paper-based VAS assessments of pain, as well as other secondary efficacy assessments, were summarized by treatment group and visit. These data were analyzed at each post-baseline visit using an ANCOVA model, with treatment group and study center as factors and the baseline value as a covariate. All analyses were performed using SAS Version 9.1.3.

RESULTS

Patient disposition. A total of 1639 patients were screened for inclusion in the study. Of these, 888 (54%) were randomly assigned to receive placebo (n = 223), milnacipran 100 mg/day (n = 224), or milnacipran 200 mg/day (n = 441) (Figure 1). At the end of the 6-month study, 42.3% of randomized patients had discontinued. The most frequent reason for discontinuation among the milnacipran-treated patients compared to placebo was adverse events (10.3%, placebo; 27.0%, milnacipran 200 mg/day; 19.6%, milnacipran 100 mg/day). Therapeutic failure was the main reason for discontinuation among placebo patients (15.2%) compared to milnacipran-treated patients (11.1%, milnacipran 200 mg/day; 11.6%, milnacipran 100 mg/day). During double-blind treatment, overall medication compliance was excellent (89%–93%).

Patient demographics and baseline characteristics. There were no statistically significant between-group differences in demographic or baseline characteristics (Table 1). The majority of the patients were female (95.6%) and White (93.6%). Patients' mean duration of FM was 5.6 years. Almost all patients experienced functional impairment at baseline, as assessed on the FIQ and the SF-36 PCS. Average BDI scores at baseline ranged from 13.2 to 14.4 across treatment groups, reflecting the presence of mild to moderate depressive symptoms. There were no notable differences among the treatment groups for any of the demographic or baseline characteristics.

Primary efficacy outcomes. At 15 weeks, by BOCF analysis of a composite criterion involving pain, patient global impression of change, and physical function as determined collaboratively with the FDA, a significantly higher percentage of patients treated with milnacipran met the criteria as FM composite responders as compared to patients receiving placebo (milnacipran 200 mg/day, p = 0.017; milnacipran 100 mg/day, p = 0.028). An analysis of patients meeting criteria as composite responders for pain of FM showed statistical significance among the 200 mg/day treated patients (26.8%, p = 0.032) and a trend among the 100

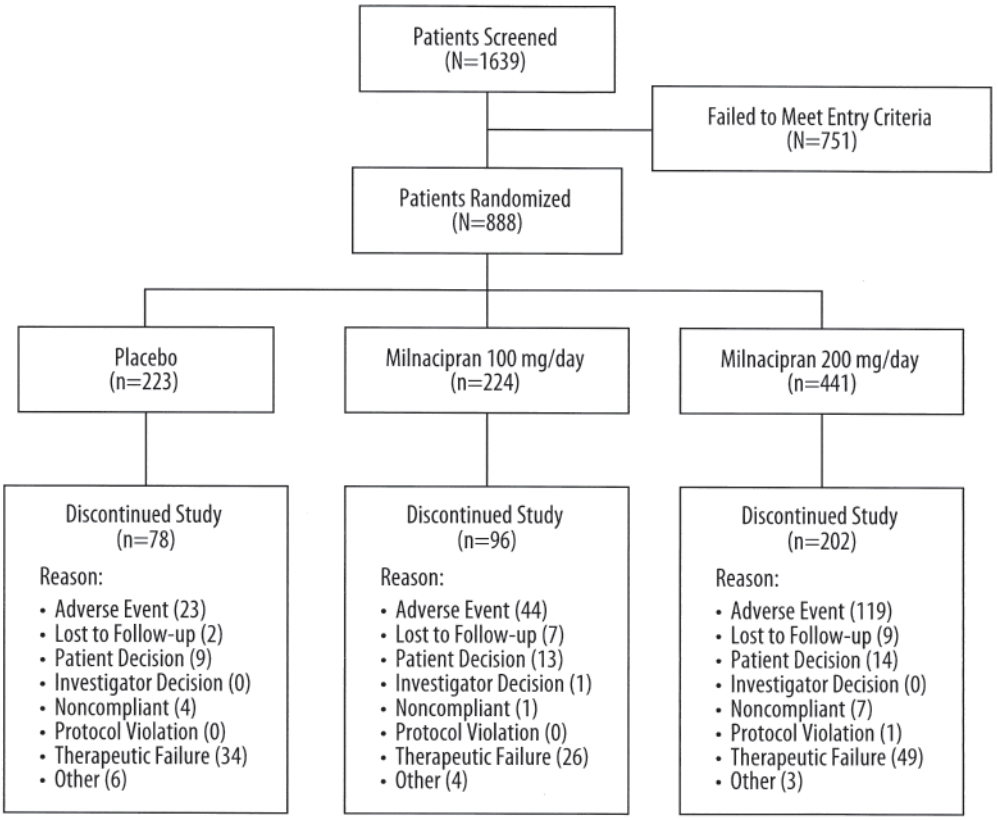

Figure 1. Patient flow through the trial.

Table 1. Patient demographics and baseline characteristics.

Characteristic	Placebo, n = 223	Treatment Group Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441
Age, mean (SD), years	49.4 (10.1)	49.9 (10.6)	49.2 (11.0)
Sex, n (%)			
Female	213 (95.5)	213 (95.1)	423 (95.9)
Male	10 (4.5)	11 (4.9)	18 (4.1)
Race, n (%)			
White	211 (94.6)	208 (92.9)	412 (93.4)
American-Indian/Alaska Native	1 (0.4)	2 (0.9)	2 (0.5)
Asian	1 (0.4)	1 (0.4)	3 (0.7)
Black	7 (3.1)	12 (5.4)	17 (3.9)
Other	3 (1.3)	1 (0.4)	7 (1.6)
Weight, mean (SD), lb	181.9 (40.7)	180.6 (41.4)	181.3 (44.3)
BMI, mean (SD)	30.4 (6.5)	30.4 (6.6)	30.6 (7.4)
FM duration, mean (SD), yrs	6.0 (5.9)	5.6 (5.3)	5.5 (5.1)
PED daily morning recall pain score (SD), range 0–100	68.3 (11.9)	68.3 (11.5)	69.4 (11.9)
Paper VAS 24-h recall pain score (SD), range 0–100	74.3 (15.1)	73.0 (16.0)	73.9 (16.3)
FIQ total score (SD), range 0–100	64.7 (13.4)	65.1 (13.7)	64.3 (14.4)
SF-36 PCS score (SD)	31.4 (7.8)	30.8 (7.6)	31.4 (8.0)
SF-36 MCS score (SD)	42.1 (12.1)	42.4 (11.4)	41.5 (11.7)
BDI score (SD), range 0–63	14.1 (9.5)	13.2 (7.7)	14.4 (8.6)
MFI total score (SD), range 20–100	67.0 (13.0)	67.5 (13.1)	67.8 (13.3)
MASQ total score (SD), range 38–190	88.5 (19.2)	88.4 (19.7)	89.4 (18.1)

BDI: Beck Depression Inventory; BMI: body mass index; FIQ: Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; MFI: Multidimensional Fatigue Inventory; MASQ: Multiple Ability Self-Report Questionnaire; PED: patient experience diary; PCS: Physical Component Summary; VAS: visual analog scale.

Table 2. Composite responder rates at 15 and 27 weeks.

Composite Responder Analyses	Placebo, n = 223	15 Weeks Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441	Placebo, n = 223	27 Weeks Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441
Fibromyalgia[a]						
BOCF/LOCF[c], %	12.1	19.6 (0.028)	19.3 (0.017)	13.0	18.3 (0.245)	18.1 (0.105)
Observed cases, %	17.3	32.8 (0.003)	32.8 (< 0.001)	19.4	33.3 (0.056)	31.9 (0.017)
Fibromyalgia pain[b]						
BOCF/LOCF[c], %	19.3	27.2 (0.056)	26.8 (0.032)	18.4	25.9 (0.072)	25.6 (0.034)
Observed cases, %	27.2	45.2 (0.003)	45.4 (< 0.001)	27.9	43.8 (0.021)	45.2 (0.001)

Values in parentheses represent p values vs placebo. Composite responder rates determined as follows: [a] FM patients reporting ≥ 30% improvement from baseline in patient experience diary (PED) 24-h morning recall pain; Patient Global Impression of Change (PGIC) = 1 or 2; and ≥ 6-point improvement from baseline in SF-36 Physical Component Summary (PCS); [b] Fibromyalgia pain: patients reporting ≥ 30% improvement from baseline in PED 24-h morning recall pain and PGIC = 1 or 2. [c] Statistical methodology was baseline observation carried forward (BOCF) for patients discontinuing before Week 15 and last observation carried forward (LOCF) for patients completing Week 15 landmark but discontinuing before Week 27.

mg/day patients (27.2%, p = 0.056) as compared to patients on placebo (19.3%) (Table 2). By LOCF analysis, using the original protocol-specified definitions for responder criteria, the differences between groups in FM composite responder rates were not statistically significant, although the proportion of patients defined as FM pain composite responders trended toward greater improvement than placebo at 15 weeks (milnacipran 200 mg/day, p = 0.058; milnacipran 100 mg/day, p = 0.187).

At 27 weeks, using the modified BOCF/LOCF methods defined above, a greater percentage of milnacipran-treated patients met criteria as FM and FM pain composite responders as compared to patients on placebo. The FM pain composite responder rate in the 200 mg/day group also achieved statistical significance compared to placebo using BOCF/LOCF (25.6% vs 18.4%, p = 0.034; Table 2).

An analysis of the primary responder endpoint using an OC dataset is instructive regarding the efficacy attainable in

patients who remained in the study. The percentage of OC patients who met criteria as FM composite responders was significantly higher with both doses of milnacipran compared to patients on placebo [15 weeks: 17.3%, placebo; 32.8%, milnacipran 200 mg/day ($p < 0.001$); 32.8%, milnacipran 100 mg/day ($p = 0.003$); and 27 weeks: 19.4%, placebo; 31.9%, milnacipran 200 mg/day ($p = 0.017$); 33.3%, milnacipran 100 mg/day ($p = 0.056$)] (Table 2). Similarly, the percentage of patients meeting criteria as FM pain composite responders was significantly higher with milnacipran compared to patients on placebo at 15 and 27 weeks [15 weeks: 27.2%, placebo; 45.4%, milnacipran 200 mg/day ($p < 0.001$); 45.2%, milnacipran 100 mg/day ($p = 0.003$); and 27 weeks: 27.9%, placebo; 45.2%, milnacipran 200 mg/day ($p = 0.001$); 43.8%, milnacipran 100 mg/day ($p = 0.021$)].

Secondary efficacy outcomes

Pain. Pain results are presented in Table 3. At baseline, VAS pain scores were similar among the treatment groups, with mean scores varying from 66 (weekly average of PED real-time pain) to 77 (weekly recall of paper-based pain). Secondary pain assessments, using a variety of recall intervals on the PED, showed significant improvements at Weeks 15 and 27 among patients treated with milnacipran 200 mg/day, relative to placebo, including: weekly average of 24-h morning recall pain scores, weekly average of real-time pain scores, and weekly recall pain scores (15 weeks: $p = 0.006$, $p = 0.009$, $p = 0.019$, respectively; and 27 weeks: $p = 0.01$ and $p = 0.013$ for weekly averages of 24-h recall and real-time pain scores, respectively). Pain improvements were generally similar between milnacipran 200 mg/day and 100 mg/day, but the smaller sample size of the 100 mg/day treatment arm led to decreased power to detect significant differences.

The weekly average changes from baseline in PED 24-h morning recall pain scores are shown in Figure 2. Mean baseline scores were 68.3 for placebo, 69.4 for milnacipran 200 mg/day, and 68.3 for milnacipran 100 mg/day. A significant reduction in pain was observed after 1 week of treatment in both milnacipran groups compared to placebo based on OC data. The differences between placebo and milnacipran 200 mg/day were significant at every timepoint after 1 week. Similar results were observed for milnacipran 100 mg/day, with the exception of Week 15 data. Maximal pain relief was observed after 9 weeks of treatment in both milnacipran treatment groups and maintained throughout the remainder of the study.

Table 3. Secondary pain and PGIC assessments (OC).

Variable[a]	Placebo, n = 223		Milnacipran 100 mg/day, n = 224				Milnacipran 200 mg/day, n = 441			
	n	Mean (SEM)	n	Mean (SEM)	LS Mean Difference (95% CI)	p	n	Mean (SEM)	LS Mean Difference (95% CI)	p
15 Weeks										
PED 24-h recall pain scores (weekly average)	164	49.55 (1.75)	144	44.50 (1.97)	–5.03 (–10.33, 0.27)	0.063	276	43.36 (1.39)	–5.80 (–9.93, –1.67)	0.006
PED real-time pain scores (weekly average)	164	48.66 (1.81)	143	44.19 (1.97)	–4.11 (–9.28, 1.06)	0.119	277	42.67 (1.40)	–5.48 (–9.57, –1.39)	0.009
PED weekly recall pain scores	163	51.37 (1.85)	142	46.92 (2.00)	–4.53 (–10.05, 1.00)	0.108	273	45.58 (1.49)	–5.47 (–10.04, –0.90)	0.019
Paper VAS 24-h recall pain scores	161	50.61 (2.19)	140	45.26 (2.42)	–4.64 (–11.36, 2.09)	0.175	264	42.86 (1.76)	–5.99 (–11.46, –0.51)	0.032
Paper VAS 7-day recall pain scores	161	51.73 (2.06)	140	47.97 (2.38)	–3.71 (–10.29, 2.87)	0.268	264	44.27 (1.73)	–6.07 (–11.39, –0.74)	0.026
PGIC	161	3.09 (0.10)	140	2.68 (0.11)	–0.40 (–0.69, –0.10)	0.009	264	2.59 (0.08)	–0.42 (–0.67, –0.18)	< 0.001
27 Weeks										
PED 24-h recall pain scores (weekly average)	128	50.86 (2.11)	115	43.31 (2.21)	–8.01 (–14.13, –1.88)	0.011	204	43.42 (1.77)	–7.11 (–12.53, –1.70)	0.010
PED real-time pain scores (weekly average)	126	50.33 (2.21)	116	43.43 (2.20)	–6.72 (–12.82, –0.62)	0.031	204	42.39 (1.77)	–6.91 (–12.33, –1.49)	0.013
PED weekly recall pain scores	123	52.24 (2.11)	110	46.65 (2.35)	–6.48 (–13.00, 0.03)	0.051	195	45.86 (1.88)	–5.62 (–11.46, 0.21)	0.059
Paper VAS 24-h recall pain scores	145	52.36 (2.33)	128	44.09 (2.59)	–8.31 (–15.24, –1.39)	0.019	239	42.84 (1.93)	–7.92 (–14.07, –1.76)	0.012
Paper VAS 7-day recall pain scores	145	53.93 (2.30)	128	44.58 (2.47)	–10.33 (–17.22, –3.45)	0.003	239	44.97 (1.91)	–7.79 (–13.92, –1.66)	0.013
PGIC	145	3.07 (0.11)	128	2.78 (0.12)	–0.30 (–0.63, 0.03)	0.071	239	2.52 (0.08)	–0.48 (–0.75, –0.21)	< 0.001

[a] Unless otherwise indicated, comparisons to placebo are based on least square (LS) mean change from baseline (ANCOVA), with treatment group and study center as factors and baseline value as covariate. OC: observed cases; PED: patient experience diary; PGIC: Patient Global Impression of Change; SEM: standard error of the mean; VAS: visual analog scale.

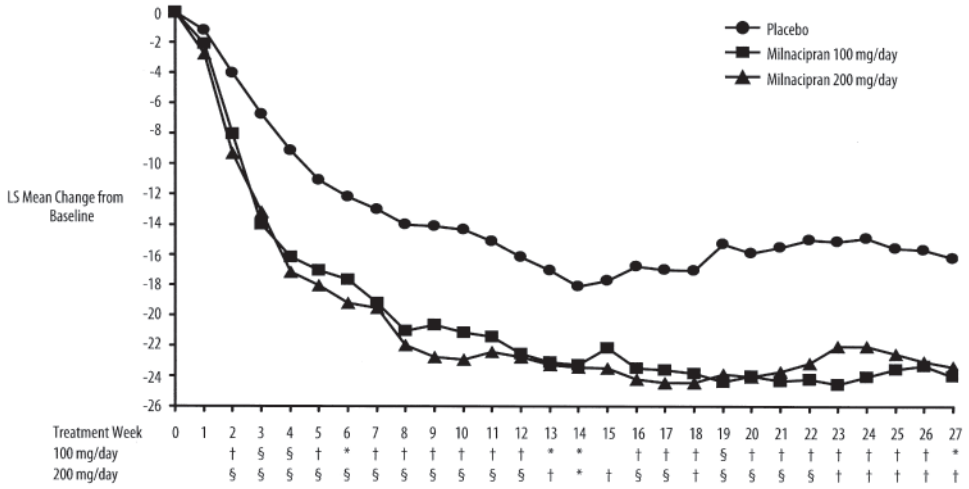

Figure 2. Least-squares (LS) mean change from baseline in weekly average 24-hour morning recall pain scores (from patient experience diary). Observed case analysis: *$p < 0.05$ vs placebo; †$p \leq 0.01$ vs placebo; §$p \leq 0.001$ vs placebo.

An improvement of ≥ 30% in pain scores is a commonly used definition of a clinically important improvement[42], and the more stringent criterion of ≥ 50% improvement in pain scores is also informative. At the 15-week primary endpoint, OC analysis of PED 24-h morning recall pain scores of patients (including those who used rescue medications) revealed that a significantly greater percentage of patients receiving milnacipran achieved ≥ 30% improvement in pain relief as compared to patients on placebo (40.2%, placebo; 56.2%, milnacipran 200 mg/day, p = 0.001; 52.8%, milnacipran 100 mg/day, p = 0.028). Similarly, a significantly greater percentage of patients receiving milnacipran 200 mg/day (37.0%) achieved ≥ 50% improvement in pain relief as compared to patients on placebo (26.2%) (p = 0.021). In addition, 34.7% of patients receiving milnacipran 100 mg/day achieved ≥ 50% improvement in pain relief (p = 0.106 vs placebo).

Patient global assessment. Patients receiving both doses of milnacipran reported greater overall improvements in terms of their FM based on the PGIC at Week 15 compared to placebo (milnacipran 200 mg/day, p < 0.001; milnacipran 100 mg/day, p = 0.009; Table 3). PGIC scores for patients on milnacipran 200 mg/day were significantly improved over patients on placebo at 27 weeks (p < 0.001). On an OC basis, the PGIC response rate at 15 weeks favored milnacipran, with 78% (p < 0.001) and 76% (p = 0.006) of patients on 200 mg/day and 100 mg/day, respectively, achieving PGIC responder criteria ("very much improved" or "much improved"), compared to a placebo response rate of 61%. Improvements on the PGIC were statistically significant at every clinic visit after randomization for patients on both doses of milnacipran (LOCF; p < 0.05).

Multidimensional functioning (SF-36). Significant improvements with milnacipran 200 mg/day versus placebo were demonstrated at 15 weeks in the SF-36 domains of physical functioning (p = 0.026), bodily pain (p = 0.003), and mental health (p = 0.008) (Table 4). At Week 27, both doses of milnacipran showed improvements in the SF-36 domains of bodily pain (milnacipran 200 mg/day, p = 0.004; milnacipran 100 mg/day, p = 0.043) and mental health (milnacipran 200 mg/day, p = 0.015; milnacipran 100 mg/day, p = 0.007) (Table 4).

Fatigue. Treatment with milnacipran 200 mg/day significantly reduced fatigue, as measured by the MFI total score, relative to treatment with placebo at both 15 and 27 weeks (15 weeks, p = 0.016; 27 weeks, p = 0.035) (Table 4, Figure 3). Patients on milnacipran 100 mg/day showed significant fatigue reductions at 15 weeks (p = 0.042) and a similar, although not significant, treatment effect at 27 weeks as compared to patients on placebo. The reduced motivation subscale seemed to be particularly sensitive to changes in the FM population.

Cognition. Changes from baseline in the MASQ total scores, which assessed differences in patients' perception of their cognitive function, were significantly improved for patients on milnacipran 200 mg/day as compared to patients on placebo at 15 and 27 weeks (15 weeks, p = 0.025; 27 weeks, p = 0.016; Table 4).

Sleep quality. No difference was noted between placebo and milnacipran treatment in terms of quality or quantity of sleep as measured by the MOS-Sleep Problems Indices (Table 4).

Safety. The incidence of treatment-emergent adverse events was 85.2% among placebo patients, and 90.7% and 83.9% among patients on milnacipran 200 mg/day and 100 mg/day, respectively. Most adverse events were mild to moderate (92.4%, placebo; 93.0%, milnacipran 200 mg/day; 90.5%, milnacipran 100 mg/day). Adverse events occurring in at

Table 4. Mean change from baseline: additional secondary efficacy assessments at 15 and 27 weeks (LOCF).

Variable	15 Weeks			27 Weeks		
	Placebo, n = 223	Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441	Placebo, n = 223	Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441
FIQ total score	–15.91	–17.68	–17.27	–14.98	–17.73	–16.69
MDHAQ Disability subscale score	–2.44	–2.91	–3.11	–2.46	–2.63	–3.12
ASEX total score	–0.14	–0.74	–0.41	–0.36	–0.71	–0.46
PGDS total score	–17.78	–17.04	–19.20	–16.48	–16.13	–18.48
MFI total score	–3.04	–5.15[b]	–5.62[b]	–3.35	–5.00	–5.80[b]
MASQ total score	0.10	–1.60	–2.28[b]	0.16	–1.56	–2.68[b]
MOS-Sleep Problems Index I[c]	–1.57	–1.68	–0.99	–0.06	0.12	–1.65
MOS-Sleep Problems Index II[c]	–2.09	–2.17	–1.43	–0.96	–0.43	–2.11
SF-36						
Physical functioning	2.24	3.27	3.55[b]	2.43	2.99	3.34
Role limit-physical	5.25	5.40	5.48	4.91	5.07	5.21
Bodily pain	4.07	5.48	6.05[a]	3.78	5.22[b]	5.86[a]
General health perception	1.90	2.27	2.25	1.67	2.23	1.97
Energy/vitality	4.43	5.39	5.71	3.59	4.84	5.23
Social functioning	3.92	5.25	5.13	3.74	5.00	4.99
Role limit-emotional	1.90	3.90	3.60	1.41	3.09	2.92
Mental health	1.50	2.68	3.70[a]	0.97	3.00[a]	3.07[b]

[a] $p < 0.01$ vs placebo; [b] $p < 0.05$ vs placebo; comparisons to placebo are based on least squares mean changes from baseline (ANCOVA), with treatment group and study center as factors and baseline value as covariate. [c] MOS-Sleep Problems Index scores are adjusted for sleep medication use. ASEX: Arizona Sexual Experiences Scale; FIQ: Fibromyalgia Impact Questionnaire; LOCF: last observation carried forward; MASQ: Multiple Ability Self-report Questionnaire; MDHAQ: Multidimensional Health Assessment Questionnaire; MFI: Multidimensional Fatigue Index; MOS: Medical Outcomes Study; PGDS: Patient Global Disease Status.

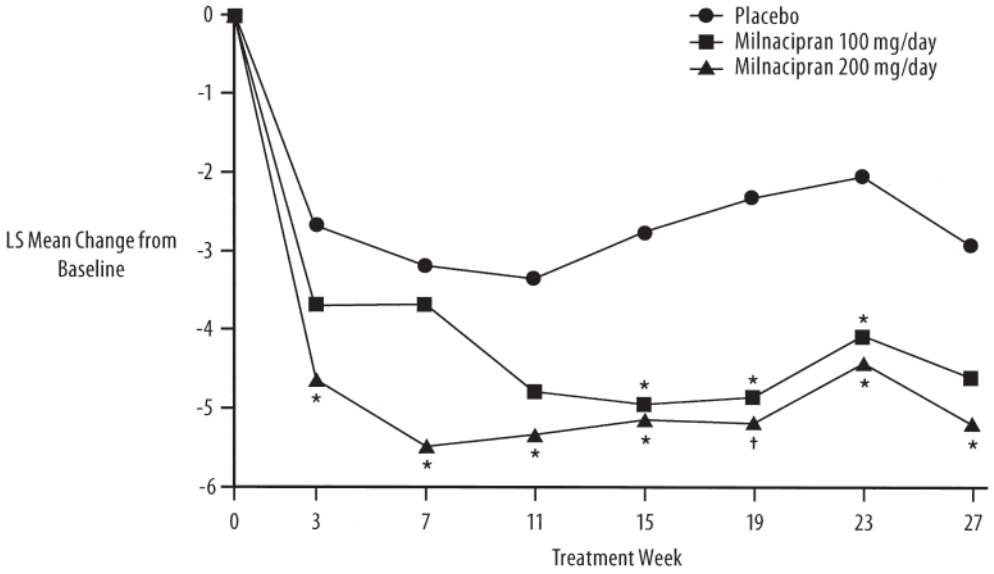

Figure 3. Least-squares (LS) mean change from baseline in Multidimensional Fatigue Inventory total scores. Last observation carried forward analysis: *$p < 0.05$ vs placebo; †$p \leq 0.01$ vs placebo.

least 5% of patients in either milnacipran treatment group, and at an incidence of at least 2 times that of placebo patients, included constipation, hyperhidrosis, hot flush, vomiting, heart rate increased, dry mouth, palpitations, and hypertension. The most common adverse event in all treatment groups was nausea (Table 5), which tended to be dose related, mild to moderate in severity, and typically resolved in 1 to 2 weeks with continued therapy.

Adverse events resulted in the premature discontinuation of 10.3%, 27.0%, and 19.6% of placebo and milnacipran 200 and 100 mg/day patients, respectively. The only events that resulted in the discontinuation of at least 2% of mil-

Table 5. Summary of most frequently reported treatment-emergent adverse events. Adverse events were reported by at least 5% of patients in the milnacipran 200 mg/day group.

Adverse Event, n (%)	Placebo, n = 223	Milnacipran 100 mg/day, n = 224	Milnacipran 200 mg/day, n = 441
Nausea	47 (21.1)	73 (32.6)	177 (40.1)
Headache	26 (11.7)	35 (15.6)	78 (17.7)
Constipation	6 (2.7)	41 (18.3)	63 (14.3)
Hyperhidrosis	5 (2.2)	22 (9.8)	55 (12.5)
Dizziness	15 (6.7)	26 (11.6)	50 (11.3)
Hot flush	6 (2.7)	22 (9.8)	46 (10.4)
Insomnia	15 (6.7)	24 (10.7)	41 (9.3)
Vomiting	4 (1.8)	11 (4.9)	36 (8.2)
Sinusitis	18 (8.1)	11 (4.9)	32 (7.3)
Heart rate increased	5 (2.2)	12 (5.4)	32 (7.3)
Dry mouth	6 (2.7)	13 (5.8)	31 (7.0)
Upper respiratory tract infection	16 (7.2)	20 (8.9)	30 (6.8)
Palpitations	2 (0.9)	18 (8.0)	25 (5.7)
Diarrhea	16 (7.2)	10 (4.5)	23 (5.2)

nacipran-treated patients, and at an incidence greater than that in the placebo group, were nausea and palpitations.

Rates of serious adverse events did not differ across the placebo (2.7%) or milnacipran 200 mg/day (2.5%) or 100 mg/day (1.3%) groups. Three patients had serious adverse events that were judged to be possibly or probably related to study medication, including 1 case each of chest discomfort, exercise-induced intermittent rapid heart rate and chest pain, and nausea. Cardiac assessments in the first 2 cases revealed no evidence of coronary ischemia and neither patient experienced longterm sequelae. The first patient went on to complete the study, as well as the subsequent 6-month extension study. The second and third patients terminated from the study due to their serious adverse events.

For all patients, the mean changes from baseline in laboratory values were not clinically important, and there were no clinically relevant differences among the treatment groups. Patients on milnacipran 200 and 100 mg/day tended to lose more weight (–1.47 pounds, $p < 0.001$; –1.79 pounds, $p < 0.001$, respectively) after 3 months of treatment as compared to patients on placebo (+0.94 pounds). On average, after 6 months of treatment, patients on milnacipran 200 and 100 mg/day lost more weight (–3.25 lb, $p < 0.001$; –4.04 lb, $p < 0.001$, respectively) compared to placebo-treated patients (+1.49 pounds).

Changes of clinical interest. At the end of the study, mean supine systolic blood pressure increased by 3.3 mm Hg from baseline in both the milnacipran 200 and 100 mg/day groups compared to a 0.1 mm Hg increase in the placebo group. Mean supine diastolic blood pressure increased by 2.5 mm Hg and 3.5 mm Hg from baseline values in the milnacipran 200 and 100 mg/day groups, respectively, compared to a 0.4 mm Hg increase in the placebo group. Mean change from baseline in supine heart rate was a 0.5 bpm increase for the placebo group compared to a 7.6 bpm and 6.1 bpm increase for the milnacipran 200 and 100 mg/day groups, respectively.

Potentially clinically significant changes in supine heart rate (≥ 120 bpm with an increase of ≥ 20 bpm from baseline) were observed in 0%, 1.8%, and 0.7% of patients treated with placebo, milnacipran 100 mg/day, and milnacipran 200 mg/day, respectively. The frequency of potentially clinically significant changes in supine systolic (≥ 180 mm Hg with an increase of ≥ 20 mm Hg from baseline) or diastolic blood pressure (≥ 110 mm Hg with an increase of ≥ 15 mm Hg from baseline) was comparable among milnacipran-treated and placebo-treated patients. An increase in potentially clinically significant changes in supine systolic blood pressure was seen in 0.5% of patients treated with placebo or milnacipran 100 mg/day. No patient in the study had a potentially clinically significant decrease in supine systolic blood pressure. A potentially clinically significant increase in supine diastolic blood pressure was seen in 0.9% of patients in both placebo and milnacipran 200 mg/day groups and in 1.8% of patients on milnacipran 100 mg/day. A potentially clinically significant decrease in supine diastolic blood pressure was observed in 0.5% of patients on placebo and milnacipran 100 mg/day.

Sustained increases in supine systolic blood pressure (≥ 140 mm Hg with a ≥ 20 mm Hg increase from baseline on at least 3 consecutive visits) were uncommon; they were observed in 1 patient (0.5%) receiving milnacipran 100 mg/day, 4 (0.9%) receiving milnacipran 200 mg/day, and no placebo-treated patients. Sustained increases in supine diastolic blood pressure (≥ 90 mm Hg with a ≥ 10 mm Hg increase from baseline on at least 3 consecutive visits) were observed in 6 patients (2.7%) receiving milnacipran 100 mg/day, 6 (1.4%) receiving milnacipran 200 mg/day, and 1 (0.5%) placebo-treated patient.

DISCUSSION

Our study examined the safety and efficacy of milnacipran in the management of FM. "FM composite responders"

were patients who concurrently (1) experienced a decrease in pain of at least 30% from baseline (PED 24-h morning recall, VAS); (2) reported that overall their FM was either "very much improved" or "much improved" (PGIC); and (3) reported a clinically significant increase in physical functioning (≥ 6-point improvement on the SF-36 PCS score). "FM pain composite responders" were patients who concurrently met the pain improvement and PGIC thresholds outlined above. As to the clinical relevance of these composite responder classifications, previous studies have suggested that either a 30% improvement of a pain measure or a rating of "much" and "very much" improved on global measures of disease states associated with chronic pain is clinically meaningful[42,43]. The threshold of a ≥ 6-point improvement on the SF-36 PCS score in the composite responder analysis used in our study is higher than the minimal clinically important differences represented in most rheumatic disorders, which require a 2.5-point to 5-point improvement[44-50].

At 15 weeks, a significantly higher percentage of patients with FM treated with either 200 or 100 mg/day of milnacipran met the 3-way FM composite responder threshold as compared to patients taking placebo. At both 15 and 27 weeks, a significantly higher percentage of patients treated with 200 mg/day milnacipran met the 2-way FM pain composite responder threshold as compared to patients taking placebo. A comparable treatment effect was observed for the 100 mg/day dose of milnacipran, but differences from placebo were not significant, most likely due to the smaller size of this lower-dose group. An examination of group mean differences on measures of pain severity and patient global impression of change further confirmed the results of the more rigorous composite responder analyses.

In addition to measures of pain and patient global assessment, outcomes that evaluate multidimensional functioning, fatigue, cognition, and sleep quality are recognized by the independent Outcome Measures in Rheumatology (OMERACT) group as important domains to be included in FM clinical trials[3,51]. After 15 weeks of therapy, patients treated with either dose of milnacipran reported significant improvements in their fatigue compared to patients taking placebo, as measured by the total score on the MFI. Self-reported problems with cognition also improved among patients treated with milnacipran 200 mg/day compared to patients on placebo, as measured by the MASQ total score after both 15 and 27 weeks of therapy.

Study discontinuation due to an adverse event occurred in 10% of placebo patients, and in about twice as many patients treated with milnacipran. Similar to other FM trials with dual reuptake inhibitors[52,53], the most common adverse event reported with milnacipran was nausea, although in most patients it was mild to moderate in severity and often dissipated with continued therapy. The median time to resolution of nausea while taking study medication was 7.5 days for placebo, 6 days for milnacipran 200 mg/day, and 9.5 days for milnacipran 100 mg/day (analysis of patients with valid event start and stop dates). Other side effects included constipation and sweating.

A small percentage of milnacipran-treated patients (< 2%) experienced a potentially clinically significant rise in supine heart rate relative to placebo groups. Other drugs in this class that augment norepinephrine and serotonin function also raise supine heart rate[54]. Mean changes in blood pressure and heart rate, as well as potentially clinically significant changes or sustained increases in vital signs were similar in milnacipran- and placebo-treated patients.

At baseline, FM patients in our study had a mean body mass index (BMI) that exceeded the threshold for obesity (BMI ≥ 30). Milnacipran-treated patients tended to lose weight compared to patients on placebo, with a net clinical effect of weight neutrality. Nausea rates were not elevated among patients who lost weight compared to those who did not lose weight and are, therefore, unlikely to account for the observed weight loss. Future research should examine the relationship between excess body weight and FM, and clinical attention should be given to the influence of FM therapies on comorbid obesity.

Several limitations of the current trial should be noted. Our results may not be generalizable to FM patients typically seen in clinical practice. FM is comorbid with a number of different disorders, including major depression, with about 20% of FM patients reporting current episodes of depression[1,55]. Patients with a current major depressive episode were excluded from our study; however, 35% of randomized patients had a history of depression. Additionally, patients discontinued medications commonly used to treat FM. Further, 42% of randomized patients prematurely discontinued from this 6-month study. However, it should be noted that this discontinuation rate is congruous with the long duration of the study and is comparable to the discontinuation rates reported in other FM studies[52,53,56,57].

Our study does not address the use of milnacipran monotherapy in the treatment of FM beyond 6 months. Many of the results reported here were maintained through Week 27 (the final time point in this study) and up to 12 months in an extension study[58]. FM, however, is a chronic disease, and further research is needed to better characterize the safety and efficacy of milnacipran as a longer term therapy for patients with FM. Last, FM is difficult to treat and is often managed with polypharmacy. Importantly, milnacipran has a low potential for drug interactions due to its low protein binding, low degree of hepatic metabolism, and lack of significant effect on CYP450 enzymes. Future studies should directly examine the efficacy of milnacipran when used in combination with other medications and interventions used to manage FM.

Recent FM trials have been designed to last 3 to 6 months, and as a result, relatively high dropout rates have been experienced, necessitating a strategy to analyze effica-

cy data in the face of large amounts of missing data. LOCF takes the last available efficacy value and imputes this value to the endpoint, while BOCF uses the patient's baseline score as the endpoint score in the case of a dropout. OC analysis is the simplest method to handle missing data, because the reported values are based on only those patients who reach the primary endpoint, with no assumptions being made about what values would have been at endpoint if dropouts had not occurred. Consistent with the general experience in the pain field, LOCF analysis of continuous variables such as group mean change in pain scores yields more favorable results than BOCF. However, for binary responder variables such as the composite response analyses used in this trial, BOCF analysis will decrease the overall responder rates and the variability in rate, which may increase the statistical power to demonstrate a treatment effect. In our study, this was in fact the case, with BOCF analysis providing marginally better significance values as compared to LOCF when binary analyses were undertaken.

In conclusion, milnacipran is an inhibitor of serotonin and norepinephrine reuptake, with a preference for norepinephrine reuptake inhibition. Consistent with earlier preliminary efficacy with milnacipran used to treat FM[11], results from this large, 27-week controlled clinical trial demonstrate the efficacy of milnacipran in the management of FM through the use of composite endpoints requiring simultaneous improvements in pain, patient global impression of change in FM, and improvements in physical functioning. Milnacipran was safe and well tolerated in the majority of patients. These results are consistent with a growing body of knowledge that the multiple symptoms of FM, including pain, fatigue, and physical functioning, can be addressed through simultaneous augmentation of norepinephrine and serotonin function.

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