Longterm Therapeutic Response to Milnacipran Treatment for Fibromyalgia. A European 1-Year Extension Study Following a 3-Month Study

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ABSTRACT. ***Objective.*** This double-blind, 1-year extension study investigated the longterm efficacy and safety of milnacipran 100, 150, and 200 mg/day in the treatment of fibromyalgia (FM) in completers of a 3-month European double-blind lead-in study of milnacipran 200 mg/day versus placebo.

Methods. A total of 468 patients with FM successfully completing the lead-in study were either blindly maintained on milnacipran 200 mg/day (MLN200:MLN200, n = 198) or (if previously receiving placebo) rerandomized to milnacipran 100 mg/day (PBO:MLN100, n = 91), 150 mg/day (PBO:MLN150, n = 92), or 200 mg/day (PBO:MLN200, n = 87) for an additional 12 months (including a 4-week dose escalation). The main efficacy endpoint was a 2-measure composite responder rate (relative to lead-in study baseline) incorporating the weekly-recall pain score recorded on a visual analog scale and the Patient Global Impression of Change score. A panel of other assessments including the Fibromyalgia Impact Questionnaire explored the multidimensional aspects of FM. Descriptive analyses using the last observation carried forward approach were performed.

Results. At the 1-year endpoint, the proportion of composite responders (relative to the lead-in study baseline) ranged from 27.5% (PBO:MLN100) to 35.9% (MLN200:MLN200), and had increased from the extension study baseline by 15.2% (PBO:MLN150) to 20.7% (PBO:MLN200 and MLN200:MLN200). At endpoint, an improvement from both baselines was shown in all groups on pain, fatigue, sleep, and quality of life measures. Up to 1 year, all doses of milnacipran were safe and well tolerated. The most common drug-related adverse events were hyperhidrosis and nausea.

Conclusion. Over 1 year, milnacipran 100, 150, and 200 mg/day exhibited sustained and safe therapeutic effects on predominant symptoms of FM. Registered as trial no. NCT00757731. (First Release April 1 2011; J Rheumatol 2011;38:1403–12; doi:10.3899/jrheum.101025)

Key Indexing Terms:
FIBROMYALGIA PAIN MILNACIPRAN LONGTERM SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Fibromyalgia (FM) is a chronic disorder characterized by a constellation of symptoms including widespread pain, tenderness, fatigue, sleep disturbances, 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 approximately 2% to 5% of the European[4,5,6,7,8,9,10] and United States populations[2,11], the disorder being approximately 7 times more common in women than in men. In 1990, the American College of Rheumatology (ACR) established the following criteria[1] for FM: history of widespread pain (in all 4 quadrants of the body) for at least 3 months; presence of axial skeletal pain; and pain in at least 11 of 18 tender points on palpation. As FM is not limited to pain, the ACR has recently proposed a new set of diagnostic criteria combining a widespread pain

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index, and a symptom severity scale summing categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and a number of somatic symptoms[12]. Although the pathogenesis of FM is not well understood, increasing evidence points to malfunctions within the central nervous system, including descending inhibitory pain pathways[13].

Recent evidence-based recommendations for the management of FM have been published by the European League Against Rheumatism (EULAR)[14]. The management of FM generally requires a combination of pharmacological and nonpharmacological therapies, such as exercise and cognitive behavioral therapy.

Dual reuptake inhibitors of serotonin and norepinephrine (SNRI) have demonstrated analgesic effects in animal models, suggesting the importance of these neurotransmitters in pain modulation[15,16]. The use of SNRI in the 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[17]. 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[18,19].

Milnacipran is an SNRI with greater selectivity for norepinephrine over serotonin[20]. 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[21]. 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[22]. The pharmacokinetic profile of milnacipran may be beneficial for the treatment of FM patients, who often have overlapping disorders and require multiple concomitant medications.

Milnacipran is approved by the US Food and Drug Administration for the management of FM. Several double-blind, placebo-controlled trials conducted in the US and Europe have demonstrated the efficacy of milnacipran in the treatment of FM[23,24,25,26]. 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 100 mg/day and 200 mg/day are well tolerated, especially when administered in divided doses (i.e., 50 mg bid or 100 mg bid administration[23]).

A recent 3-month study involving 884 FM patients randomized to placebo or milnacipran 200 mg/day confirmed the efficacy and safety of milnacipran treatment for pain and other core symptoms of FM in a European population[26], and was the lead-in to this 1-year extension study.

FM is a chronic disorder and patients may benefit from longterm treatment. A US extension trial has reported efficacy of milnacipran 100 and 200 mg/day up to 12 months[27].

The objectives of this longterm extension study were (1) to determine whether the improvements in pain and other FM symptoms achieved with milnacipran 200 mg/day at 3 months could be sustained over an additional 1 year; (2) to evaluate the efficacy of milnacipran 100, 150, or 200 mg/day in patients who were switched from placebo during the lead-in study to 1 of the 3 dosages of milnacipran in the extension study; and (3) to confirm the longterm safety and tolerability of milnacipran in the treatment of FM.

MATERIALS AND METHODS

Entry criteria. Male or female patients aged 18–71 years, meeting the 1990 ACR diagnostic criteria for FM[1] at entry to the lead-in study[26], and having successfully completed the 3-month course of the lead-in study, were eligible for entry to this extension study if they met the following: willing to continue withdrawal from all therapies commonly used for FM, either centrally acting (including antidepressants, anticonvulsants, and opioids) or peripherally acting (including trigger or tender point injections, acupuncture, intramuscular or percutaneous anesthetics); and for women of childbearing potential, negative urine test prior to randomization and use of a medically acceptable form of contraception. Key exclusion criteria included a major depressive episode, a moderate to severe suicidal risk, or a generalized anxiety disorder (all assessed by the Mini-International Neuropsychiatric Interview[28]) at inclusion (Day 1); a Beck Depression Inventory (BDI)[29] score > 25 and BDI item 9 (self-punitive wishes) > 1 at screening (Day –7) or inclusion; alcohol or other drug abuse; history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease; autoimmune disease; systemic infection; cancer or current cancer therapy; or sleep apnea, active peptic ulcer, or inflammatory bowel disease.

Study design. This 1-year, randomized, multicenter, double-blind, extension study was conducted at 70 centers in 11 European countries from September 19, 2006, to October 2, 2008. The study was approved by the ethics committee(s) and authorized by the competent authority of each country and was conducted in accord with the Guidelines for Good Clinical Practice[30]. All patients gave a written informed consent. Registered as trial no. NCT00757731.

Patients completing the 3-month lead-in study (in which they received double-blind treatment with milnacipran 200 mg/day or placebo, bid administration) and eligible for enrollment entered this extension study at the end of the last visit of the lead-in study. Those patients fulfilling all selection criteria were included 1 week later. Patients initially randomized to the milnacipran 200 mg/day group in the lead-in study were blindly maintained on milnacipran 200 mg/day, and those patients previously in the placebo group were rerandomized at a 1:1:1 ratio to milnacipran 100 mg/day (50 mg bid), or 150 mg/day (50 mg AM, 100 mg PM), or 200 mg/day (100 mg bid). At randomization, following a 3-week period without study treatment or prohibited medications (i.e., 2 weeks post-treatment in the lead-in study and 1 week post-entry into the extension study), patients were scheduled to receive 48 weeks of treatment at the target dose, preceded by a 4-week dose escalation starting at 25 mg/day (Table 1), and followed by a 9-day down-titration (Figure 1). During the target dose phase, in case of tolerability issues incompatible with maintenance of treatment for the duration of the study, the investigator could decide either to withdraw the patient or to reduce the dose by 50 mg/day, i.e., to a dose of 50, 100, or 150 mg/day for patients receiving the target dose of 100, 150, or 200 mg/day, respectively. Only one dose reduction was allowed; if tolerability issues persisted at this lower dose level, the patient was withdrawn from the study. All analgesic medications were prohibited during the study except paracetamol, aspirin, ibuprofen, ketoprofen, and dipyron. Short-term hypnotics and anxiolytics (1 speciality of each by country) were allowed for patients requiring adjunctive treatment of insomnia or anxiety. These authorized medications were to be prescribed at the lowest dose and for the shortest period of time and had to be discontinued 48 hours before each scheduled visit.

Table 1. Four-week dose escalation schedule.

Duration, days	Milnacipran Daily Dose at Target Dose Phase		
	200 mg	150 mg	100 mg
2	25 mg AM		
5	50 mg*		
7	100 mg*		
7	150 mg*	150 mg*	100 mg*
7	200 mg*	150 mg*	100 mg*

* bid administration of equally divided doses except for 150 mg/day: 50 mg AM and 100 mg PM.

Assessment visits were organized at screening (Day –7), randomization [Day 1, baseline of this extension study except for laboratory tests (samples at screening)], at the end of the dose escalation (Week 4), at Weeks 8, 12, 20, 28, 36, 44, and at the ends of the target treatment (Week 52), 9-day down-titration, and 2-week post-treatment followup phases.

Efficacy and safety outcome measures. Since the study was an extension of a previous study, we selected key efficacy variables related to or identical to those employed in the lead-in study, namely:

1. Patient-reported weekly-recall pain (average level of pain over the previous week) based on a 0–100 paper visual analog scale (VAS) with anchors of "no pain" and "worst possible pain" (in contrast to an electronic diary daily pain recall in the lead-in study).

2. Patient Global Impression of Change (PGIC), where patients rated their impression of overall change in FM since entering the lead-in study using a 7-point scale (1 = very much improved; 7 = very much worse). The PGIC allows for the patients to aggregate all the components of their experience into a single overall measure of their perception of the advantages and disadvantages of the treatment received (same as the lead-in study).

3. Fibromyalgia Impact Questionnaire (FIQ) total score (scoring range: 0 = no impact to 100 = maximum impact). This validated self-rated questionnaire[31] is the only available FM-specific measure; it measures the various domains of the syndrome: physical functioning, work status, depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being (same as the lead-in study).

A composite responder rate, closely related to the primary criterion of the lead-in study, was defined as the proportion of patients reaching the end of dose escalation and attaining (relative to the lead-in study baseline) ≥ 30% improvement in the weekly-recall pain VAS score and a "much" or "very much improved" PGIC score.

Additional efficacy measures included most of the lead-in study secondary efficacy criteria: (1) paper VAS 0–100 of: current pain, 24-hour recall pain (0 = no pain, 100 = worst possible pain), weekly-recall fatigue (0 = no fatigue, 100 = extreme fatigue), and weekly-recall sleep (0 = totally rested, 100 = not rested at all); (2) scores derived from the following multidimensional self-rated patient questionnaires: Brief Pain Inventory-

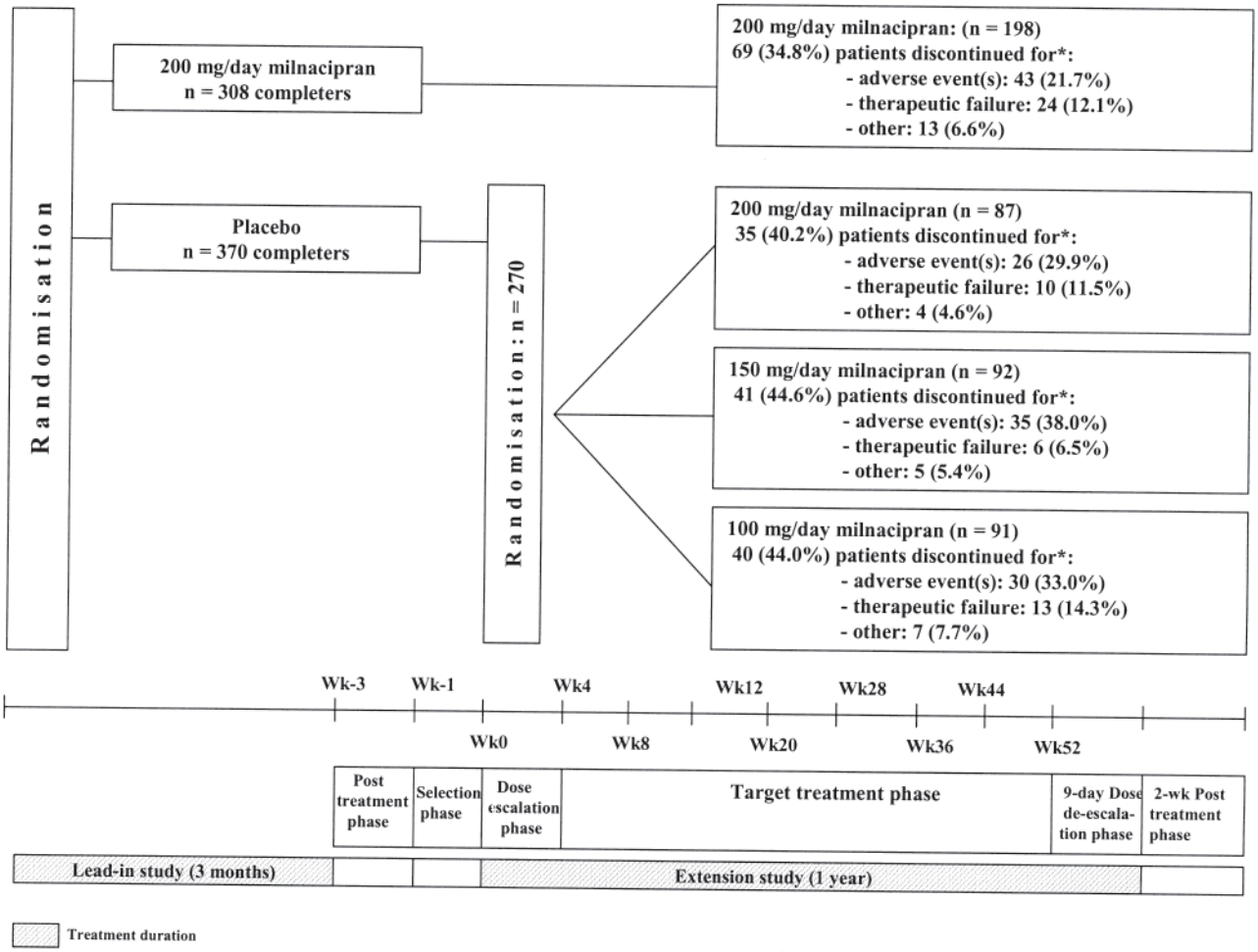

Figure 1. Study design and disposition of patients with respect to completion of the lead-in study, randomization in the extension study, and discontinuation from the extension study. *Some patients discontinued because of adverse events and therapeutic failure; whereas patients classified as discontinued for "other" reasons had no associated reason of adverse event or therapeutic failure.

Short Form (BPI-SF) derived scores 0–10 of pain intensity and interference with quality of life[32]; the Medical Outcomes Study Short Form-36 (SF-36) questionnaire[33] that provides 2 component summaries of physical (SF-36-PCS 0–100) and mental health (SF-36-MCS 0–100); the Multidimensional Fatigue Inventory (MFI 20–100)[34]; Multiple Ability Self-Report Questionnaire (MASQ 38–190)[35]; BDI 0–63; and the state part of the State-Trait Anxiety Inventory (STAI-S 20-80)[36].

For all efficacy variables except SF-36 derived scores, higher scores indicate more severe disorder. All efficacy assessments were performed at all scheduled visits from the randomization visit, except those of SF-36, MFI, and MASQ, which were performed post-baseline at Weeks 28 and 52, and at the end of study visits.

Tolerability/safety evaluations were based on adverse events spontaneously reported or observed at each study visit; on vital signs [supine heart rate and systolic/diastolic blood pressure (SBP/DBP), weight] measured at each study visit; and on electrocardiographic (ECG) and standard laboratory tests performed at screening and at Weeks 28 and 52.

Statistical analysis. Efficacy and safety analyses were based on the full analysis set of data, i.e., from patients having taken at least 1 dose of study treatment in the present extension study. Only descriptive statistics (number and percentage of patients, mean, standard deviation, standard error of the mean) were presented by sequence of treatments received in the lead-in study and the current study. Changes in efficacy scores were calculated from the lead-in study and extension study baselines using both the last observation carried forward (LOCF) approach and observed case approach (initially, for PGIC, the LOCF approach was used only for results at Week 52 endpoint and the observed case approach was used for results over time); all results presented in the text are derived from the LOCF approach, which is more conservative. Treatment-emergent adverse events (TEAE) were defined relative to the time of first study drug administration in the extension study. Changes in vital signs, ECG, and laboratory measures were calculated from baseline-lead-in value.

RESULTS

Patient disposition and baseline characteristics. Of the 678 patients who completed the 3-month lead-in study (308 receiving milnacipran 200 mg/day and 370 placebo), 490 (72.3%) entered this 1-year extension study and 468 (69.0%) were included and received at least 1 dose of the extension treatment: 198 patients on milnacipran 200 mg/day in the lead-in study were maintained on milnacipran 200 mg/day (ML200:MLN200), and 270 patients on placebo in the lead-in study were rerandomized to milnacipran 100 mg/day (PBO:MLN100, n = 91), or 150 mg/day (PBO:MLN150, n = 92), or 200 mg/day (PBO:MLN200, n = 87; Figure 1). There were no relevant differences in demographic and other baseline characteristics between treatment groups, except for a higher proportion of patients unemployed due to FM in the PBO:MLN200 group (27.6% vs 18.9% in all other groups combined; Table 2). Most patients were female (93.6%) and Caucasian (99.1%). Mean age was 49.7 years and mean body mass index (BMI) was 26.8 kg/m^2. At baseline-lead-in, the mean duration of FM was 8.9 years since first symptoms and 3.6 years since diagnosis. The weekly-recall pain rated by the paper VAS could be described as severe at baseline-lead-in, and moderate to severe at baseline-extension (mean scores 68.0 and 56.4, respectively)[37]. The impact of FM on quality of life rated on the FIQ total score was moderate to severe at baseline-lead-in, and moderate at baseline-extension (mean scores 56.4 and 48.8, respectively)[38]. At both baselines, and in accord with inclusion requirements, the mean BDI scores were consistent with no or minimal depressive mood (10.5 and 8.9, respectively)[39].

A total of 283 (60.5%) randomized patients completed the 1-year extension study. Overall, premature withdrawals due to adverse events occurred in 28.6% of patients, and withdrawals due to therapeutic failure in 11.3% of patients (a patient may have had multiple reasons for withdrawal). The MLN200:MLN200 group differed from the groups who had received placebo in the lead-in study by a lower proportion of withdrawals overall (34.8% vs 43.0% of patients taking placebo in the lead-in study) and withdrawals for tolerability reasons (21.7% vs 33.7%, respectively; Figure 1).

Key efficacy outcomes. On Day 1 (following 3 weeks without study and prohibited treatments), the proportions of composite responders (relative to baseline-lead-in) were similar in all groups, ranging from 11.0% (PBO:MLN100) to 16.3% (PBO:MLN150). At the 1-year extension endpoint, these proportions were 27.5% (PBO:MLN100), 31.5% (PBO:MLN150), 32.2% (PBO:MLN200), and 35.9% (MLN200:MLN200); and had increased from baseline-extension by 15.2% (PBO:MLN150), 16.5% (PBO:MLN100), and 20.7% (PBO:MLN200 and MLN200:MLN200; Figure 2). Weekly-recall pain improvements from both baselines were slightly higher with milnacipran 150 and 200 mg/day as shown by mean VAS scores over time (Figure 3). At Week 52, mean decrease in weekly-recall VAS pain score from baseline-lead-in was 20.9 in the 100 mg/day group compared to 26.5 to 27.9 in the higher dosed groups, and the corresponding proportion of weekly-recall pain responders was 46.6% compared to 55.2% to 59.3%, respectively. The proportion of PGIC responders at Week 52 was similar across the 3 groups who switched from placebo to milnacipran (36.7% to 38.0%); in the MLN200:MLN200 group, this proportion was higher (43.9%) but the magnitude of its increase over the extension period was lower than those in the other groups because of a higher PGIC responder rate at baseline-extension (36.9% vs 17.2% to 28.3% in the groups who switched from placebo). Time profiles of weekly-recall pain and PGIC showed that response had almost reached its maximum at 8 weeks of treatment and was sustained throughout the 10 following months of treatment (Figure 3).

FIQ total improvements were slightly greater with milnacipran 150 and 200 mg/day from baseline-lead-in to Week 52 (mean decreases of 16.2 to 17.8, as compared with 11.7 for the 100 mg/day group), and to a lesser degree from baseline-extension (mean decreases of 7.9 to 9.3 as compared with 6.0 for the 100 mg/day group).

Other efficacy outcomes. After 1 year of extension treatment, improvement in pain, fatigue, and sleep was shown from both baselines with all milnacipran dosages through all related assessments (Table 3): improvements from baseline-lead-in were greater with milnacipran 150 mg/day and

Table 2. Patient demographic and other baseline characteristics (baseline at the beginning of the lead-in study).

Lead-in Study Treatment	Placebo			Milnacipran 200 mg/day	
Extension Study Treatment	Milnacipran 100 mg/day, n = 91	Milnacipran 150 mg/day, n = 92	Milnacipran 200 mg/day, n = 87	Milnacipran 200 mg/day, n = 198	Total, n = 468
Characteristic					
Sex, n (%)					
Male	8 (8.8)	4 (4.3)	9 (10.3)	9 (4.5)	30 (6.4)
Female	83 (91.2)	88 (95.7)	78 (89.7)	189 (95.5)	438 (93.6)
Age, mean (SD), yrs	50.0 (9.9)	48.7 (9.7)	51.9 (8.9)	49.1 (9.1)	49.7 (9.4)
Weight, mean (SD), kg	74.0 (16.4)	72.4 (15.9)	73.3 (14.3)	70.9 (15.2)	72.2 (15.4)
Body mass index, mean (SD), kg/m^2	27.3 (5.3)	27.0 (5.4)	27.0 (4.6)	26.4 (5.2)	26.8 (5.2)
Race, n (%)					
Caucasian	89 (97.8)	91 (98.9)	86 (98.9)	198 (100)	464 (99.1)
Other	2 (2.2)	1 (1.1)	1 (1.1)	—	4 (0.9)
Unemployed, n (%)					
Total	39 (42.9)	43 (46.7)	53 (60.9)	88 (44.4)	223 (47.6)
Due to fibromyalgia (FM)	14 (15.4)	16 (17.4)	24 (27.6)	42 (21.2)	96 (20.5)
FM duration, mean (SD), yrs	8.0 (8.1)	8.1 (7.4)	9.7 (8.9)	9.2 (8.2)	8.9 (8.1)
Weekly-recall pain VAS score, mean (SD), range 0–100*	68.0 (13.5)	69.5 (16.2)	68.3 (13.4)	67.2 (15.6)	68.0 (14.9)
24h-recall pain VAS score, mean (SD), range 0–100*	68.0 (13.1)	67.6 (16.2)	68.2 (15.8)	67.3 (16.0)	67.7 (15.4)
FIQ total score, mean (SD), range 0–100*	56.1 (11.8)	58.9 (10.8)	55.9 (11.1)	55.5 (11.7)	56.4 (11.5)
SF-36 PCS, mean (SD), range 100–0*	33.8 (6.9)	33.6 (6.2)	34.1 (6.8)	33.7 (6.5)	33.8 (6.6)
SF-36 MCS, mean (SD), range 100–0*	47.6 (9.2)	44.8 (9.3)	46.6 (9.4)	47.1 (9.6)	46.6 (9.5)
BDI total score, mean (SD), range 0–63*	10.5 (6.3)	11.4 (6.6)	10.6 (6.4)	10.1 (6.9)	10.5 (6.6)
MFI total score, mean (SD), range 20–100*	64.5 (13.4)	68.9 (12.0)	66.3 (14.5)	65.6 (13.7)	66.1 (13.5)
Weekly-recall sleep VAS score, mean (SD), range 0–100*	67.4 (18.0)	70.6 (17.6)	66.8 (16.7)	65.5 (17.5)	67.1 (17.5)
MASQ total score, mean (SD), range 38–190*	85.1 (24.0)	86.5 (24.6)	86.6 (25.3)	88.2 (25.8)	87.0 (25.1)
STAI-S score, mean (SD), range 20–80*	37.8 (10.5)	39.1 (10.7)	38.2 (10.2)	38.0 (10.3)	38.2 (10.3)

* Range from best to worst possible value. BDI: Beck Depression Index; FIQ: Fibromyalgia Impact Questionnaire; MASQ: Multiple Ability Self-report Questionnaire; MFI: Multidimensional Fatigue Inventory; STAI-S: State-Trait Anxiety Inventory-State; VAS: visual analog scale.

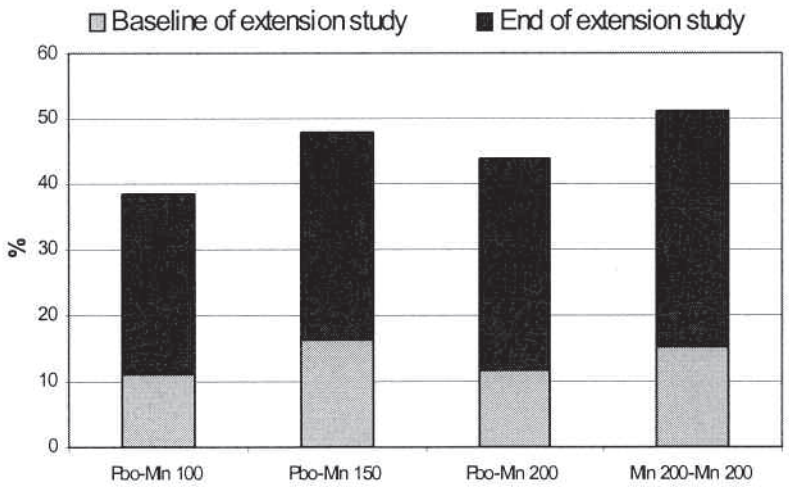

Figure 2. Responder rates at baseline and at 1-year endpoint (last observation carried forward) of the extension study on the 2-measure composite criterion, i.e., from lead-in study baseline: (1) ≥ 30% improvement in patient weekly-recall pain VAS score; and (2) Patient Global Impression of Change rating of 1 "very much improved" or 2 "much improved." Pbo: placebo; Mln: milnacipran.

200 mg/day, while those from baseline-extension were either similar across groups (24-hour recall pain, BPI pain intensity, total MFI) or were greater with milnacipran 200 mg/day (BPI pain interference) or 150 mg/day (week-

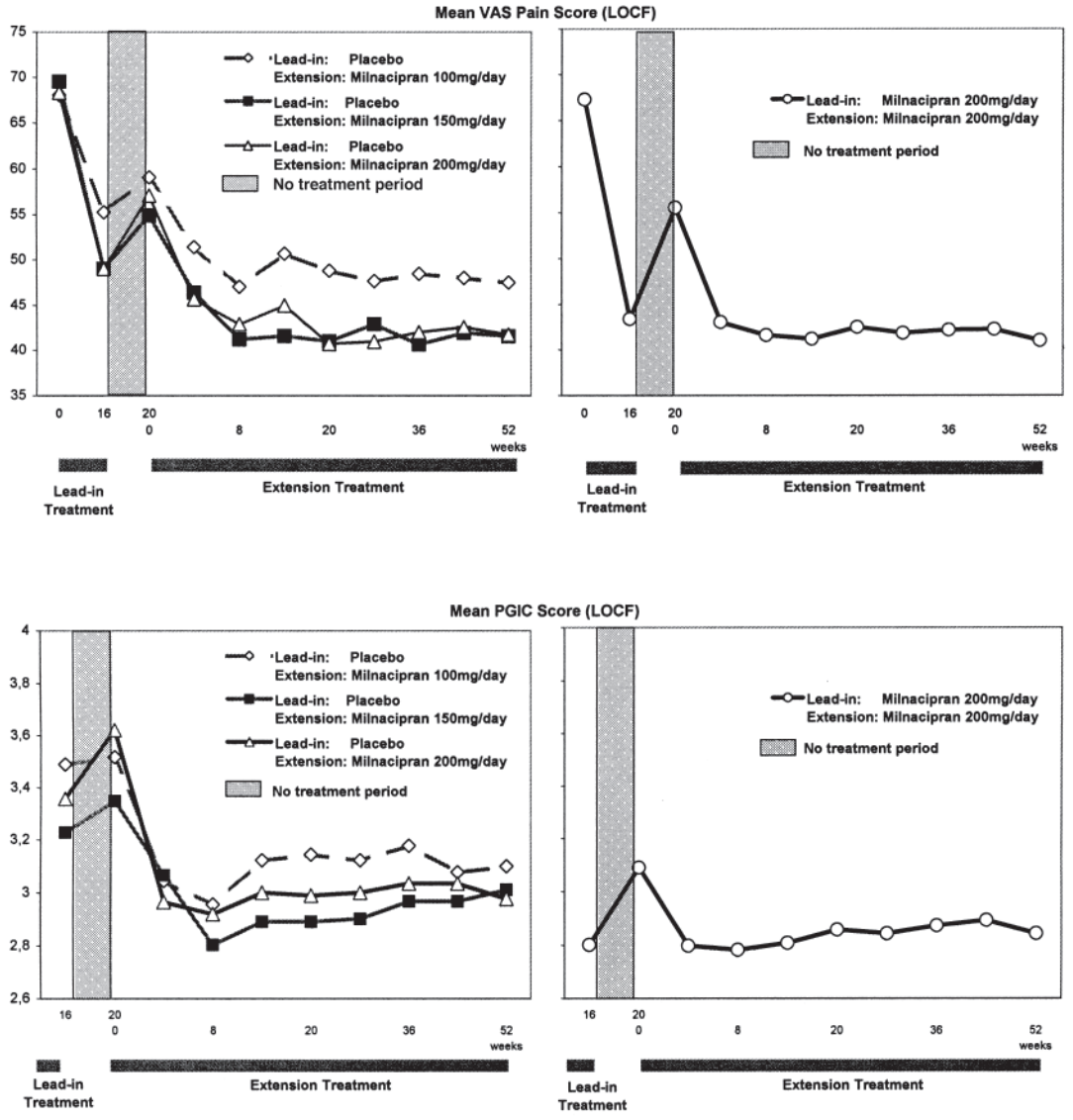

Figure 3. Mean weekly-recall VAS pain and Patient Global Impression of Change (PGIC) scores over time [last observation carried forward (LOCF)], at baseline of the lead-in study (for VAS pain score), at the end of the lead-in treatment period (16 weeks = post-hoc calculation), and through the extension treatment period. The grey area represents the 4-week interval (1 week of down-titration and 3 weeks off study treatment) between the 2 treatment periods.

ly-recall fatigue and weekly-recall sleep). In all treatment groups, the reduction of cognitive complaints from baseline-lead-in (rated on the MASQ total score) observed at baseline-extension was maintained throughout the extension year (Table 4).

During this extension study, all assessments of depression, anxiety, and mental status were unchanged, as expected in a population whose status was either not impaired or minimally impaired in these respects because of inclusion restrictions.

Tolerability and safety. None of the safety assessments showed a trend for worsening in safety and tolerability with extended treatment with milnacipran over a 1-year period.

During the extension study, the overall incidences of TEAE and related TEAE were 91.7% and 78.0%, respectively, and were not different between groups. The most common related TEAE (≥ 10% in all groups) were, in decreasing order of frequency for all patients: hyperhidrosis (18.7% to 26.1%), nausea (17.2% to 27.6%), headache (14.6% to 21.8%), tachycardia (or heart rate increased: 11.6% to 18.7%), and hypertension (or blood pressure increased: around 13% in any group). The incidence of these common related TEAE was similar across all groups including those who had received placebo in the lead-in study (apart from nausea, which appeared more frequently in the PBO:MLN200 group). The incidence of related adverse events leading to dose reduction was 23.9% overall, and incidence of related adverse events leading to definitive dis-

Table 3. Mean (SD) changes in pain, fatigue, and sleep scores from baseline (BSL) lead-in and BSL extension at the 1-year endpoint. Data are last observation carried forward (LOCF)/observed case (OC), in-patients receiving placebo (PBO) or milnacipran (MLN) 100, 150, or 200 mg/day.

Characteristic	PBO:MLN100, n = 91	PBO:MLN150, n = 92	PBO:MLN200, n = 87	MLN200:MLN200, n = 198
Pain				
Weekly-recall pain change from				
BSL lead-in	–20.9 (25.5)/–26.0 (24.5)	–27.9 (26.9)/–36.4 (23.4)	–26.6 (26.8)/–34.2 (24.3)	–26.5 (29.0)/–31.5 (28.3)
BSL extension	–11.6 (22.6)/–17.9 (20.6)	–13.5 (22.5)/–20.0 (23.2)	–15.3 (22.5)/–21.3 (22.5)	–14.7 (24.2)/–19.6 (23.5)
24-hour-recall pain change from				
BSL lead-in	–23.3 (26.6)/–29.9 (23.9)	–25.7 (26.9)/–34.2 (24.9)	–27.5 (26.2)/–34.2 (27.2)	–26.9 (27.6)/–31.4 (27.0)
BSL extension	–14.3 (22.7)/–20.7 (20.1)	–14.2 (23.6)/–20.9 (24.9)	–16.6 (22.1)/–23.6 (23.2)	–14.1 (23.5)/–18.2 (23.9)
BPI pain intensity change from				
BSL lead-in	–1.47 (2.24)/–2.07 (2.16)	–1.82 (2.02)/–2.41 (1.95)	–1.79 (1.98)/–2.22 (2.12)	–1.95 (2.34)/–2.42 (2.18)
BSL extension	–0.98 (1.95)/–1.61 (1.55)	–1.18 (1.98)/–1.78 (1.80)	–1.17 (1.82)/–1.71 (1.84)	–1.21 (1.91)/–1.62 (1.87)
BPI pain interference change from				
BSL lead-in	–1.31 (2.19)/–1.64 (1.90)	–1.35 (2.41)/–1.78 (2.53)	–1.92 (2.07)/–2.23 (2.25)	–1.68 (2.42)/–2.13 (2.27)
BSL extension	–0.57 (1.87)/–1.08 (1.66)	–0.41 (1.86)/–0.85 (1.85)	–0.93 (1.78)/–1.34 (1.85)	–0.91 (1.96)/–1.25 (1.88)
Fatigue				
Total MFI change from				
BSL lead-in	–3.93 (16.25)/–5.22 (16.97)	–6.69 (14.39)/–9.07 (15.54)	–6.44 (16.81)/–8.68 (17.86)	–6.71 (16.27)/–8.54 (15.97)
BSL extension	–2.77 (13.93)/–4.20 (15.76)	–2.32 (13.25)/–5.30 (12.07)	–2.25 (13.57)/–4.98 (13.35)	–3.25 (12.57)/–4.99 (11.83)
Weekly-recall fatigue change from				
BSL lead-in	–15.8 (27.1)/–19.0 (28.0)	–22.0 (30.1)/–27.3 (28.8)	–20.9 (23.4)/–28.6 (22.5)	–20.4 (30.4)/–25.2 (30.0)
BSL extension	–8.3 (22.8)/–13.7 (19.7)	–14.2 (24.9)/–18.5 (25.3)	–9.6 (18.9)/–14.5 (19.5)	–10.3 (25.3)/–13.2 (24.0)
Sleep				
Weekly-recall sleep change from				
BSL lead-in	–11.9 (26.5)/–17.2 (27.9)	–21.1 (28.6)/–27.4 (28.9)	–20.2 (24.6)/–26.9 (24.9)	–19.9 (30.7)/–24.9 (29.5)
BSL extension	–6.6 (24.0)/–11.0 (21.6)	–13.6 (27.1)/–18.7 (29.0)	–9.2 (17.8)/–13.4 (17.2)	–10.9 (26.7)/–14.4 (24.9)

BPI: Brief Pain Inventory.

Table 4. Mean (SD) changes in quality of life/functional status and cognitive dysfunction scores from baseline (BSL) lead-in and BSL extension at the 1-year endpoint. Data are last observation carried forward (LOCF)/observed case (OC), in-patients receiving placebo (PBO) or milnacipran (MLN) 100, 150, or 200 mg/day.

Characteristic	PBO:MLN100, n = 91	PBO:MLN150, n = 92	PBO:MLN200, n = 87	MLN200:MLN200, n = 198
Quality of life/functional status				
FIQ total change from				
BSL lead-in	–11.72 (21.66)/–16.37 (23.45)	–17.79 (20.77)/–22.75 (21.49)	–16.21 (19.19)/–21.46 (20.07)	–17.06 (22.02)/–21.40 (20.94)
BSL extension	–6.02 (16.53)/–11.49 (14.06)	–9.19 (16.38)/–13.57 (15.93)	–7.90 (13.76)/–12.60 (12.68)	–9.30 (18.05)/–12.91 (17.46)
SF-36 PCS change* from				
BSL lead-in	4.38 (7.19)/5.63 (7.22)	3.94 (8.54)/5.33 (9.34)	4.23 (7.22)/4.83 (7.57)	4.96 (7.74)/5.49 (7.43)
BSL extension	2.47 (6.60)/3.10 (6.74)	2.28 (6.17)/3.17 (6.61)	2.28 (6.01)/3.16 (5.47)	2.72 (6.57)/3.07 (6.98)
SF-36 MCS change* from				
BSL lead-in	–0.66 (10.29)/–0.68 (10.07)	2.86 (9.40)/4.14 (8.49)	1.99 (9.69)/3.43 (8.96)	1.50 (10.06)/2.83 (9.77)
BSL extension	–0.47 (9.61)/0.40 (9.97)	0.51 (7.69)/1.45 (7.24)	0.21 (8.34)/1.66 (7.81)	0.37 (8.70)/1.50 (8.27)
Cognitive dysfunction				
MASQ total change from				
BSL lead-in	–5.88 (19.18)/–3.91 (18.31)	–4.19 (22.14)/–5.52 (22.71)	–6.01 (19.74)/–3.71 (20.51)	–8.40 (21.87)/–9.11 (21.37)
BSL extension	0.87 (15.13)/1.67 (15.12)	0.46 (14.25)/–0.72 (13.42)	0.03 (17.04)/–0.16 (18.03)	–1.69 (15.69)/–3.70 (15.48)

* Increase reflects improvement. FIQ: Fibromyalgia Impact Questionnaire; SF-36: Medical Outcomes Study Short-form 36; PCS: physical component summary; MCS: mental component summary; MASQ: Multiple Ability Self-Report Questionnaire.

continuation was 25% overall. About a quarter of the patients who had a dose reduction due to an adverse event subsequently discontinued due to that adverse event. The most common adverse events (≥ 2% of all patients) resulting in premature discontinuation were, in decreasing order of frequency overall: hyperhidrosis, nausea, tachycardia, headaches, hypertension, and dizziness. The frequency of onset of most TEAE was highest during the dose escalation phase and tended to decrease during the target dose phase; for cardiovascular TEAE, this decrease tended to start after 3

months of exposure. Frequencies and descriptions of post-treatment emergent adverse events reported do not suggest any adverse reaction to withdrawal from milnacipran. There were no deaths reported during the study. Serious adverse events were reported in 39 (8.3%) patients during the 1-year extension study period, with 8 related events (a cardiac failure in the PBO:MLN100 group; serotoninergic manifestations, an increased blood creatine phosphokinase, and a gastritis in the PBO:MLN150 group; a vertigo in the PBO:MLN200 group; an angioneurotic edema, an aortic dissection, and a macular hole in the MLN200:MLN200 group). There were no clinically relevant mean changes (from baseline-lead-in) in any of the laboratory measures tested. Only 2 noteworthy abnormal laboratory values (both elevated alanine-aminotransferase levels < 3-fold the upper limit of normal) were reported as related TEAE: 1 case in the PBO:MLN100 group at Week 6 resolved on treatment after a dose reduction; 1 case in the MLN200:MLN200 group at Week 52 concomitant to a cytolytic hepatitis that improved at the end of followup (< 2-fold upper limit of normal).

Potentially clinically significant (PCS) increases (from baseline-lead-in) in supine SBP or DBP (≥ 20 mm Hg and ≥ 15 mm Hg, respectively) resulting in a PCS value (≥ 180 mm Hg and ≥ 105 mm Hg) occurred in 3.5% of patients in the MLN200:MLN200 group and in 3.3% (PBO:MLN150) to 8.8% (PBO:MLN100) in the rerandomized patients. PCS increases in supine heart rate (≥ 15 bpm) resulting in a PCS value (≥ 120 bpm) occurred in 0% (PBO:MLN200) to 3.3% (PBO:MLN150) of patients. Mean weight at baseline-lead-in was similar across the 4 treatment groups (72.2 kg overall), and there was very little mean change in weight (slightly toward decrease) during the study in any group (maximum overall mean decrease at Week 12, –0.49 kg).

DISCUSSION

The current study, conducted as an extension of a 3-month phase III lead-in placebo-controlled study of milnacipran 200 mg/day (bid administration), examined the safety and efficacy of milnacipran 100, 150, and 200 mg/day (bid administration) during longterm treatment of FM for 1 year.

The patients who had received milnacipran 200 mg/day in the lead-in study were allocated the same 200 mg/day dose in double-blind conditions. Patients who had received placebo in the lead-in study were randomized to receive milnacipran 100, 150, or 200 mg/day in a 1:1:1 ratio in double-blind conditions. The absence of a placebo control group, which represents a limitation of this extension study, was justified by the long duration of the study and the need to permit all patients access to a potentially effective treatment.

The efficacy outcomes assessed throughout the study explore a breadth of FM symptom domains. Most of these outcomes are recommended by the IMMPACT[40] and the OMERACT[2] for their relevance in chronic pain clinical trials.

As in the lead-in study, the efficacy of milnacipran in the treatment of FM was distinguished from its specific antidepressant activity by excluding patients with current major depressive episode or with moderately to severely depressed mood (BDI > 25). Also, a multidimensional analysis was performed using a 2-measure composite response criterion (based on responder status on weekly-recall pain VAS and PGIC). The response thresholds chosen for both primary variables after 12 months of target dose, i.e., a 30% reduction in VAS pain intensity and PGIC categories of "much improved" and "very much improved," are considered to be determinants of clinically significant effects[41,42].

IMMPACT-recommended outcomes were used to assess the treatment effect on other core symptoms frequently experienced in FM: physical/social/emotional and mental/anxiety/depression health-related quality of life domains (FIQ, SF-36 physical and mental summary scores), fatigue (MFI), cognitive complaints (MASQ), anxiety (STAI), and depressed mood (BDI).

The demographic and baseline characteristics of the 4 treatment groups in this extension study were comparable and (with the exception of exclusion of patients with a current major depressive episode and BDI > 25) representative of the European FM population. The patients' characteristics (93.6% female patients, mean age 49.7 yrs, mean BMI 26.8 kg/m^2) and disease history (mean time since FM symptoms 8.9 yrs and since diagnosis 3.6 yrs) were similar to those observed in the lead-in study.

In this extension study, the proportion of composite responders (relative to the lead-in study baseline) increased at most visits in all treatment groups. By Week 52, composite responder rates ranged from 27.5% (PBO:MLN100) to 35.9% (MLN200:MLN200), and increases in the composite responder rates from the extension study baseline ranged from 15.2% (PBO:MLN150) to 20.7% (PBO:MLN200 and MLN200:MLN200). Time to onset of response was short (less than 8 weeks) in the majority of patients who responded, and sustained response was observed in all treatment groups.

Slight differences between groups were seen in the proportion of responders, time to onset of and durability of effect for pain, PGIC, and on progressive improvement of secondary variables over time. Smaller improvements were seen with the 100 mg/day dosage on pain, FIQ, fatigue, and sleep scores, and greater improvement was seen with the 200 mg/day dosage on the composite response. These findings support and complement results from a 6-month US extension study in which patients treated with milnacipran 100 or 200 mg/day or placebo were randomized to an additional 6 months of treatment with milnacipran 100 mg or 200 mg/day, and who demonstrated further improvements in pain, PGIC, and FIQ[27]. Fatigue, a common symptom reported by FM patients, was reduced with milnacipran, as measured by 2 different fatigue assessments (MFI total score and fatigue weekly-recall VAS score). These improvements in

fatigue may be due to the greater effect of milnacipran on noradrenergic reuptake than on serotoninergic reuptake[43].

Another interesting finding is the loss of therapeutic effect after the 3 weeks off-treatment following the lead-in study. For both PGIC and pain, the loss of effect was greatest in the group previously taking milnacipran, confirming the need for a longterm treatment of FM. The resulting mean scores at baseline-extension (similar between groups for pain and still lower in the group previously taking milnacipran for PGIC) show the absence of any rebound effect and a slower loss of effect on PGIC than on pain.

The majority (72.3%) of patients completing the 3-month lead-in study chose to enroll in the extension study, and 60.5% of patients randomized in the extension study completed the additional year of treatment. The 39.5% discontinuation rate (42.9% in patients treated with placebo in the lead-in study) is congruent with the long study duration, and is comparable to the rates reported in longterm US studies of FM with milnacipran[24,27] and other FM treatments[44,45,46]. The MLN200:MLN200 group differed from the groups who had received placebo in the lead-in study by a lower proportion of withdrawals both overall (34.8%) and withdrawals for tolerability reasons. This is not surprising as this group consisted of the patients who tolerated milnacipran 200 mg/day well in the lead-in study. A greater PGIC response seen in this group is also probably linked to this fact.

The global incidence of related TEAE in this trial was similar in all treatment groups (78% of patients overall). The adverse events reported most commonly on treatment in this study have been previously described with milnacipran, and are consistent with the noradrenergic effects of the drug.

This longterm extension study shows the beneficial effect of milnacipran in FM at the 3 dosages tested and the maintenance of this effect over a 1-year period. This efficacy was observed for the pain and PGIC composite criterion and each of its components, as well as the other FM domains that were evaluated. The safety profile seen in our study was satisfactory and no unexpected adverse reactions or safety findings were observed with longterm FM treatment using milnacipran.

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APPENDIX

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