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Efficacy and Safety of Milnacipran 100 mg/day in Patients With Fibromyalgia

Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. **To assess the efficacy and safety of milnacipran at a dosage of 100 mg/day (50 mg twice daily) for monotherapy treatment of fibromyalgia.**

Methods. **A double-blind, placebo-controlled trial was performed to assess 1,025 patients with fibromyalgia who were randomized to receive milnacipran 100 mg/day (n = 516) or placebo (n = 509). Patients underwent 4–6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment. Two composite responder definitions were used as primary end points to classify the response to treatment. The 2-measure composite response required achievement of ≥30% improvement from baseline in the pain score and a rating of "very much improved" or "much improved" on the Patient's Global Impression of Change (PGIC) scale. The 3-measure composite response required satisfaction of these same 2 improvement criteria for pain and global status as well as improvement in physical function on the Short Form 36 (SF-36) physical component summary (PCS) score.**

Results. **After 12 weeks of stable-dose treatment, a significantly greater proportion of milnacipran-treated patients compared with placebo-treated patients showed clinically meaningful improvements, as evidenced by the proportion of patients meeting the 2-measure composite responder criteria ($P < 0.001$ in the baseline observation carried forward [BOCF] analysis) and 3-measure composite responder criteria ($P < 0.001$ in the BOCF). Milnacipran-treated patients also demonstrated significantly greater improvements from baseline on multiple secondary outcomes, including 24-hour and weekly recall pain score, PGIC score, SF-36 PCS and mental component summary scores, average pain severity score on the Brief Pain Inventory, Fibromyalgia Impact Questionnaire total score (all $P < 0.001$ versus placebo), and Multidimensional Fatigue Inventory total score ($P = 0.036$ versus placebo). Milnacipran was well tolerated by most patients, with nausea being the most commonly reported adverse event (placebo-adjusted rate of 15.8%).**

Conclusion. **Milnacipran administered at a dosage of 100 mg/day improved pain, global status, fatigue, and physical and mental function in patients with fibromyalgia.**

Fibromyalgia is a common chronic pain disorder that predominantly affects women (1). Defined by the American College of Rheumatology (ACR) as a condition characterized by chronic widespread pain and tenderness (2), fibromyalgia is often accompanied by other symptoms and functional impairment (3,4). Recent trials of fibromyalgia medication have focused primarily on

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pain outcomes, but there is growing recognition of the importance of assessing the other important common symptoms reported by patients with fibromyalgia as well as the impact of treatment on improving function. Using expert opinion and clinicians' and patients' Delphi exercises, the Outcome Measures for Rheumatology Clinical Trials fibromyalgia working group recently proposed key symptom and function domains that should be included in the assessment of patient response to fibromyalgia treatment (5). These domains include pain, fatigue, sleep, cognition (e.g., decreased concentration, forgetfulness), mood (e.g., depression, anxiety), and multidimensional function.

The primary outcome measure of several recent fibromyalgia trials has been the mean reduction in pain severity in patients receiving an active treatment compared with those receiving placebo. Although this approach provides information about the overall treatment efficacy in reducing pain, it does not determine the proportion of individual patients who experience clinically meaningful improvements in other important symptoms. Defining primary efficacy using a composite responder index to assess an individual's response to treatment allows clinicians to compare the efficacy of different therapies, define factors that predict response, and determine whether individual patients might be likely to improve with a particular treatment.

Recent pivotal trials of milnacipran were among the first to use composite responder definitions as primary outcome measures in large-scale studies of fibromyalgia (6,7). Two composite responder definitions were included in these trials to assess efficacy (2-measure and 3-measure composite responder definitions). Patients classified as 2-measure composite responders had to achieve improvements in both pain and global outcomes. In addition to improvements in pain and global assessments, 3-measure composite responders also had to demonstrate improvements in physical function. Based on the results of the pivotal trials, milnacipran was approved by the US Food and Drug Administration in January 2009 for the management of fibromyalgia (8).

Although the exact mechanisms by which milnacipran improves fibromyalgia are unknown, it is a dual reuptake inhibitor of norepinephrine and serotonin, which are important neurotransmitters in descending pain inhibitory pathways (9,10). By increasing norepinephrine- and serotonin-mediated neurotransmission, milnacipran may correct a functional deficit of these neurotransmitters and reduce pain and other symptoms (11). The present randomized, placebo-controlled, double-blind, parallel-group trial was designed to explore further the efficacy and safety of monotherapy with milnacipran 100 mg/day (50 mg twice daily) in patients with fibromyalgia.

PATIENTS AND METHODS

Study overview. This was a multicenter, randomized, double-blind, placebo-controlled study conducted at 68 outpatient clinical/research centers in the US and Canada. Enrollment began April 28, 2006; the study was completed June 30, 2008. The study protocol was reviewed and approved by each center's Institutional Review Board. The trial was conducted in accordance with the ethics principles articulated in the Declaration of Helsinki, consistent with Good Clinical Practice and applicable regulatory requirements. All patients gave their informed consent after the study was explained and before study procedures were initiated.

Entry criteria. Female or male patients 18–70 years of age who met the ACR 1990 criteria for fibromyalgia (2) were eligible for inclusion in the study. Patients with other rheumatic or medical disorders that displayed symptoms similar to fibromyalgia were excluded. Patients were required to have a raw score of $\geq$4 on the physical function domain of the Fibromyalgia Impact Questionnaire (FIQ) (12) (score range 0–33, with higher scores indicating greater impairment) at screening and a mean visual analog scale (VAS) pain score of $\geq$40 and $\leq$90 on the electronic patient experience diary (PED) 24-hour recall pain report (score range 0–100, with 100 indicating worst possible pain) during the 14-day baseline period.

Patients with any of the following criteria were excluded from the study: previous exposure to milnacipran, treatment with an investigational drug within 30 days of screening, Beck Depression Inventory (BDI) (13) score $>$25 at screening or randomization, current major depressive episode as determined by the Mini International Neuropsychiatric Interview (MINI) (14), significant risk of suicide according to the investigator's judgment or the results of the MINI or the BDI, lifetime history of psychosis, hypomania, or mania, substance abuse, other severe psychiatric illness as determined by investigator judgment, history of behavior that would, in the investigator's judgment, prohibit compliance for the duration of the study, active or pending disability claim, worker's compensation claim, or litigation, pregnancy or breastfeeding, unacceptable contraception (method other than hormonal birth control, intrauterine device, double barrier method, or barrier method plus a spermicidal agent), active or unstable medical illness, and prostate enlargement or other genitourinary disorder. Concomitant treatments considered to be criteria for exclusion included digitalis, centrally acting medications for fibromyalgia, transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anesthetic or narcotic patches. Permitted analgesic medications were acetaminophen, aspirin, and nonsteroidal antiinflammatory agents. Patients requiring short-term pain rescue medication were allowed tramadol or hydrocodone between randomization and week 4 (end of dose escalation). Triptans were permitted for acute migraine treatment. Nonbenzodiaz-

epine hypnotic agents were allowed for patients requiring treatment of insomnia.

Study design. The study involved 5 phases: screening and washout (1–4 weeks), baseline assessment (2 weeks), randomization/flexible dose escalation (4–6 weeks), stable dose (12 weeks), and randomized discontinuation (2 weeks). After undergoing screening for eligibility and completing a washout of prohibited medications, patients were trained in the use of the PED (invivodata) and entered a 2-week baseline period in which safety and efficacy data were collected. Patients who continued to meet eligibility criteria at the end of the baseline period were randomized in a 1:1 ratio to receive either milnacipran 100 mg/day (50 mg twice daily) or placebo. Assignment to treatment groups was conducted centrally (i.e., at the study level) using an interactive voice response system generated and maintained by Premier Research and securely kept by Forest Research Institute, Inc. The randomization assignments were generated in blocks of 4 so that each center would have a balanced distribution of patient assignments. Clinical staff, investigators, patients, and the study sponsor were blinded to treatment allocation.

This trial was designed to evaluate the merits of a slow and flexible dose-escalation phase. Patients assigned to the active treatment arm received milnacipran 12.5 mg on days 1–3, milnacipran 25 mg (12.5 mg twice daily) for 4 days, milnacipran 50 mg (25 mg twice daily) for 7 days, milnacipran 75 mg (37.5 mg twice daily) for 7 days, and milnacipran 100 mg (50 mg twice daily) for 7 days. If side effects developed, the dose of milnacipran could be temporarily reduced; however, the total escalation period could not exceed 6 weeks. Patients unable to tolerate the stable dosage of milnacipran 100 mg/day were discontinued from the study. For blinding purposes, placebo-treated patients underwent dose escalation in the same manner as patients receiving active medication; identical-appearing capsules were used by all patients during all phases of the study.

After completing a 12-week stable-dose phase, patients were assigned to a 2-week randomized, short-term discontinuation phase. Safety and efficacy results from the discontinuation phase will be reported elsewhere.

Outcome measures. The protocol-defined primary outcome measures were response to treatment as defined by 2 composite responder indices. The composite responder definition for the treatment of fibromyalgia consisted of 3 components: 1) ≥30% improvement from baseline in the level of pain (as assessed with the PED 24-hour recall VAS pain score; range 0–100, with 100 indicating worst possible pain), with the baseline for pain assessment defined as the 14 days immediately before and including the day of the last baseline visit (randomization) and the end point defined as the 14 days immediately before and including the day of the week 12 visit; 2) a rating of "very much improved" (score of 1) or "much improved" (score of 2) on the Patient's Global Impression of Change (PGIC) scale; and 3) ≥6-point improvement from baseline in physical function (Short Form 36 [SF-36] physical component summary [PCS] score). For the treatment of pain associated with fibromyalgia, the composite responder definition included only the pain and PGIC components described above.

Patients reported their pain intensity by responding to PED prompts several times each day and on a weekly basis. Patients recorded current pain (real-time) and recalled pain (24-hour and weekly) using a VAS pain scale. Patients also completed VAS assessments of pain using a portable tablet (SitePro; invivodata) at each study visit. For the PGIC measure, patients rated their overall change in fibromyalgia from the start of the study, using a 7-point scale (1 = "very much improved" to 7 = "very much worse"). The SF-36 was used to measure health status, and the SF-36 PCS and mental component summary (MCS) subscores were calculated by combining and weighting the individual health status domains (15).

Secondary efficacy measures included fatigue, as measured by the Multidimensional Fatigue Inventory (MFI) total score (16), and time-weighted averages (area under the curve [AUC]) of the mean weekly PED 24-hour recall pain scores, PGIC scores, and SF-36 PCS scores. Additional efficacy parameters included SitePro-based VAS assessments of pain over 24 hours and 7 days, BDI (13) and Beck Anxiety Index (BAI) (17) scores, FIQ scores (12), scores on the Multiple Ability Self-Report Questionnaire (MASQ) (for cognitive function) (18), Brief Pain Inventory (BPI) scores (19), and scores on individual domains of the SF-36. Additional electronic diary assessments included the weekly average of PED 24-hour recall pain scores, weekly average of PED real-time pain scores (morning current pain score, random-prompt pain score, and evening current pain score), and PED weekly recall pain scores.

Tolerability and safety assessments. All treatment-emergent adverse events (TEAEs) were recorded at each clinic visit along with the dates of onset and resolution. Clinical laboratory tests (hematology, chemistry, and urinalysis) were performed at screening and at the end of the stable-dose treatment phase. Vital signs, weight, and concomitant medication use were assessed at all clinic visits. Electrocardiograms (EKGs) were performed at baseline and repeated at the end of the stable-dose phase. A physical examination was performed at screening and repeated after the discontinuation phase.

Statistical analysis. All patients who received at least 1 dose of study medication were included in the intent-to-treat analyses. All statistical tests were 2-sided hypothesis tests performed at the 0.05 level of significance. For the primary efficacy analyses, the proportion of responders satisfying the 3-measure composite definition was analyzed using a logistic regression model, with treatment group, baseline pain score, and baseline SF-36 PCS score (3-measure composite only) as explanatory variables. Missing postbaseline values were imputed using the baseline observation carried forward approach at end point for the primary efficacy parameters and their components (20). Patients who lacked primary efficacy data at end point were defined as nonresponders. In addition, patients taking prohibited narcotic medications within 48 hours of the primary end point visit or on more than 2 of 14 days prior to the primary end point visit were considered nonresponders. Sensitivity analyses included using the last observation carried forward (LOCF) method for missing data imputation (21,22), an analysis based on observed cases (OC) (21,22), and a generalized linear mixed model approach (23,24).

Secondary and additional efficacy assessments were summarized by treatment group and visit. These data were analyzed at each postbaseline visit using an analysis of covariance model, with treatment group and study center as

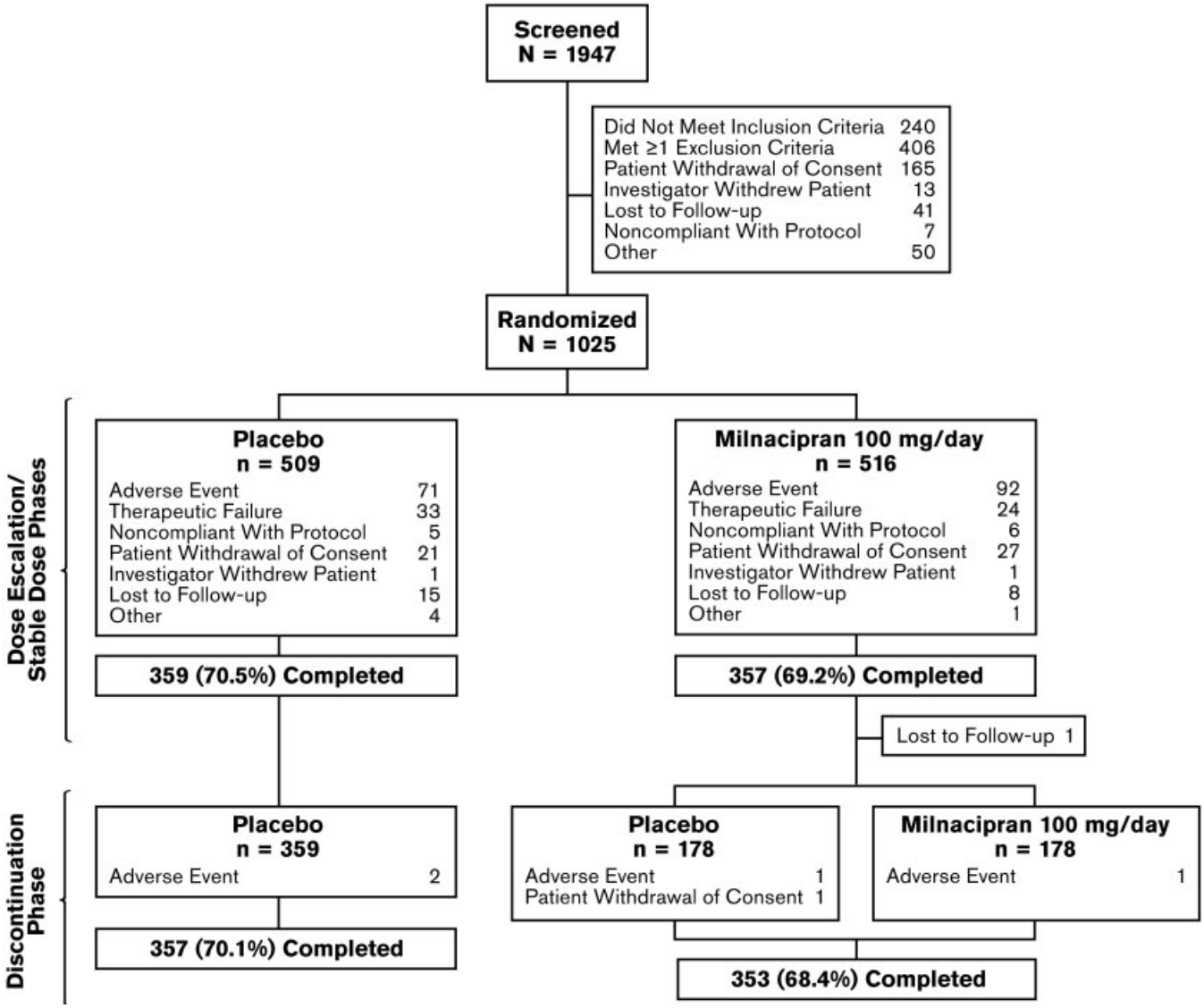

Figure 1. Flow diagram showing the distribution of patients randomized to receive milnacipran 100 mg/day or placebo during the dose-escalation, stable-dose, and discontinuation phases of the trial.

factors and the baseline value as a covariate, except for the PGIC and AUC of the PGIC, which were analyzed using analysis of variance. Analyses of secondary and additional outcomes were based on both the LOCF and OC approaches. Logistic regression with treatment group (and baseline value, when applicable) as an explanatory variable was used to evaluate the response for individual components of the 2- and 3-measure composite responder end points. All analyses were performed using SAS version 9.1.3 (SAS Institute).

To control for overall Type I error, a sequential gatekeeping, multiple-testing procedure (25) was applied to all comparisons of milnacipran versus placebo for the primary and secondary efficacy parameters. Primary efficacy end points were tested using the 3-measure composite responder analysis first, followed by the 2-measure composite responder analysis if the null hypothesis was rejected in the first analysis. If null hypotheses were rejected in both analyses, between-group comparisons for secondary efficacy parameters were performed, in the order of the AUC of PED 24-hour recall pain score, AUC of the PGIC score, MFI total score, and AUC of the SF-36 PCS score.

Safety of milnacipran was assessed by analyzing the frequency and severity of AEs, changes in vital signs and EKGs, physical examination findings, and clinical laboratory data collected during the study period.

Table 1. Patient demographic and clinical characteristics at baseline*

	Placebo (n = 509)	Milnacipran 100 mg/day (n = 516)
Age, years	48.7 ± 10.6	49.1 ± 10.8
Sex, no. (%)		
Female	477 (93.7)	500 (96.9)
Male	32 (6.3)	16 (3.1)
Race, no. (%)		
White	458 (90.0)	474 (91.9)
Black or African American	34 (6.7)	28 (5.4)
Asian	1 (0.2)	1 (0.2)
Other	16 (3.1)	13 (2.5)
Weight, lb	182.9 ± 44.4	183.0 ± 43.9
BMI, kg/m^2	30.8 ± 7.2	31.0 ± 7.1
Duration of fibromyalgia, years	10.8 ± 8.1	10.9 ± 8.0
Baseline efficacy measure		
24-hour recall pain score		
PED (range 0–100)	64.4 ± 12.7	63.1 ± 12.5
VAS (range 0–100)†	68.8 ± 17.0	66.8 ± 16.4
BPI average pain severity score (range 0–10)	6.5 ± 1.2	6.4 ± 1.2
FIQ score		
Total (range 0–100)	57.9 ± 14.1	56.7 ± 12.7
Physical function (range 0–3)	1.3 ± 0.6	1.3 ± 0.6
SF-36 score		
Physical component summary	32.9 ± 7.8	33.0 ± 7.6
Mental component summary	46.6 ± 11.4	46.7 ± 10.7
MFI total score (range 20–100)	67.6 ± 13.6	67.4 ± 12.9
MASQ total score (range 38–190)	89.5 ± 21.1	90.6 ± 19.9
BDI total score (range 0–63)	8.7 ± 6.5	9.1 ± 6.3
BAI total score (range 0–63)	12.8 ± 8.5	12.7 ± 8.3

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; PED = patient experience diary; VAS = visual analog scale; BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; SF-36 = Short Form 36 Health Survey; MFI = Multidimensional Fatigue Inventory; MASQ = Multiple Ability Self-Report Questionnaire; BDI = Beck Depression Inventory; BAI = Beck Anxiety Index.
† Collected on a SitePro wireless device.

RESULTS

Patient disposition. Of the 1,947 patients screened, 1,025 patients (52.6%) were randomly assigned to receive placebo (n = 509) or milnacipran 100 mg/day (n = 516) (Figure 1). In total, 70.5% of patients randomized to receive placebo (359 of 509) and 69.2% of patients randomized to receive milnacipran 100 mg/day (357 of 516) completed the 12-week stable-dose phase of the study.

Baseline demographic and clinical characteristics. There were no notable differences in demographic or baseline clinical characteristics between the treatment groups (Table 1). The majority of patients were female (95.3%) and white (90.9%), and patients' mean duration of fibromyalgia symptoms was 10.8 years.

Efficacy. Primary efficacy end points in this study, as assessed using the 2- and 3-measure composite responder rates, showed that a significantly greater proportion of milnacipran-treated patients improved as compared with placebo-treated patients (Figures 2A and B).

Pain assessments (Table 2), using a variety of recall intervals on the PED, all showed significant improvements from baseline to week 12 following treatment with milnacipran relative to placebo. The proportions of patients with ≥30% and ≥50% decreases in the mean PED 24-hour recall pain score from baseline to end point were significantly greater in the milnacipran treatment group than in the placebo treatment group (Table 2). Pain outcome results were similar in the OC sensitivity analyses (all $P < 0.01$ versus placebo) (results not shown).

A significant reduction in mean pain scores in the milnacipran group compared with the placebo group was observed during the second week of the dose-escalation period (i.e., 25 mg twice daily) (Figure 3). This signifi-

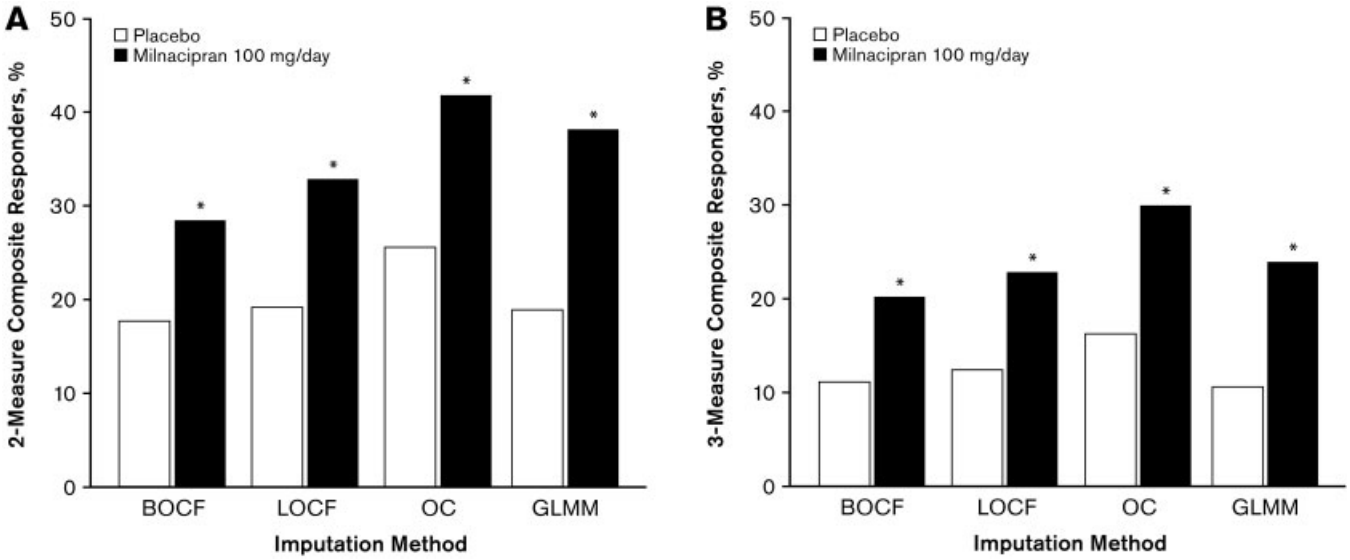

Figure 2. Composite response rates among patients receiving milnacipran 100 mg/day versus placebo, as determined in the baseline observation carried forward (BOCF) analysis, last observation carried forward (LOCF) analysis, an analysis based on observed cases (OC), and a generalized linear mixed model (GLMM), with the improvement response defined according to **A,** the 2-measure and **B,** the 3-measure composite response measures. Patients meeting 2-measure composite response criteria reported ≥30% improvement from baseline in 24-hour recall visual analog scale pain scores recorded in the patient experience diary and the Patient's Global Impression of Change scores ≤2. Patients meeting 3-measure composite response criteria reported these same improvements in pain and global status as well as a ≥6-point improvement from baseline in the Short Form 36 physical component summary score. ∗ = $P < 0.001$ versus placebo.

cant improvement was sustained through the end of the treatment period (week 12) ($P < 0.001$ versus placebo). Significant improvements from baseline in pain scores assessed as the mean change in VAS scores (determined on a SitePro instrument) and in BPI pain scores were found in milnacipran-treated patients compared with placebo-treated patients (Table 2).

At week 12, milnacipran-treated patients reported greater overall improvement on the PGIC as compared with that reported by placebo-treated patients (Table 2). Improvements in PGIC ratings were statistically significantly greater at every clinic visit after randomization to the milnacipran treatment group as compared with that after randomization to the placebo group ($P < 0.001$) (results not shown). The proportion of patients achieving the PGIC response criteria of scores ≤2 was significantly higher in the milnacipran group compared with the placebo group (Table 2). Similar results for PGIC were observed in the OC analysis (all $P < 0.001$ versus placebo) (results not shown).

SF-36 PCS response rates (i.e., percentage of patients with ≥6-point improvement in scores from baseline) were significantly higher in those treated with milnacipran compared with those treated with placebo (Table 2). At week 12, response rates for each SF-36 domain pertaining to physical health (i.e., patients reporting ≥5-point improvement in domain scores over baseline) were significantly improved in milnacipran-treated compared with placebo-treated patients (Table 2). Significant improvements in SF-36 MCS and FIQ total scores were also observed in milnacipran-treated compared with placebo-treated patients (Table 2). At week 12, results for the SF-36 and FIQ outcomes using the OC approach were similar to those obtained using the LOCF method (all $P < 0.05$ versus placebo) (results not shown).

At week 12, treatment with milnacipran 100 mg/day significantly reduced fatigue (for MFI total score, $P = 0.036$ versus placebo) and depressive symptoms (for BDI total score, $P = 0.008$ versus placebo). Both treatment groups showed improvements in anxiety symptoms, as determined on the BAI, but the improvement was statistically significantly greater in the placebo group. Treatment with milnacipran 100 mg/day was not associated with significant improvements in the MASQ total scores compared with that in the placebo group.

Tolerability and safety. TEAEs were reported in 382 (75%) of 509 placebo-treated patients and 434 (84.1%) of 516 milnacipran-treated patients. Most AEs

Table 2. Secondary and other efficacy outcomes (last observation carried forward) after 12 weeks of stable-dose treatment*

	Placebo (n = 509)	Milnacipran 100 mg/day (n = 516)	LS mean difference (95% CI)	*P*
Responders, no. (%)				
PED 24-hour recall pain score				
≥30% improvement from baseline	156 (30.6)	230 (44.6)	NA	<0.001
≥50% improvement from baseline†	92 (18.1)	143 (27.7)	NA	<0.001
PGIC, score ≤2	132 (25.9)	216 (41.9)	NA	<0.001
SF-36 score				
PCS, ≥6-point improvement from baseline	157 (30.8)	206 (39.9)	NA	0.001
Physical function domain‡				
Physical functioning	158 (31.0)	200 (38.8)	NA	0.005
Role limit—physical	156 (30.6)	193 (37.4)	NA	0.013
Bodily pain	149 (29.3)	207 (40.1)	NA	<0.001
General health perception	96 (18.9)	154 (29.8)	NA	<0.001
Time-weighted average of scores normalized by week, LS mean ± SEM AUC				
PED 24-hour recall pain score	48.31 ± 1.04	41.93 ± 1.04	−6.38 (−8.56, −4.19)	<0.001
PGIC score	3.49 ± 0.08	2.96 ± 0.08	−0.53 (−0.69, −0.38)	<0.001
SF-36 PCS score	36.20 ± 0.38	37.84 ± 0.38	1.65 (0.86, 2.44)	<0.001
PGIC score, LS mean ± SEM	3.53 ± 0.08	3.06 ± 0.08	−0.47 (−0.64, −0.29)	<0.001
Change in score from baseline, LS mean ± SEM				
PED VAS pain score				
24-hour recall pain	−10.76 ± 1.23	−17.70 ± 1.23	−6.94 (−9.53, −4.35)	<0.001
Weekly recall pain	−11.17 ± 1.30	−18.21 ± 1.30	−7.04 (−9.78, −4.31)	<0.001
Real-time pain	−8.94 ± 1.21	−15.62 ± 1.21	−6.68 (−9.22, −4.13)	<0.001
VAS pain score§				
24-hour recall pain	−12.83 ± 1.55	−19.96 ± 1.57	−7.13 (−10.41, −3.85)	<0.001
Weekly recall pain	−12.66 ± 1.56	−20.80 ± 1.58	−8.14 (−11.43, −4.85)	<0.001
BPI score				
Average pain severity	−0.81 ± 0.12	−1.46 ± 0.12	−0.65 (−0.90, −0.40)	<0.001
Pain interference	−0.91 ± 0.13	−1.49 ± 0.14	−0.58 (−0.86, −0.29)	<0.001
SF-36 score				
PCS	2.89 ± 0.42	4.62 ± 0.43	1.73 (0.84, 2.62)	<0.001
MCS	−0.50 ± 0.54	1.54 ± 0.54	2.04 (0.91, 3.17)	<0.001
Physical functioning	2.16 ± 0.44	3.98 ± 0.45	1.82 (0.89, 2.74)	<0.001
Role limit—physical	1.75 ± 0.47	3.43 ± 0.47	1.68 (0.70, 2.67)	<0.001
Bodily pain	2.87 ± 0.44	5.47 ± 0.44	2.60 (1.68, 3.52)	<0.001
General health perception	0.19 ± 0.43	1.85 ± 0.43	1.67 (0.76, 2.57)	<0.001
Energy/vitality	2.56 ± 0.56	4.43 ± 0.57	1.87 (0.69, 3.05)	0.002
Social functioning	2.04 ± 0.55	4.00 ± 0.55	1.96 (0.81, 3.11)	<0.001
Role limit—emotional	−1.28 ± 0.59	1.01 ± 0.60	2.29 (1.04, 3.53)	<0.001
Mental health	−0.18 ± 0.51	1.83 ± 0.51	2.00 (0.94, 3.07)	<0.001
FIQ score				
Total	−7.12 ± 1.08	−12.34 ± 1.09	−5.22 (−7.46, −2.98)	<0.001
Physical function	−0.17 ± 0.03	−0.27 ± 0.03	−0.10 (−0.17, −0.03)	0.005
MFI total score	−2.61 ± 0.77	−4.31 ± 0.77	−1.69 (−3.27, −0.11)	0.036
MASQ total score	−2.36 ± 0.77	−3.89 ± 0.77	−1.52 (−3.11, 0.06)	0.060
BDI total score	−1.24 ± 0.31	−2.12 ± 0.31	−0.89 (−1.54, −0.23)	0.008
BAI total score	−1.73 ± 0.40	−0.74 ± 0.40	0.99 (0.15, 1.82)	0.020

* LS = least squares; 95% CI = 95% confidence interval; PED = patient experience diary; NA = not applicable; PGIC = Patient's Global Impression of Change; PCS = physical component summary; AUC = area under the curve; VAS = visual analog scale; BPI = Brief Pain Inventory; MCS = mental component summary; FIQ = Fibromyalgia Impact Questionnaire; MFI = Multidimensional Fatigue Inventory; MASQ = Multiple Ability Self-Report Questionnaire; BDI = Beck Depression Inventory; BAI = Beck Anxiety Index.
† Responder status was determined without consideration of rescue medication use.
‡ Defined as patients with a ≥5-point improvement from baseline in the Short Form 36 (SF-36) Health Survey physical function domain scores.
§ Collected on a SitePro wireless device.

were mild to moderate in severity (92% mild-to-moderate in both the placebo and milnacipran treatment groups). AEs occurring in ≥5% of patients in either treatment group are listed in Table 3. The most common AE in both treatment groups was nausea (placebo-adjusted rate of 15.8%), which tended to be mild to

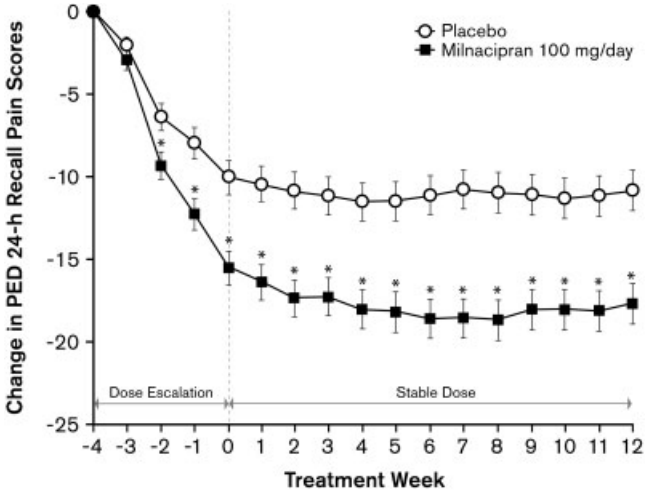

Figure 3. Least squares mean change from baseline in the average weekly patient experience diary (PED) 24-hour recall visual analog scale pain scores during the dose-escalation phase (4–6 weeks prior to week 0) and stable-dose phase (week 0 to week 12), determined in the last observation carried forward analysis. Week 0 is the start of the stable-dose period for all patients. Bars show the mean ± SEM. * = $P < 0.001$ versus placebo.

moderate in severity. Approximately 70% of the episodes of nausea in both treatment groups resolved within 3 weeks after onset (72.1% in the placebo group and 69.5% in the milnacipran group). AEs led to premature study discontinuation in 71 (13.9%) of 509 patients in the placebo group and 92 (17.8%) of 516 patients in the milnacipran group. Nausea was the only AE that led to study discontinuation in ≥2% of milnacipran recipients and that occurred at a higher incidence than in the placebo group (1.0% of the placebo group versus 3.5% of the milnacipran group). The proportion of patients experiencing serious AEs was comparable between the treatment groups (6 [1.2%] of 509 in the placebo group versus 8 [1.6%] of 516 in the milnacipran group). No deaths were reported during the study.

The effect of milnacipran on laboratory parameters was minimal. One milnacipran-treated patient discontinued the study because of a TEAE related to an abnormal laboratory result (fatigue associated with transient elevation in alanine aminotransferase and aspartate aminotransferase levels [<2 times the upper limit of normal]) after 6 weeks of stable-dose treatment. A second patient discontinued because of a serious AE of severe hyponatremia that occurred after milnacipran had been discontinued and after receiving hydrochlorothiazide for hypertension.

Changes in vital signs were determined from baseline to the end of the stable-dose phase at week 12. The mean supine systolic blood pressure (SBP) increased by 2.2 mm Hg in milnacipran-treated patients compared with a decrease of 2.5 mm Hg in the placebo group. The mean supine diastolic blood pressure (DBP) increased from baseline by 2.7 mm Hg in the milnacipran group compared with a decrease of 1.1 mm Hg in the placebo group. The mean change from baseline in supine heart rate was an increase of 7.0 beats per minute (bpm) for the milnacipran group compared with a decrease of 0.5 bpm for the placebo group. Potentially clinically significant increases in supine SBP (≥180 mm Hg, with an increase of ≥20 mm Hg from baseline) were noted in 3 (0.6%) of 509 milnacipran-treated patients and 1 (0.2%) of 503 placebo-treated patients. Potentially clinically significant increases in supine DBP (≥110 mm Hg, with an increase of ≥15 mm Hg from baseline) were likewise noted in 3 (0.6%) of 509 milnacipran-treated patients versus 1 (0.2%) of 503 placebo-treated patients. Potentially clinically significant increases in supine heart rate (≥120 bpm, with an increase of ≥20 bpm from baseline) were noted in 1 (0.2%) of 509 milnacipran-treated patients and no placebo-treated patients. Low incidences of sustained supine SBP (≥140 mm Hg, with a ≥20 mm Hg increase from baseline on at least 3 consecutive visits) and DBP (≥90 mm Hg, with a ≥10 mm Hg increase from baseline on at least 3 consecutive visits) were observed in both treatment groups (for SBP, 0.2% in the placebo group versus 0.4% in the milnacip-

Table 3. Treatment-emergent adverse events (TEAEs) reported in ≥5% of patients in either treatment group*

Adverse event	Placebo (n = 509)	Milnacipran 100 mg/day (n = 516)
Any TEAE	382 (75.0)	434 (84.1)
Nausea	106 (20.8)	189 (36.6)
Headache	80 (15.7)	92 (17.8)
Constipation	20 (3.9)	76 (14.7)
Hot flush	18 (3.5)	56 (10.9)
Dizziness	26 (5.1)	54 (10.5)
Insomnia	41 (8.1)	51 (9.9)
Hyperhidrosis	7 (1.4)	40 (7.8)
Palpitations	15 (2.9)	38 (7.4)
Fatigue	22 (4.3)	31 (6.0)
Tachycardia	5 (1.0)	28 (5.4)
Hypertension	5 (1.0)	27 (5.2)
Dyspepsia	31 (6.1)	25 (4.8)
Diarrhea	26 (5.1)	23 (4.5)
Upper respiratory tract infection	27 (5.3)	19 (3.7)

* Values are the number (%) of patients experiencing TEAEs in the dose-escalation and stable-dose phases.

ran group; for DBP, 0.2% in the placebo group versus 1.6% in the milnacipran group).

Patients completing 3 months of treatment with milnacipran tended to lose weight (average decrease of 2.0 lb over 3 months), in contrast to patients receiving placebo (average increase of 0.2 lb over 3 months). A potentially clinically significant increase (≥7%) from baseline in body weight occurred in 20 (4.0%) of 503 placebo-treated patients compared with 9 (1.8%) of 509 milnacipran-treated patients. A potentially clinically significant decrease (≥7%) in body weight from baseline was reported in 8 (1.6%) of 503 placebo-treated patients compared with 26 (5.1%) of 509 milnacipran-treated patients.

DISCUSSION

At the end of the 12-week stable-dose phase of this randomized, double-blind, placebo-controlled trial, a significantly greater proportion of patients treated with milnacipran monotherapy at 100 mg/day (50 mg twice daily) than those treated with placebo met the response criteria for improvement according to the 2-measure (decreased pain and improved global status) and 3-measure (decreased pain, improved global status, and improved physical function) composite response indices. The results of this trial are consistent with those of 2 previous pivotal studies of milnacipran using the same composite response criteria (6,7). Use of the composite responder definition in these studies allows for an assessment of clinically meaningful improvements across multiple symptom and function domains in individual patients.

One distinguishing feature of this study and other clinical trials of milnacipran in fibromyalgia (6,7) is the inclusion of the SF-36 PCS in the primary composite responder analysis. For the 3-measure composite responder analysis, the SF-36 PCS was chosen as a measure of physical function, because scores on the physical function subscale of the FIQ did not correlate with changes in pain, global status, or other functional status measures (26). Recently, a revised version of the FIQ has been developed in an attempt to correct some of the problems of the original version, such as outdated wording, omissions, sex bias, and scoring problems (27). The new FIQ contains complete revisions of several domains to reflect the relative importance of function in assessing the overall impact of fibromyalgia on functional ability and the overall impact of fibromyalgia on the perception of reduced function. Importantly, the revised FIQ physical function domain was most highly correlated with the SF-36 physical functioning subscale as well as with the pain score.

Several secondary outcomes provided additional information about the effect of milnacipran on the pain associated with fibromyalgia. Compared with patients receiving placebo, those receiving milnacipran demonstrated significant improvement on VAS 24-hour and weekly recall pain scores, average BPI pain severity and interference scores, and the SF-36 bodily pain scale. On the basis of the results reported for a variety of recall intervals on the PED, milnacipran was observed to significantly reduce pain when assessed by all recall measures (real-time, daily, and weekly). Statistically significant differences in the reduction of mean pain scores with milnacipran treatment as compared with placebo were detected at week 2 of the double-blind dose-escalation phase; this improvement was sustained through the end of the treatment period.

Fatigue is one of the most common symptoms associated with fibromyalgia and is sometimes rated by fibromyalgia patients as more disabling than pain (3). Notably, as one of the multiplicity-controlled secondary outcomes in this study, and consistent with previous trials of milnacipran in fibromyalgia (6,7), fatigue was significantly improved with milnacipran compared with placebo, as measured by the self-reported MFI and the energy/vitality domain of the SF-36. Compared with placebo, milnacipran also significantly improved depressive symptoms, an important symptom domain often reported by patients with fibromyalgia (5). Both treatment groups showed improvements in anxiety symptoms, but the improvement in BAI scores was statistically significantly greater in the placebo group. However, it should be noted that 8 of the 21 items in the BAI instrument are accepted side effects of milnacipran administration, which could provide an explanation for the statistically significant difference between the groups. These side effects include numbness or tingling (paresthesias), feeling hot (hot flush, flushing), dizziness or lightheadedness, heart pounding/racing (palpitations, tachycardia), hands trembling (tremor), difficulty in breathing (dyspnea), face flushed, and hot/cold sweats (hyperhidrosis).

Cognition, another common symptom domain, did not significantly improve with milnacipran treatment when evaluated using a self-report questionnaire assessing perceived cognitive problems (the MASQ). These results differ from those in previous trials, in which treatment with a higher dosage of milnacipran 200 mg/day (100 mg twice daily) led to significant improvements in cognitive function after 3 and 6 months of

treatment (6,7). More studies using structured cognitive testing in addition to self-report measures are needed to assess further the cognitive function of patients with fibromyalgia and the response of cognitive symptoms to treatment.

Patients with fibromyalgia often report substantial impairment in several areas of physical and mental function (3). In addition to the primary outcome responder definition for efficacy that included a clinically meaningful change in physical function, other measures of function that significantly improved with milnacipran compared with placebo included scores on the SF-36 PCS, SF-36 MCS, and SF-36 domains (physical function, physical role limitations, social function, emotional role limitations, mental health, and general health), as well as the FIQ total and FIQ physical function scores. At end point, milnacipran-treated patients reported greater overall improvement in global status (on the PGIC) compared with placebo-treated patients. These results suggest that milnacipran has benefits for patients with fibromyalgia that extend beyond symptom relief and include improvements in function and health-related quality of life.

A "start low, go slow" dosing strategy may minimize the risk of AEs and improve compliance in patients receiving fibromyalgia medications (28,29). Milnacipran dosing in this study was escalated to 100 mg/day over a 4–6-week period, depending on patient tolerability. This flexible dose-titration schedule was more gradual than was used in the 2 previous trials of milnacipran in patients with fibromyalgia (6,7), in which escalation to milnacipran 100 mg/day occurred over a 2-week period. Milnacipran was tolerated by most of the patients in the present study. The proportion of milnacipran-treated patients (17.8%) compared with placebo-treated patients (13.9%) who withdrew from the study due to AEs was somewhat less than was reported in the 2 previous pivotal fibromyalgia trials of milnacipran, in which about twice as many patients in the 50 mg twice daily group withdrew from the studies due to AEs as compared with the placebo group (6,7). Although the incidences of nausea and other TEAEs in this study were generally similar to previously reported data, the overall TEAE incidence rates do not reflect severity or other factors that might contribute to discontinuation.

Consistent with the previous trials of milnacipran, the most common AE was nausea, which was reported by most patients to be mild to moderate in severity. Notably, the majority of patients (~70%) in both the milnacipran and placebo groups experienced resolution of the nausea within 3 weeks after onset. Taking milnacipran with food and slowly escalating the dose may decrease nausea (30).

Milnacipran treatment was associated with mean increases in supine SBP of 2.2 mm Hg, supine DBP of 2.7 mm Hg, and supine heart rate of 7.0 bpm. Potentially clinically important increases in supine SBP, DBP, or heart rate occurred in <1% of patients receiving milnacipran. These results are consistent with the findings in other trials of milnacipran in fibromyalgia (6,7). Based on the fibromyalgia clinical trial data related to milnacipran treatment, it is recommended that blood pressure and heart rate be measured prior to initiating treatment with milnacipran and periodically throughout treatment with milnacipran (8).

Many patients with fibromyalgia are overweight and sedentary, and recent studies suggest that obesity in patients with fibromyalgia is associated with increased dysfunction (31,32). Similar to the previous fibromyalgia trials, the mean baseline body mass index for the participants in this trial was ~31 kg/m^2, which exceeds the World Health Organization threshold for obesity (33). Notably, 5.1% of milnacipran-treated patients experienced a ≥7% decrease from baseline in body weight compared with 1.6% of placebo-treated patients, and 1.8% of milnacipran-treated patients had a ≥7% increase from baseline in body weight compared with 4.0% of placebo-treated patients. The weight changes in this study are consistent with those from the 3-month (7) and 6-month (6) pivotal trials, as well as those from the 6-month extension of the 6-month pivotal trial (34).

Several limitations of this study should be considered. First, the results are based on a stable-dose treatment duration of 12 weeks, and the results may not be generalizable to a longer duration of treatment. However, previously reported results in patients with fibromyalgia who received 12 months of continuous treatment with milnacipran indicate that its effects on pain and other symptoms are durable (34). Second, the study results may not be generalizable to all patients with fibromyalgia because of the study-entry criteria used. For example, individuals with a current major depressive episode, some other forms of psychopathology, comorbid pain disorders, and certain medical problems were excluded from the study. Furthermore, patients receiving disability compensation were excluded, and before enrollment, patients were required to discontinue medications used to treat fibromyalgia, which may have excluded patients with more severe fibromyalgia. However, the mean duration of fibromyalgia in this patient population was ~10 years, and patients had

moderate-to-severe levels of pain and dysfunction at baseline.

In summary, results from the 12-week stable-dose phase of this randomized, placebo-controlled trial of 100 mg/day (50 mg twice daily) of milnacipran monotherapy confirms previous findings that treatment with milnacipran improves pain, global status, physical and mental function, and fatigue in patients with fibromyalgia and is tolerated by most patients.

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