A European Multicenter Randomized Double-blind Placebo-controlled Monotherapy Clinical Trial of Milnacipran in Treatment of Fibromyalgia

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ABSTRACT. ***Objective.*** This randomized, double-blind, placebo-controlled, multicenter study investigated the efficacy and safety of milnacipran in the treatment of fibromyalgia (FM) in a European population.
Methods. Outpatients diagnosed with FM according to 1990 American College of Rheumatology criteria (N = 884) were randomized to placebo (n = 449) or milnacipran 200 mg/day (n = 435) for 17 weeks (4-week dose escalation, 12-week stable dose, 9-day down-titration), followed by a 2-week posttreatment period. The primary efficacy criterion was a 2-measure composite responder analysis requiring patients to achieve simultaneous improvements in pain (≥ 30% improvement from baseline in visual analog scale, 24-hour morning recall) and a rating of "very much" or "much" improved on the Patient Global Impression of Change scale. If responder analysis was positive, Fibromyalgia Impact Questionnaire (FIQ) was included as an additional key primary efficacy measure.
Results. At the end of the stable dose period (Week 16), milnacipran 200 mg/day showed significant improvements from baseline relative to placebo in the 2-measure composite responder criteria (p = 0.0003) and FIQ total score (p = 0.015). Significant improvements were also observed in multiple secondary efficacy endpoints, including Short-Form 36 Health Survey (SF-36) Physical Component Summary (p = 0.025), SF-36 Mental Component Summary (p = 0.007), Multidimensional Fatigue Inventory (p = 0.006), and Multiple Ability Self-Report Questionnaire (p = 0.041). Milnacipran was safe and well tolerated; nausea, hyperhidrosis, and headache were the most common adverse events.
Conclusion. Milnacipran is an effective and safe treatment for pain and other predominant symptoms of FM. Registered as trial no. NCT00436033. (First Release Feb 15 2010; J Rheumatol 2010;37:851–9; doi:10.3899/jrheum.090884)

Key Indexing Terms:
FIBROMYALGIA MILNACIPRAN PAIN FATIGUE PHYSICAL FUNCTION

Fibromyalgia (FM) is a chronic disorder characterized by widespread pain, tenderness, fatigue, sleep disturbances, and a constellation of symptoms such as morning stiffness, decreased physical function and dyscognition[1,2]. Reduced physical function and impaired quality of life are common and often result in decreased participation at work and diminished social life[3]. According to general population estimates, FM affects 2% to 5% of European populations[4-10] and 2% to 4% of the US population[2,11], the disorder being about 7 times more common in women than in men. In 1990, the American College of Rheumatology (ACR) established the following criteria for FM: widespread pain in all 4 quadrants of the body; presence of axial skeletal pain; and pain in at least 11 of 18 tender points on palpation[1]. Although the pathogenesis of FM is not well understood, increasing evidence points to malfunctions within the central nervous system, including descending inhibitory pain pathways[12].

Recent evidence-based recommendations for the management of FM syndrome have been published by the European League Against Rheumatism[13]. The management of FM generally requires a combination of pharmacologic and nonpharmacologic therapies, such as exercise and cognitive behavioral therapy.

Dual-reuptake inhibitors of serotonin and norepinephrine (SNRI) have demonstrated analgesic effects in animal mod-

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els, suggesting the importance of these neurotransmitters in pain modulation[14,15]. The use of SNRI in treatment of FM is also supported by studies showing that FM patients have lower cerebrospinal fluid (CSF) levels of norepinephrine and serotonin metabolites than control subjects[16]. In addition, reduced CSF levels of norepinephrine and dopamine have been linked to symptoms commonly associated with FM, such as fatigue, memory problems, and lack of motivation[17,18].

Milnacipran is an SNRI with greater selectivity for norepinephrine over serotonin[19]. Although milnacipran is similar to tricyclic antidepressants like amitriptyline in its ability to inhibit the reuptake of these 2 neurotransmitters, it has a much lower affinity for muscarinic, cholinergic, histaminergic, and alpha-adrenergic receptor targets, which may account for its relatively favorable tolerability profile[20]. Milnacipran also has a low potential for drug-drug interactions due to its pharmacokinetic properties, including low plasma protein-binding (13%), lack of activity on the cytochrome P450 system, and limited hepatic metabolism[21]. The pharmacokinetic profile of milnacipran may be beneficial for the treatment of patients with FM, who often have overlapping disorders and require multiple concomitant medications.

Milnacipran is approved by the US Food and Drug Administration (FDA) for the management of FM. Several double-blind, placebo-controlled trials conducted in the US have demonstrated the efficacy of milnacipran in the treatment of FM[22-24]. At doses of 100 and 200 mg/day, milnacipran significantly improved pain and other FM symptoms, versus placebo, for up to 6 months. These studies also demonstrated that milnacipran 200 mg/day was well tolerated, especially when administered in divided doses (i.e., 100 mg bid). In one study, the benefits of milnacipran on pain and other symptoms were independent of severity of depression, measured by the Beck Depression Inventory (BDI), suggesting that these positive therapeutic effects were independent of any effects on depressive symptoms[22].

The aim of our study was to confirm the efficacy and safety of milnacipran 200 mg/day for the treatment of FM in a European population.

MATERIALS AND METHODS

Patients. Patients included male and female subjects between the ages of 18 and 70 years meeting the 1990 ACR criteria for FM[1]. The study was conducted from February 21, 2006, to September 4, 2007, in 89 outpatient clinical/research centers in 13 European countries.

Patients were required to meet the following baseline entry criteria: raw score ≥ 3 on the physical function component of the FIQ[25]; willingness and ability to rate pain intensity using an electronic patient experience diary (PED) loaded with a visual analog scale (VAS); and a baseline VAS pain intensity rating between 40 and 90 (0 to 100 scale). Patients were required to use the PED device daily for a minimum of 21 weeks and to complete at least 10 out of 14 morning reports during the 2-week baseline period. Patients also had to be willing to use a contraceptive (if female) and to discontinue medications and nonpharmacologic treatments commonly used to treat FM, including antidepressants, anticonvulsants, centrally-acting analgesics, mood stabilizers, benzodiazepines, muscle relaxants, hypnotics, anesthetics, and systemic steroids (> 10 mg prednisone equivalent per day), transcutaneous electrical nerve stimulations, tender/trigger point or joint injections, and acupuncture. Authorized medications were discontinued 48 hours before each scheduled visit and were prescribed at the minimum dose and duration required to effectively manage symptoms.

Patients with severe psychiatric illness including generalized anxiety disorder or current major depressive episode (assessed by the Mini-International Neuropsychiatric Interview[26]) or BDI[27] score > 25 were excluded from the study. Other exclusion criteria included alcohol/substance abuse; significant cardiovascular, respiratory, rheumatoid, rheumatic, hepatic, renal, or other medical condition; systemic infection; epilepsy; active cancer; severe sleep apnea; unstable endocrine disease; active peptic ulcer or inflammatory bowel disease; prostatic enlargement or other genitourinary disorders (in male patients); pregnancy or breastfeeding; and history or behavior that would prohibit compliance for the duration of the study.

Study design. This was a randomized, double-blind, placebo-controlled, monotherapy trial consisting of a 17-week (4-week dose escalation, 12-week stable dose, 9-day down-titration) treatment and 2-week posttreatment followup period that evaluated the safety and efficacy of milnacipran 200 mg/day for treatment of FM. The study was performed in accord with the Declaration of Helsinki and Good Clinical Practice Guidelines[28,29]. Registered as trial no. NCT00436033.

After a 1- to 4-week washout period from disallowed medications, eligible patients entered a 2-week period in which they were trained in the use of the PED, and baseline safety and efficacy data were recorded. At the end of the baseline period, patients were randomized at a 1:1 ratio to either placebo or milnacipran 200 mg/day (100 mg bid), starting with a 4-week dose escalation phase. The dose escalation schedule was as follows: 25 mg once daily (evening dose, Days 1 and 2); 25 mg bid (Days 3–7); 50 mg bid (Days 8–14); 50 mg (morning dose) and 100 mg (evening dose, Days 15–21); and 100 mg bid (Days 22–28). In patients receiving placebo, twice-daily sham dosing was used to maintain blinding. Patients then entered the 12-week stable-dose treatment period, followed by a 9-day down-titration phase and a 2-week followup phase without treatment. Patients who completed the study had a total of 17 weeks and 2 days of treatment exposure.

Nine mandatory study visits were planned at the following timepoints: screening; beginning of baseline; randomization (Week 0); end of dose escalation (Week 4); after 4, 8, and 12 weeks of stable dose (Weeks 8, 12, and 16, respectively); end of down-titration (Week 17 plus 2 days); and posttreatment followup (Week 19 plus 2 days). Another study visit during the dose-escalation phase was optional.

Efficacy outcomes. The primary efficacy analysis was based on 2 stepwise criteria. The first criterion was a 2-measure composite responder rate [pain VAS + Patient Global Impression of Change (PGIC)], defined as the percentage of patients meeting both the following criteria: ≥ 30% improvement from baseline in PED 24-hour morning recall pain VAS scores collected from daily PED morning reports and averaged for the 2 weeks immediately preceding and including study visit days; and a score of 1 (“very much improved”) or 2 (“much improved”) on the PGIC, a 7-point scale. If this composite criterion was positive, the FIQ total score was included as a key additional primary efficacy measure. The FIQ is a disease-specific instrument to assess the overall effect on FM symptomatology[25]. Upon receiving daily (morning and evening) and weekly prompts from the PED, patients were asked to record current daily and recalled pain (24-hour morning recall and weekly recall) using a VAS pain scale ranging from 0 to 100 with anchors of “no pain” and “worst possible pain.” Patients also reported pain intensity using paper VAS assessments during study visits.

Secondary efficacy measures included the individual components of the 2-measure composite responder criteria for pain VAS and PGIC; PED and paper VAS pain ratings; FIQ subscales; Brief Pain Inventory-Short Form (BPI-SF)[30]; Short-Form 36 Health Survey (SF-36) Physical Component

Summary (PCS), Mental Component Summary (MCS), and individual dimensions[31]; Multidimensional Fatigue Inventory (MFI)[32]; Multiple Ability Self-Report Questionnaire (MASQ)[33]; BDI; State-Trait Anxiety Inventory, state-related (STAI-S)[34]; and Medical Outcomes Study (MOS)-Sleep Index I and Index II[35]. PED weekly fatigue recall scores (VAS, 0 = "no fatigue" to 100 = "extreme fatigue") and weekly sleep recall scores (VAS, 0 = "totally rested" to 100 = "not rested at all") were also collected.

Safety assessments. Safety assessments included physical examinations (all study visits), vital signs and weight (all study visits), and clinical laboratory tests (screening, Week 4, and Week 16). Adverse events (AE) were assessed throughout the study based on spontaneous reporting by patients, investigators' use of nonleading questions, and clinical evaluation.

Statistical analysis. Safety analyses were conducted on the safety dataset (877 patients), defined as all randomized patients receiving at least 1 dose of study treatment. Efficacy analyses were performed on the full analysis set (FAS; 876 patients), defined as patients in the safety dataset who had at least 1 baseline and 1 postbaseline PED 24-hour recall pain score. The per-protocol dataset (715 patients) consisted of all patients in the FAS who had no major protocol deviations and were exposed to study treatment for at least 4 weeks. The demonstration of efficacy of milnacipran versus placebo in FM was based on a closed-test procedure that preserves the α risk from the multiplicity of the analyses. This was a sequential procedure that consisted of first testing the composite criterion; if statistically significant, a second test on the FIQ total score was performed. All statistical tests were 2-sided hypothesis tests performed at significance level of 0.05, and confidence intervals (CI) were 2-sided 95% CI.

The 2-measure composite responder rate and its pain components were analyzed using a logistic regression model with baseline pain score as a covariate and treatment as a fixed factor. Change from baseline in FIQ score was analyzed using a covariance analysis (ANCOVA) model with baseline FIQ score as a covariate and country and treatment as fixed factors. Changes from baseline in other secondary efficacy assessments were similarly analyzed using ANCOVA.

For composite responder analyses, missing data were imputed using last observation carried forward (LOCF) for the FAS dataset. Sensitivity analyses conducted for the FAS dataset included: baseline observation carried forward (BOCF) and observed cases (OC). LOCF analysis of the per-protocol dataset was also performed. For secondary efficacy endpoints, changes from baseline in clinical assessment scores were conducted using LOCF. Differences between treatment groups in change from baseline over time were assessed using a mixed-effect model for repeated measures analysis adjusted for baseline, country, and interactions of baseline by visit and treatment by visit.

RESULTS

Patients. Of 1406 screened patients, 884 (62.9%) were randomized to either milnacipran 200 mg/day (n = 435) or placebo (n = 449; Figure 1). A total of 678 (76.7%) randomized patients completed the study. The most common reasons for discontinuation were tolerability/safety (22.1% milnacipran vs 9.8% placebo) and therapeutic failure (5.5% milnacipran vs 7.3% placebo). Mean duration of treatment was 102 days with milnacipran and 111 days with placebo.

Seven randomized patients were excluded from the safety population (n = 877): 4 due to good clinical practices concerns in a single study center and 3 for not receiving any study treatment. An additional patient was excluded from FAS (n = 876) analyses due to a missing baseline evaluation of PED pain.

In the FAS dataset, both groups were similar with respect to patient demographics, FM history, body mass index, impaired functioning, and other clinical baseline characteristics (Table 1).

Efficacy. At the end of the stable-dose period (Week 16), significantly greater improvement in the 2-measure composite response rate (pain VAS + PGIC) in the FAS was observed with milnacipran 200 mg/day versus placebo using LOCF (odds ratio 1.90, 95% CI 1.34 to 2.68, p = 0.0003; Figure 2). This result was supported by sensitivity analyses using BOCF (OR 1.97, 95% CI 1.38 to 2.80, p = 0.0002), OC (OR 2.44, 95% CI 1.70 to 3.50, p < 0.0001), and LOCF repeated in the per-protocol sample (OR 2.26, 95% CI 1.58 to 3.24, p < 0.0001).

A significant improvement in the additional primary efficacy endpoint, FIQ total score, was also found based on the least-squares mean difference between milnacipran and placebo (–3.00; p = 0.015; Table 2). This result (LOCF) was confirmed by similar findings in the per-protocol dataset (–4.26; p = 0.001) and OC analysis (FAS) (–4.18; p = 0.002).

At Week 16, the pain responder rate (patients with ≥ 30% improvement from baseline in PED 24-hour recall pain; LOCF, FAS) was significantly higher with milnacipran compared to placebo (38.6% vs 30.0%; p = 0.007, OR 1.48, 95% CI 1.11 to 1.96). The PGIC responder rate (patients with a self-assessed rating of 1 "very much improved" or 2 "much improved"; LOCF, FAS) was also significantly higher with milnacipran (33.3% vs 20.6%; p < 0.0001, OR 1.92, 95% CI 1.41 to 2.60).

At Week 16, significant least-squares mean differences between milnacipran and placebo were found in multiple pain measures, including PED 24-hour recall pain (–4.52; p = 0.001), PED weekly recall pain (–4.74; p = 0.001), paper VAS 24-hour recall pain (–5.81; p = 0.0007), paper VAS weekly recall pain (–5.71; p = 0.0008), PED current daily morning pain (–6.32; p < 0.0001), PED current daily evening pain (–5.77; p = 0.0004), FIQ pain (–4.08; p = 0.009), SF-36 bodily pain (3.55; p = 0.006), BPI-SF pain intensity (–0.44; p = 0.0008), and BPI-SF pain interference (–0.33; p = 0.014) (Table 2).

In addition to reducing pain, treatment with milnacipran was associated with significant improvements in a number of secondary measures (Table 2). Overall improvements in multidimensional functioning were confirmed by significant least-squares mean differences between milnacipran and placebo in SF-36 PCS (0.98; p = 0.025), SF-36 MCS (1.45; p = 0.007), and other SF-36 domains. Treatment with milnacipran significantly reduced fatigue compared with placebo, as assessed by changes from baseline in MFI total (–2.41; p = 0.006) and PED weekly recall fatigue scores (–4.47; p = 0.004). Improvements in cognition were also observed, as indicated by changes from baseline in MASQ total score (–2.45; p = 0.041).

MOS-Sleep scale scores did not differ between placebo and milnacipran (Table 2). However, milnacipran-treated

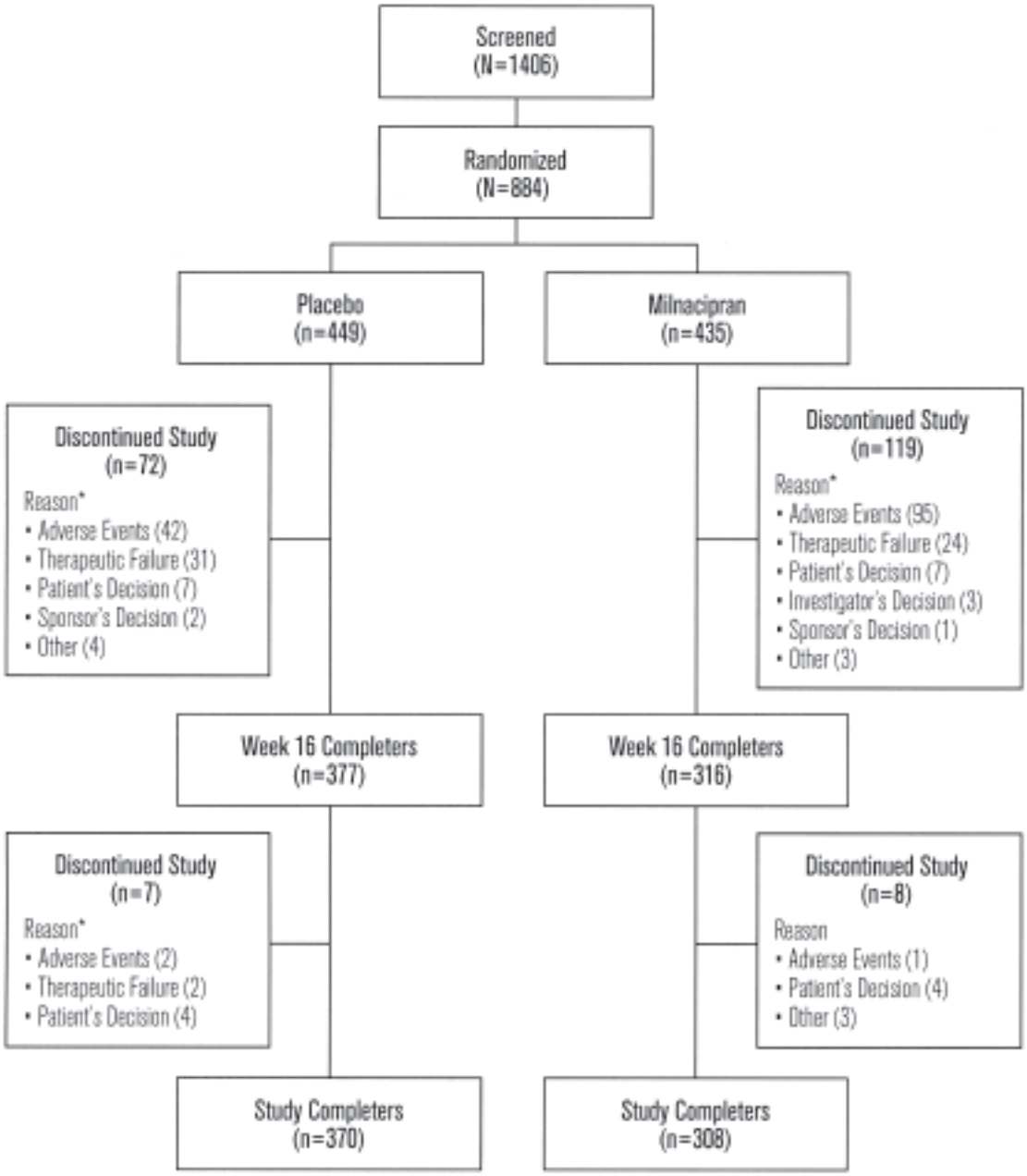

Figure 1. Disposition of patients in the study. *Some patients had multiple reasons for discontinuation.

patients had improved quality of sleep, as indicated by a significant least-squares mean difference between milnacipran and placebo in PED weekly recall sleep scores (–4.27; p = 0.007; Table 2).

Safety. A total of 331 (74.2%) placebo-treated patients and 363 (84.2%) milnacipran-treated patients experienced at least 1 treatment-emergent AE. Most events were mild or moderate in severity (93%, both groups) and occurred mainly during the dose-escalation phase. The treatment-emergent AE occurring in ≥ 5% of any group are reported in Table 3. The most common treatment-emergent AE in the milnacipran group were nausea, hyperhidrosis, and headache (Table 3). Discontinuation rates due to AE were 9.9% for placebo and 22.3% for milnacipran. AE that resulted in a definitive treatment discontinuation in the milnacipran group in more than 2% of patients were hyperhidrosis (4.2%), headache (3.5%), nausea (3.0%), and tachycardia (2.1%). During the 2-week posttreatment period, no withdrawal syndrome was reported, nor was any suspected by the presence of possibly related symptoms.

No deaths were reported during the study. Sixteen serious AE were reported in 11/446 (2.5%) placebo-treated patients;

Table 1. Key patient demographic and clinical characteristics at baseline (full analysis dataset).

Characteristic	Placebo, n = 446	Milnacipran 200 mg/day, n = 430
Female, %	93.5	95.1
Age, mean (SD) yrs	49.2 (10.3)	48.3 (9.3)
BMI, mean (SD) kg/m^2	26.7 (5.0)	26.7 (5.4)
Obese, %*	22.0	22.6
FM duration, mean (SD) yrs	9.5 (9.0)	9.5 (8.2)
PED 24-hour recall pain, mean (SD), range 0–100	65.0 (12.7)	65.5 (12.9)
FIQ total score, mean (SD), range 0–100	57.0 (11.8)	56.7 (11.9)
MFI total score, mean (SD), range 20–100	67.2 (13.4)	65.9 (13.4)
SF-36 PCS, mean (SD), range 100–0	33.7 (6.8)	33.4 (6.7)
SF-36 MCS, mean (SD), range 100–0	46.3 (9.8)	47.0 (9.8)
MASQ total score, mean (SD), range 38–190	86.4 (24.0)	86.8 (26.2)
BDI total score, mean (SD), range 0–63	10.9 (6.7)	10.3 (6.6)
STAI-S, mean (SD), range 20–80	38.6 (10.7)	38.1 (10.6)

* Body mass index ≥ 30. BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; MASQ: Multiple Ability Self-Report Questionnaire; MCS: Mental Component Summary; MFI: Multidimensional Fatigue Inventory; PCS: Physical Component Summary; PED: patient experience diary; SF-36: Short-Form 36 Health Survey; STAI-S: State-Trait Anxiety Inventory, state related.

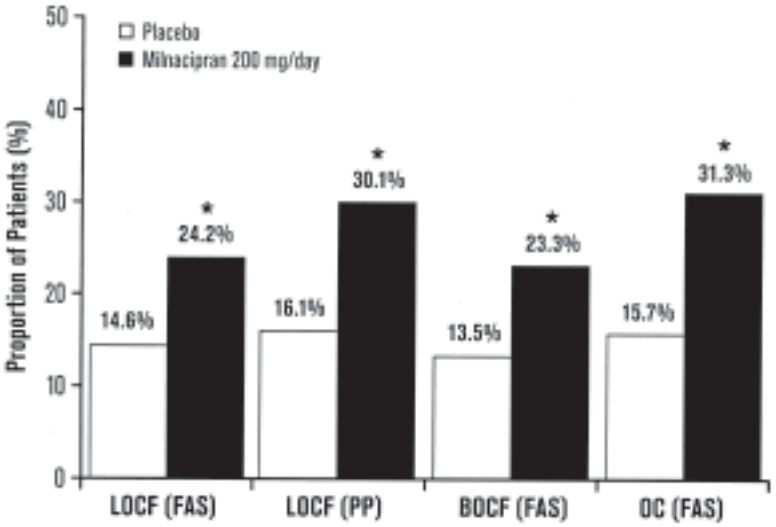

Figure 2. Proportion of patients meeting the following 2-measure composite responder criteria: (1) ≥ 30% improvement from baseline in patient experience diary 24-hour recall pain; and (2) Patient Global Impression of Change rating of 1 "very much improved" or 2 "much improved." The 2-measure composite responder analysis was conducted in each individual patient. All outcomes are statistically significant based on the prespecified multiple comparison procedure ($p < 0.001$). BOCF: baseline observation carried forward; FAS: full analysis set; LOCF: last observation carried forward; OC: observed cases; PP: per-protocol dataset. *$p < 0.001$ compared to placebo.

14 serious AE were reported in 11/431 (2.6%) milnacipran-treated patients. Four serious AE in 2 placebo patients and 5 serious AE in 3 milnacipran patients were determined by investigators as having a nonexcluded or nonassessable relationship with study treatment.

At endpoint, mean changes from baseline in vital signs for milnacipran compared to placebo were as follows: supine systolic blood pressure (BP), +2.3 mm Hg versus –2.3 mm Hg; supine diastolic BP, +2.8 mm Hg versus –1.9 mm Hg; supine heart rate +10.0 beats per minute (bpm) versus +0.1 bpm. Potentially clinically significant increases in supine systolic BP (≥ 180 mm Hg with ≥ 20 mm Hg increase from baseline), diastolic BP (≥ 105 mm Hg with ≥ 15 mm Hg increase from baseline), and heart rate (≥ 120 bpm with

Table 2. Other efficacy endpoints, least-squares mean (LSM) change from baseline at Week 16 landmark visit (full analysis dataset, last observation carried forward analysis).

Variable*	Placebo (n = 446), LSM Change (SEM)	Milnacipran 200 mg/day (n = 430) LSM Change (SEM)	Difference from Placebo (95% CI)	p
FIQ total score**	–11.18 (0.99)	–14.18 (1.03)	–3.00 (–5.42, –0.58)	0.015
PED 24-hour recall pain	–11.97 (1.14)	–16.50 (1.18)	–4.52 (–7.29, –1.76)	0.001
PED weekly recall pain	–11.60 (1.20)	–16.34 (1.24)	–4.74 (–7.64, –1.83)	0.001
Paper VAS 24-hour recall pain	–16.09 (1.37)	–21.90 (1.42)	–5.81 (–9.15, –2.47)	0.0007
Paper VAS weekly recall pain	–15.76 (1.35)	–21.47 (1.41)	–5.71 (–9.03, –2.40)	0.0008
PED current daily morning pain	–10.83 (1.27)	–17.15 (1.39)	–6.32 (–9.46, –3.19)	< 0.0001
PED current daily evening pain	–12.76 (1.28)	–18.53 (1.40)	–5.77 (–8.93, –2.61)	0.0004
BPI-SF pain intensity	–1.03 (0.10)	–1.47 (0.11)	–0.44 (–0.69, –0.18)	0.0008
BPI-SF pain interference	–0.93 (0.11)	–1.26 (0.11)	–0.33 (–0.60, –0.07)	0.014
FIQ physical function	–0.22 (0.03)	–0.31 (0.03)	–0.09 (–0.16, –0.01)	0.021
FIQ pain	–14.60 (1.26)	–18.68 (1.31)	–4.08 (–7.14, –1.02)	0.009
SF-36 scores				
Physical Component Summary	3.57 (0.35)	4.55 (0.36)	0.98 (0.12, 1.83)	0.025
Mental Component Summary	–0.23 (0.43)	1.23 (0.45)	1.45 (0.39, 2.52)	0.007
Physical functioning	7.10 (0.88)	9.40 (0.92)	2.30 (0.13, 4.46)	0.037
Role limitation-physical	6.25 (1.14)	8.85 (1.19)	2.60 (–0.20, 5.39)	0.068
Bodily pain	9.79 (1.04)	13.34 (1.08)	3.55 (1.01, 6.09)	0.006
General health perception	4.08 (0.83)	6.39 (0.87)	2.31 (0.28, 4.35)	0.026
Energy/vitality	5.08 (0.98)	7.75 (1.02)	2.67 (0.27, 5.07)	0.029
Social functioning	3.24 (1.15)	6.69 (1.20)	3.45 (0.63, 6.26)	0.016
Role limit-emotional	–0.47 (1.19)	2.57 (1.24)	3.05 (0.13, 5.96)	0.041
Mental health	0.52 (0.84)	3.60 (0.87)	3.08 (1.03, 5.13)	0.003
MFI total score	–3.53 (0.70)	–5.94 (0.73)	–2.41 (–4.12, –0.71)	0.006
PED weekly recall fatigue	–10.71 (1.25)	–15.17 (1.29)	–4.47 (–7.49, –1.44)	0.004
MASQ total score	–3.42 (0.96)	–5.88 (1.00)	–2.45 (–4.80, –0.10)	0.041
BDI	–0.29 (0.34)	–0.74 (0.36)	–0.44 (–1.29, 0.40)	0.302
MOS-Sleep Index I	–6.73 (0.95)	–6.28 (0.99)	0.45 (–1.88, 2.78)	0.703
MOS-Sleep Index II	–7.40 (0.93)	–6.93 (0.97)	0.47 (–1.81, 2.75)	0.685
PED weekly recall sleep	–9.59 (1.28)	–13.86 (1.32)	–4.27 (–7.36, –1.18)	0.007
STAI-S	0.01 (0.52)	–0.96 (0.54)	–0.98 (–2.26, 0.30)	0.133

* Negative values represent improvement, except SF-36, where positive values reflect improvement. ** Included in primary stepwise analysis. BDI: Beck Depression Inventory; BPI-SF: Brief Pain Inventory-Short Form; FIQ: Fibromyalgia Impact Questionnaire; MASQ: Multiple Ability Self-Report Questionnaire; MFI: Multidimensional Fatigue Inventory; MOS: Medical Outcomes Study; PED: patient experience diary; SF-36: Short-Form 36 Health Survey; STAI-S: State Trait Anxiety Inventory, state related; VAS: visual analog scale.

Table 3. Treatment-emergent adverse events reported in ≥ 5% of patients in any treatment group.

Incidence, n (%)	Placebo, n = 446	Milnacipran 200 mg/day, n = 431
Nausea	50 (11.2)	112 (26.0)
Hyperhidrosis	13 (2.9)	102 (23.7)
Headache	55 (12.3)	73 (16.9)
Constipation	10 (2.2)	54 (12.5)
Dizziness	34 (7.6)	44 (10.2)
Palpitations	13 (2.9)	34 (7.9)
Insomnia	24 (5.4)	33 (7.7)
Nasopharyngitis	33 (7.4)	33 (7.7)
Hot flash	5 (1.1)	30 (7.0)
Tachycardia	3 (0.7)	29 (6.7)
Vomiting	15 (3.4)	22 (5.1)

≥ 15 bpm increase from baseline) were observed in 0.9%, 3.5%, and 1.4%, respectively, of patients treated with milnacipran, compared with 1.1%, 2.0%, and 0.2%, respectively, for placebo-treated patients.

Mean changes of weight from baseline fluctuated between –0.48 kg and –0.69 kg in the milnacipran group, and between +0.05 kg and +0.30 kg in the placebo group.

DISCUSSION

This study demonstrated that milnacipran 200 mg/day (100 mg bid) was safe and effective for treatment of FM in a European population. After 16 weeks of treatment, a significantly higher percentage of milnacipran-treated patients met the 2-measure composite responder criteria, which included concurrently achieving (1) at least 30% improve-

ment from baseline in PED 24-hour recall pain scores; and (2) a score of either 1 ("very much improved") or 2 ("much improved") on the PGIC. Both these criteria have been identified as clinically meaningful measures of improvement in chronic pain diseases[36,37]. Analyses on each component of the 2-measure composite responder rate further demonstrated that patients treated with milnacipran 200 mg/day experienced a significant reduction in pain as well as global improvement of FM symptoms.

Composite response measures have been used to identify treatment success in illnesses such as rheumatoid arthritis and osteoarthritis, where optimal therapy requires improvements across multiple symptom domains[38,39]. Based on results from patient and physician Delphi exercises, the Outcome Measures in Rheumatology (OMERACT) working group has suggested that such measures may be similarly useful in assessing the multiple dimensions of FM[40]. In addition to our study, several clinical trials of FM (primarily with milnacipran) have utilized composite response measures[23,24,41-43]. In general, these measures were developed to reflect the areas that investigators and regulatory bodies have identified as being core FM symptom domains, such as pain, patient-reported global status, and multidimensional functioning[44]. Although there is no current consensus on the specific outcome measures to be used in FM clinical trials, a project is under way to develop a consensus-driven and evidence-based responder index that can assess the efficacy of FM therapies[44].

In addition to the composite response endpoint used in our study, various pain-rating measures were also implemented, including PED VAS (24-hour recall, weekly recall, current daily morning, and current daily evening) and paper VAS (24-hour recall and weekly recall) scores. A significant improvement with milnacipran over placebo was found for these pain measures at all study visits.

Although widespread pain is a core feature of FM, this disease is characterized by other clinically important symptoms including fatigue, muscle stiffness, mood disorders, physical/mental dysfunction, and sleep disturbances. Given the importance of assessing the multidimensional symptoms of FM in clinical trials as documented by OMERACT[40], it was imperative to establish that treatment with milnacipran 200 mg/day would have therapeutic benefits in addition to relieving pain. Both steps of the primary analysis met this goal. The inclusion of the patient-reported PGIC in the composite responder criterion took into account each patient's global assessment of disease and satisfaction with treatment. The FIQ criterion measured the effect of milnacipran on physical function and daily activities as well as the severity of pain, fatigue, stiffness, and anxiety/mood. The multidimensional benefits of milnacipran were demonstrated by significant improvements over placebo on the PGIC and in the FIQ total and subscale scores.

A number of other secondary outcome measures were used to assess the various dimensions of FM, including mental and physical functioning (SF-36), fatigue (MFI, PED weekly recall fatigue), cognitive complaints (MASQ), and sleep (MOS-Sleep, PED weekly recall sleep). Milnacipran had a significant effect on all these measures except the MOS-Sleep scale. However, changes in PED weekly recall sleep, which allows patients to define and evaluate their own experience of refreshing sleep, were significantly greater in the milnacipran group compared with placebo.

The incidence of AE leading to study discontinuation was approximately twice as high with milnacipran compared with placebo. However, milnacipran was well tolerated during the study, with no unexpected tolerability/safety concerns reported. The most commonly observed AE were consistent with the well documented safety profile of milnacipran and are similar to AE reported for this class of drugs[45,46].

The demographic and baseline characteristics of this study sample corresponded to the general profile of FM populations. However, randomized patients in this study did not have a current major depressive episode or generalized anxiety disorder, as reflected by baseline scores for BDI (10.9 for placebo and 10.3 for milnacipran) and baseline STAI-S (38.6 for placebo and 38.1 for milnacipran). In addition, FM is a chronic disorder and patients seen in the clinic may need treatment beyond 16 weeks. However, US clinical trials have reported efficacy of milnacipran up to 6[23] and 12 months[47] in patients with FM.

As noted, European and US populations have similar rates of FM prevalence (2%–5% and 2%–4%, respectively)[4-10]. Further, function and quality of life are similarly impaired in both populations[3,6], and FM patients in Europe are associated with considerably higher annual total costs in primary care settings compared with non-FM patients[48]. Demonstrating that the efficacy and tolerability of milnacipran in a European population are equivalent to those in a US population[22-24] is important in addressing the substantial healthcare burden of FM in Europe.

The results from this European study are consistent with those of 3 US studies[22-24] that showed the safety and efficacy of milnacipran 200 mg/day (100 mg bid) in treating the pain and multidimensional symptoms (fatigue, physical and mental functioning, sleep, and cognitive complaints) of FM.

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