



Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): A 6-month, double-blind, placebo-controlled trial with pregabalin

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Abstract

This was a multicenter, double-blind (DB), placebo-controlled, randomized discontinuation trial to evaluate the efficacy of pregabalin monotherapy for durability of effect on fibromyalgia (FM) pain. The trial included a 6-week open-label (OL) pregabalin-treatment period followed by 26-week DB treatment with placebo or pregabalin. Adults with FM and ≥ 40 -mm score on 100-mm pain visual analog scale (VAS) were eligible. During OL weeks 1–3, patients received escalating dosages of pregabalin to determine their optimal dosages. During OL weeks 4–6, patients received their optimal fixed dosages (300, 450, 600 mg/d). To be randomized, patients must have had $\geq 50\%$ decrease in pain VAS and a self-rating of “much” or “very much” improved on Patient Global Impression of Change (PGIC) at the end of OL. Double-blind treatment was with placebo or the patient’s optimal fixed dosage of pregabalin. Primary outcome was time to loss of therapeutic response (LTR), defined as $<30\%$ reduction in pain (from OL baseline) or worsening of FM. A total of 1051 patients entered OL; 287 were randomized to placebo, 279 to pregabalin. Time to LTR was longer for pregabalin versus placebo ($P < .0001$). Kaplan–Meier estimates of time-to-event showed half the placebo group had LTR by Day 19; half the pregabalin group still had not lost response by trial end. At the end of DB, 174 (61%) placebo patients met LTR criteria versus 90 (32%) pregabalin patients. Pregabalin was well tolerated, though 178 (17%) discontinued during OL for treatment-related adverse events (AE), and more pregabalin than placebo patients discontinued for AEs during DB. In those who respond, pregabalin demonstrated durability of effect for relieving FM pain.

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1. Introduction

Fibromyalgia (FM) is a common condition that causes significant morbidity and disability [32]. The treatment of FM has been focused primarily on relieving

pain, its cardinal symptom. However, the frequent presence of associated symptoms render improvement of fatigue, sleep disturbance, and function important for overall treatment effectiveness as well [20].

The analgesic action of pregabalin is mediated by its ability to bind with high affinity to the α_2 - δ subunit of voltage-gated calcium channels in CNS tissues [10]. Pregabalin acts as a presynaptic modulator of excessive release (in hyperexcited neurons) of excitatory

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neurotransmitters, including glutamate, noradrenaline, substance P, and calcitonin gene-related peptide [5,30].

Multiple authors (e.g., as reviewed by Staud [29]) have suggested that central sensitization plays an important role in the pathology of FM. Similarly, there is strong evidence that central sensitization is involved in neuropathic pain syndromes [2,3]. Based on the likelihood of such a shared pathway and the efficacy of pregabalin (Lyrica®) for treating neuropathic pain [7,11,17,23–25,28,31], a clinical program for treatment of pain associated with FM was undertaken. The results of a randomized, placebo-controlled, 8-week trial comparing pregabalin 150, 300, and 450 mg/d (TID) with placebo in 529 patients with FM showed that 450 mg/d pregabalin significantly improved pain, disturbed sleep, fatigue, Patient and Clinical Global Impression of Change (PGIC, CGIC) and several domains of health-related quality of life (HRQoL) [4]. Pregabalin was generally well tolerated, and although dizziness and somnolence were common, particularly at higher dosages, these adverse events (AEs) were typically mild to moderate in intensity.

The current trial was designed to assess durability of the beneficial effect of pregabalin (300, 450, or 600 mg/d [BID]) in those patients who have initial improvement in both PGIC and pain related to FM and who tolerated the medication over an additional 26-week period of time. Pregabalin was also evaluated for its ability to sustain improvements in patients' impression of their overall health status, sleep disturbance, fatigue, and functional status and for its safety.

2. Methods

2.1. Overview

The fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM) trial was a multicenter, double-blind (DB), placebo-controlled, randomized discontinuation trial conducted in 4 phases. During the 1-week baseline phase, patients were evaluated for inclusion/exclusion criteria. Physical examinations, clinical chemistry, hematology, urinalysis, pregnancy testing, electrocardiogram, and an abbreviated neurologic examination were conducted. This was followed by an open-label (OL), 6-week treatment phase to find each patient's optimal dosage as described below. Patients meeting response criteria at the end of the OL treatment phase were eligible for the 26-week, DB treatment phase into which they were randomized to placebo or to remain at their optimal dosage of pregabalin. Following the DB treatment phase, there was a 1-week follow-up visit.

The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki (Revised Edinburgh, 2000), Institutional Review Boards/Independent Ethics Committees, informed consent regulations, International Conference on Harmonisation Good Clinical Practices guidelines, and US FDA regulations at 95 centers in the US. Patients were informed of all aspects of the trial, and written informed consent was obtained.

2.2. Prohibited medications

Patients who had taken potential retinotoxins, including thioridazine, vigabatrin, hydroxychloroquine, and deferoxamine, were excluded. Because the trial evaluated patients' response to pregabalin monotherapy for relief of FM-associated pain and disturbed sleep, medications used to treat pain or insomnia were discontinued prior to the screening visit. Prohibited pain medications included but were not limited to: skeletal muscle relaxants, tricyclic anti-depressants, selective and multiple reuptake inhibitors, anti-epileptic drugs, steroids, benzodiazepines, narcotic analgesics, mexiletine, anti-Parkinson medications, tramadol, dextromethorphan, non-steroidal anti-inflammatory drugs. Prohibited insomnia medications included but were not limited to: benzodiazepines, zolpidem, diphenhydramine, melatonin. Required medication washout periods were at least 1–7 days, depending on drug class (fluoxetine required a 30-day washout), and no tender point injections were permitted within 1 month of screening. Patients were allowed to take up to 4 g/d acetaminophen, as needed, during the trial.

2.3. Key inclusion criteria

Male and female (non-pregnant, non-lactating; if not postmenopausal, using an appropriate method of contraception) patients aged ≥ 18 years were eligible. Patients were required to meet 1990 American College of Rheumatology criteria for FM (widespread pain for ≥ 3 months and pain in ≥ 11 of 18 tender points) [34], and they must have scored their pain over the previous week as ≥ 40 mm on the 0–100-mm pain visual analog scale (pain VAS) at screening and baseline visits. The pain VAS is a horizontal line 100 mm in length. It is self-administered by the subject in order to rate pain over the prior week from 0 “no pain” to 100 “worst possible pain”; the range of scores is 0–100 [13].

2.4. Key exclusion criteria

Patients with conditions that could confound assessment of FM symptoms, with severe depression or other severe psychiatric or severe medical conditions that made entry into a clinical trial inappropriate in the judgment of the investigator, or who had previously participated in a pregabalin clinical trial were excluded. Because pregabalin clearance is directly proportional to creatinine clearance (CL_{cr}) [22], patients with $CL_{cr} \leq 60$ mL/min were excluded, as were patients with other abnormal laboratory values, or clinically relevant abnormal 12-lead electrocardiograms. Patients with pending or settled worker's compensation, civil litigation, or disability claims pertinent to the patient's FM were also excluded.

2.5. Open-label phase procedures

Patients who met entry criteria were enrolled in the 6-week OL phase to evaluate their response to pregabalin monotherapy. During the first 3 weeks of OL, patients' optimal pregabalin dosage (300, 450, or 600 mg/d, BID) was established by escalating from 150 mg/d, BID, based on pain control and tolerability, using a flexible dosage-escalation

schedule. Investigators were given a decision tree on dosage optimization to standardize-escalation procedures among sites. After 3 days of treatment with 150 mg/d, dosage was escalated to 300 mg/d for 4 days. Patients who could not tolerate this dosage (at Day 7) were withdrawn; those who had good pain relief and tolerability remained on 300 mg/d for the remainder of the trial; and those who had inadequate pain relief but good tolerability were increased to 450 mg/d. After 7 days of treatment at 450 mg/d, patients unable to tolerate this dosage (at Day 14) were reduced to 300 mg/d; those with good pain relief and tolerability remained at 450 mg/d; and those with inadequate pain relief but good tolerability were escalated to 600 mg/d. After 7 days at 600 mg/d, patients unable to tolerate this dosage (at Day 21) were decreased to 450 mg/d; those with good pain relief and good tolerability remained at 600 mg/d; and those with inadequate pain relief but good tolerability were withdrawn for lack of efficacy. During the last 3 weeks of OL treatment, all patients still in the trial received pregabalin at their optimal fixed dosages.

Visits occurred weekly during OL treatment. At each weekly visit, prior to interaction with the investigators, patients were asked to place a mark at the position on the 100-mm pain VAS that best described their pain during that past week and to describe any change they had experienced since beginning study medication by checking the appropriate box (1. very much improved; 2. much improved; 3. minimally improved; 4. no change; 5. minimally worse; 6. much worse; 7. very much worse) on the Patient Global Impression of Change (PGIC).

2.6. Double-blind phase entry criteria

As the trial was designed to assess the durability of response to pregabalin monotherapy, only those patients who were responders to pregabalin at the conclusion of the 6-week OL treatment phase were eligible for the 26-week DB phase. Responders were identified by 2 criteria: $\geq 50\%$ reduction in pain VAS score from OL baseline and a self-rating of overall improvement on the PGIC scale of “much improved” or “very much improved.” Both these criteria were required to have been met at week 4 or 5 and also at week 6. Those who completed the OL, but did not meet responder criteria, were assessed as non-responders and were ineligible to enter the DB phase of the trial.

2.7. Double-blind study procedures

A telorandomization system randomized responders to either matching placebo or optimal OL dosage of pregabalin (1:1). Patients randomized to placebo were tapered off pregabalin treatment during the first week of DB in a blinded manner. The 600 and 450 mg/d groups had 2 days at 450 mg/d, 2 days at 300 mg/d, 2 days at 150 mg/d, and then placebo. Taper to placebo for the 300 mg/d group consisted of 2 days at 150 mg/d before receiving placebo. After the randomization visit (visit 8, week 6), patients had a scheduled visit at week 8 and every 4 weeks thereafter through week 32. At each visit, patients were administered a battery of instruments to evaluate efficacy and were assessed for AEs.

2.8. Determination of sample size

The maintenance of response rate was estimated to be 35% for patients on placebo and 50% for patients treated with pregabalin. Approximately 220 patients per group randomized to the DB maintenance phase would provide 90% power to detect at least a 15% difference in rates between the 2 treatment groups at 6 months ($\alpha = 0.05$, two-sided), assuming no dropouts prior to 6 months other than for loss of therapeutic response (LTR) events. Assuming 15% of patients would discontinue before LTR or completion of the DB trial, 510 randomized patients would be required, and 1020 patients would need to be enrolled into the OL phase.

2.9. Primary efficacy analysis

The primary and secondary efficacy analyses were performed on the intent-to-treat population (ITT), defined as all patients who were randomized at the end of the OL treatment phase. All inferential testing was analyzed as time-to-event. Patients who completed the 6-month DB phase or who withdrew prior to LTR were censored (i.e., were considered to not have had an LTR) at their last observation. ITT patients with no post-baseline observations were included but were censored at Day 1. Sensitivity analyses used different censoring rules to test various assumptions.

The primary efficacy parameter was time to LTR, measured in days, and defined as having either $<30\%$ reduction in pain VAS score relative to OL baseline value at 2 consecutive visits of the DB phase (the first of the two visits defined the time to LTR; the second was for confirmation) or worsening, in the judgment of the investigator, of FM symptoms necessitating alternate treatment. The 30% threshold was set as the reduction in pain that is clinically meaningful [9]. Patients who met either criterion for LTR were discontinued. Patients who had $<30\%$ reduction in pain VAS at one visit but not at the second confirmatory visit were allowed to continue treatment.

Because patients were randomized to their optimal dosages attained during the OL treatment phase, the primary comparison was of all pregabalin patients versus all placebo patients. The primary statistical analysis was performed using a Kaplan–Meier Survival Analysis with time to LTR as the response of interest. Kaplan–Meier estimates of the time to LTR were compared using the log-rank statistic obtained from SAS Proc Lifetest [27]. The trial would be considered positive if the test was significant in favor of pregabalin at $\alpha = .05$ level (two-sided). Events were censored at 28 days after last dose of study medication (to ensure that while drug was still possibly present in patients' systems, AEs would be reported and collected), and patients who discontinued DB treatment for reasons other than LTR were censored. As supplemental analyses, each pregabalin dosage group was compared individually with its corresponding placebo group. All analyses were prespecified.

2.10. Sensitivity analyses

Six sensitivity analyses were performed to confirm the findings of the primary analysis. They considered

1. All patients who withdrew early to have had LTR, regardless of reason for withdrawal. *Assumption:* censored patients were at high risk for LTR.
2. All patients who withdrew early to have maintained pain relief as long as anyone else in the trial. *Assumption:* censored patients were at low risk for LTR.
3. All patients who withdrew early due to AEs to have had LTR rather than being considered censored. *Assumption:* occurrence of an AE represented an LTR.
4. All patients with a <30% reduction in pain relative to baseline to have had LTR at the first such visit, regardless of response at confirmatory visit. *Assumption:* first evidence of LTR constituted LTR.
5. All patients who withdrew before Day 8 to be censored. *Assumption:* early withdrawals represented unblinding as patients tapered to placebo.
6. All patients who withdrew because of worsening of FM to be censored, unless lack of 30% response was also demonstrated based on DB pain VAS scores for the same visit. *Assumption:* objective evidence of LTR required.

2.11. Post hoc sensitivity analyses

Two additional sensitivity analyses were performed post hoc to account for possible unblinding as patients transitioned from open-label treatment to double-blind treatment

1. All patients who withdrew before Day 15 were considered censored. *Assumption:* early withdrawals represented unblinding as patients tapered to placebo.
2. All patients who had dizziness and somnolence during open-label treatment for whom these effects did not resolve prior to entering double-blind treatment were censored. *Assumption:* dizziness and somnolence are the most commonly reported AEs associated with pregabalin treatment, so patients who experienced such AEs throughout the OL period could become unblinded after assignment to placebo if these AEs then resolved.

2.12. Secondary efficacy analyses

Analyses of secondary endpoints compared time to worsening of these endpoints between pregabalin and placebo patients during the DB phase. If a response on these parameters was established in the OL phase, this analysis would determine the difference in loss of this response between patients treated with pregabalin and those who received placebo. Comparisons were based on the log-rank statistic. All randomized patients were evaluated for time to worsening of these secondary parameters, as defined below, regardless of whether they had primary LTR:

- PGIC (evaluates patients' impression of their overall health status): indicating less improvement than "much improved."
- Fibromyalgia Impact Questionnaire (FIQ, measures aspects of pain, symptoms of disturbed mood, and functioning [1]): 5-point increase from DB baseline for FIQ

Total and 1-point change from DB baseline for each subscale depending on the directionality of the subscale (Dunkl et al. suggested that a 1-point change in subscale scores represented a meaningful difference [6]).

- Medical Outcomes Study (MOS)–Sleep Scale (evaluates multiple aspects of patients' sleep profile as well as their overall sleep problems): 8-point change from DB baseline for each subscale (with exception of Sleep Quantity and Optimal Sleep subscales) and total score depending on directionality of the subscale. (Wolfe et al. suggested that standard error of the measurement [SEM] is a reasonable approximation of minimally important clinical difference [MCID] [33]. In their study of the MOS–Sleep Scale applied to patients with rheumatoid arthritis, SEMs for the subscales ranged from 7.3 to 14.4.)
- Multidimensional assessment of fatigue (MAF, a global index of fatigue): 10-point change from DB baseline on Global Fatigue Index. (Kherani et al. identified a score of 10.4 as being the MCID for worsening of fatigue in patients with rheumatoid arthritis [14].)
- Short-Form 36 Health Survey (SF-36 describes patients' assessment of their physical and mental health and their ability to fulfill roles): 5-point decrease from DB baseline for each subscale. (Hays and Morales cite a 3- to 5-point change in subscale scores as MCID based on a review of the literature by Samsa et al. [12,26].)

Safety was assessed in all patients who took at least one dose of study medication by review of AE information via non-specific questioning and spontaneous reporting, vital signs, physical examination, abbreviated neurologic examination, and clinical laboratory evaluations. During DB treatment, adverse events were defined as those AEs that either were not reported during the OL phase or that were reported in the OL phase and worsened during DB treatment. No inferential safety analyses were planned.

3. Results

3.1. Patients

A total of 1777 patients were screened; 1051 entered OL treatment. Reasons for failing screening included inability to comply with visit schedule, inability or unwillingness to wash out prior pain medication, and laboratory results outside of protocol limits. Of these, 663 completed OL treatment, and 566 met the 2 responder criteria and elected to continue in the trial. Of patients who were randomized to DB treatment, 55/287 (19%) who were assigned to placebo completed the trial, while 107/279 (38%) patients assigned to continue pregabalin treatment completed the trial. Proportions of completers by dosage were 48% of 300 mg/d, 33% of 450 mg/d, and 37% of 600 mg/d. Reasons for discontinuation are displayed in Fig. 1.

The majority of patients who entered the OL phase were female (93%) and white (88%). Mean age at OL

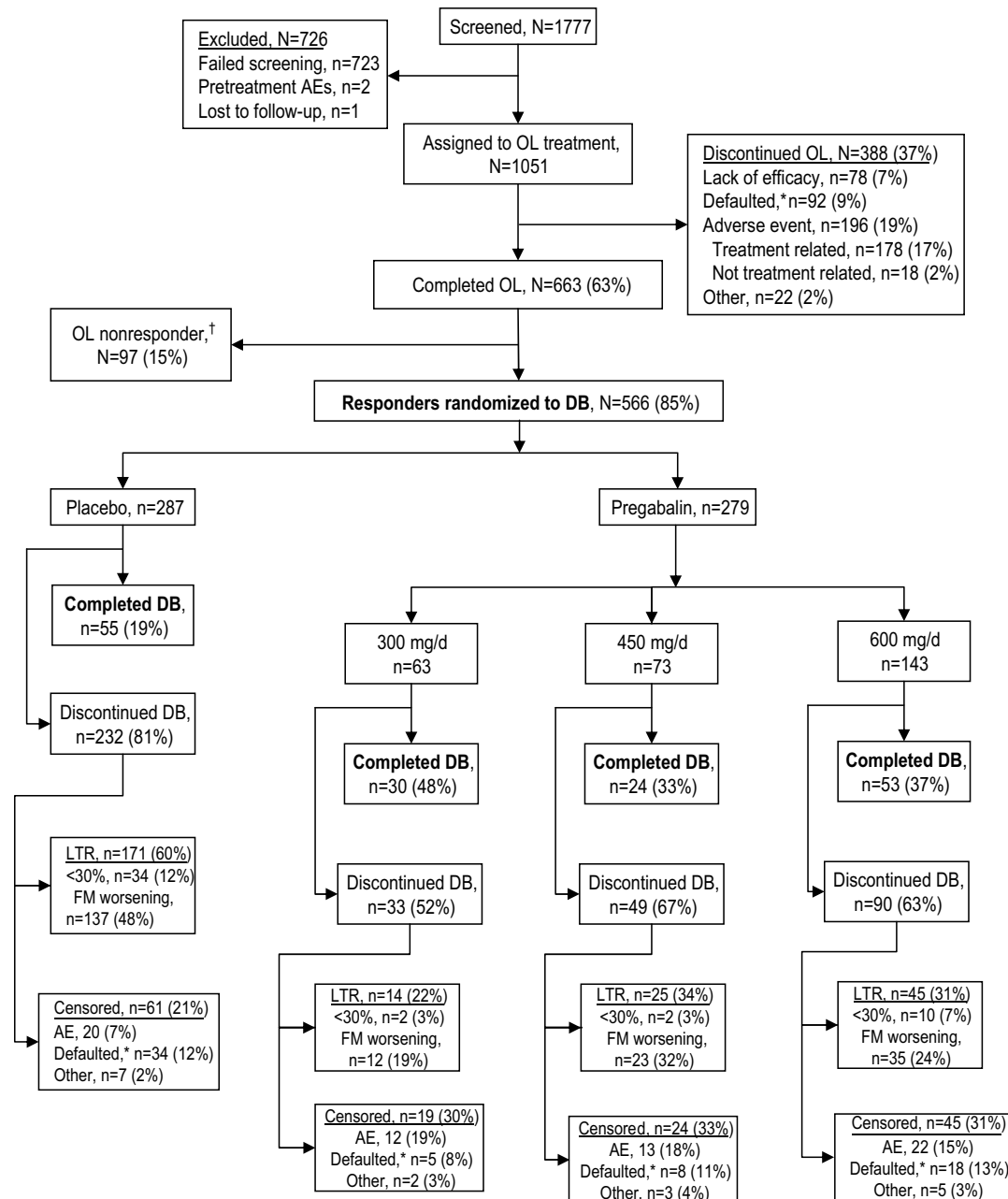


Fig. 1. Patient disposition. LTR, loss of therapeutic effect, defined as <30% improvement from baseline in mean pain VAS score or as worsening FM such that alternate treatment was required. *Discontinuations due to withdrawn consent or lost to follow-up. †Patients completing OL but who did not demonstrate either a $\geq 50\%$ improvement from BL in pain VAS score or a “much” or “very much” improved rating on the PGIC. These patients were not randomized.

baseline was 49.5 years. There were no meaningful differences in demographic characteristics between those who entered OL treatment and those who were randomized to DB treatment, nor were there meaningful differences between the treatment groups (Table 1). At the start of the trial, 985 patients (94%) had ongoing medical conditions as identified by their medical histories taken prior to entering open-label treatment. The 3 most frequently reported comorbidities at baseline were

hypertension (299 patients [29%]), insomnia (295 patients [28%]), and depression (269 patients [26%]).

Baseline FM-related characteristics were also similar between the placebo and pregabalin treatment groups and across the pregabalin dosage groups. Patients' FM duration was longstanding, with a median of 7.8 years. For at least half of patients, pain was present in all 18 tender points. Baseline pain VAS score was 78 mm. Baseline scores on all secondary efficacy

Table 1
Patients' open-label and double-blind demographic and baseline characteristics

	Treatment period					
	6-week OL phase		26-week DB phase			
	Pregabalin, <i>n</i> ^b = 1051	Placebo, <i>n</i> ^b = 287	Pregabalin 300 mg/d, <i>n</i> ^b = 63	Pregabalin 450 mg/d, <i>n</i> ^b = 73	Pregabalin 600 mg/d, <i>n</i> ^b = 143	Pregabalin all, <i>n</i> ^b = 279
Female, <i>n</i> (%)	982 (93%)	270 (94%)	60 (95%)	69 (95%)	130 (91%)	259 (93%)
Race, <i>n</i> (%)						
White	927 (88%)	252 (88%)	56 (89%)	68 (93%)	130 (91%)	254 (91%)
Black	52 (5%)	11 (4%)	3 (5%)	3 (4%)	3 (2%)	9 (3%)
Other	72 (7%)	24 (8%)	4 (6%)	2 (3%)	10 (7%)	16 (6%)
Age, years						
Mean (SD)	49.5 (11.6)	49.6 (10.5)	49.6 (12.2)	49.0 (12.7)	48.4 (11.4)	48.8 (11.9)
Range	18–78	22–77	18–78	25–71	19–74	18–78
18–44 years	334 (32%)	88 (31%)	21 (33%)	27 (37%)	53 (37%)	101 (36%)
45–64 years	623 (59%)	181 (63%)	36 (57%)	36 (49%)	82 (57%)	154 (55%)
≥65 years	94 (9%)	18 (6%)	6 (10%)	10 (14%)	8 (6%)	24 (9%)
Duration of FM, months						
Mean (SD)	123.3 (100.5)	114.0 (90.2)	118.0 (101.0)	123.8 (96.1)	135.8 (120.5)	128.7 (110.2)
Median	93	91	90	93	97	92
Range	3 to 668	4 to 420	8 to 523	7 to 403	4 to 668	4 to 668
Number of painful tender points ^a						
Mean (SD)	17.1 (1.7)	17.2 (1.6)	16.7 (2.2)	17.0 (2.1)	17.2 (1.5)	17.0 (1.8)
Median	18.0	18.0	18.0	18.0	18.0	18.0
Range	8–18	9 to 18	8 to 18	8 to 18	12 to 18	8 to 18
Pain VAS score, mean (SD)	78.0 (14)	14.8 (10.7)	14.5 (10.0)	14.1 (12.5)	16.0 (10.5)	15.1 (10.9)
FIQ Total score, mean (SD)	66.9 (13.6)	23.5 (14.0)	23.3 (12.6)	22.1 (14.9)	26.8 (15.1)	24.8 (14.6)
MOS-Sleep scale Overall Sleep Problems Index, mean (SD)	65.1 (16.0)	24.7 (16.4)	24.9 (13.6)	23.9 (16.2)	26.1 (16.2)	25.2 (15.6)
MOS-Sleep scale Sleep Disturbance	66.4 (23.4)	18.6 (20.2)	18.5 (17.2)	15.8 (18.7)	20.4 (21.8)	18.7 (20.1)
MAF Global Fatigue Index, mean (SD)	38.7 (7.2)	19.3 (8.9)	19.0 (8.6)	20.1 (9.7)	20.2 (9.6)	19.9 (9.4)
SF-36 Physical Component, mean (SD)	29.6 (8.0)	43.0 (8.6)	44.2 (8.0)	42.9 (10.2)	43.0 (8.2)	43.2 (8.7)
SF-36 Mental Component, mean (SD)	38.0 (12.7)	52.6 (9.9)	51.8 (11.0)	53.6 (10.3)	50.7 (11.0)	51.7 (10.8)

^a At screening (visit 1), all patients met the entry criterion for number of painful tender points. The data reported in this table reflect those collected at OL baseline (visit 2). The number is missing if any of 18 tender points is missing.

^b Although “*n*” was not always 100% for some parameters, in almost all cases where this applied, “*n*” was generally within 1–2% and did not deviate by more than 7%.

parameters were similar between the OL, placebo, and pregabalin groups and across the pregabalin dosage groups (Table 1).

3.2. Primary efficacy measure: time to LTR

During the 6-month, DB treatment phase, time to LTR was significantly longer for patients treated with pregabalin than for patients receiving placebo ($P < .0001$). Based on Kaplan–Meier estimates of time-to-event, 25% of patients who received placebo had LTR by Day 7 (95% CI = 5–9), compared with by Day 34 (95% CI = 21–48) for all pregabalin-treated patients (Table 2). Half the placebo group had LTR by Day 19 (95% CI = 14–36), whereas, by the end of the trial, more than half the pregabalin group still had not lost response (Fig. 2). By the end of DB, 174 placebo-treated (61%) and 90 pregabalin-treated patients

(32%) experienced an LTR (see note to Table 2). The robustness of the findings of the primary analysis was confirmed by 6 prespecified sensitivity analyses, each of which showed a significantly ($P < .0001$) longer time to LTR for pregabalin patients than for placebo patients (Table 3).

Two additional sensitivity analyses performed post hoc to account for possible unblinding as patients transitioned from open-label to double-blind treatment confirmed the superiority of pregabalin to placebo. In the first sensitivity analysis, patients who withdrew by Day 15 were considered censored along with the censored patients in the primary analysis. In this analysis, 25% of the placebo-treated patients had LTR by Day 42 compared with by Day 126 for pregabalin. The log-rank test showed a significantly longer time to LTR for pregabalin ($P = .0021$). In the second analysis, patients whose dizziness or somnolence did not resolve prior to

Table 2
Summary of Kaplan–Meier estimates of time to loss of therapeutic response (LTR) by treatment group

	Time to LTR, days (95% CI)		P-value comparison with placebo	Patients with LTR by end of DB, n (%)
	1st quartile	Median		
All placebo, N = 287	7 (5–9)	19 (14–36)		174 ^a (61)
All pregabalin, N = 279	34 (21–48)	NA	<.0001	90 ^a (32)
Dosage group comparisons				
Placebo, n = 63	4 (3–12)	15 (12–26)		42 (67)
Pregabalin 300 mg/d, n = 63	122 (42–NUL)	NA	<.0001	14 (22)
Placebo, n = 77	7 (5–13)	15 (14–42)		50 (65)
Pregabalin 450 mg/d, n = 73	25 (14–45)	NA (48–NUL)	=.0001	28 (38)
Placebo, n = 147	7 (5–13)	35 (15–85)		82 (56)
Pregabalin 600 mg/d, n = 143	26 (17–45)	NA	<.0001	48 (34)

Abbreviations: NUL, no upper limit; CI, confidence interval.

^a The numbers of patients withdrawn due to a loss of therapeutic response presented in Fig. 1 are 171 and 84, for placebo- and pregabalin-treated patients, respectively. In this table, the numbers are 174 and 90, respectively. The Kaplan–Meier analysis presented in this table captured all patients who experienced an LTR, whether or not the LTR was indicated accurately on the End of Study Case Report Form. Specifically, 3 patients from the placebo group and 6 from the pregabalin group who had an LTR – and are, therefore, included in the data in this table – were discontinued for other reasons.

entering double-blind were censored. Pregabalin again showed significantly longer time to LTR ($P < .0001$). The 25th percentiles were 7 days for placebo and 42 days for pregabalin. (Note that for the primary analysis, the 25th percentiles were 7 days for placebo and 34 days for pregabalin.)

When the individual pregabalin fixed-dosage groups of 300, 450, and 600 mg/d were compared with their corresponding placebo groups, each pregabalin treatment group was associated with a significantly longer time to LTR than placebo (Table 2). The most dramatic difference in time to LTR between pregabalin- and pla-

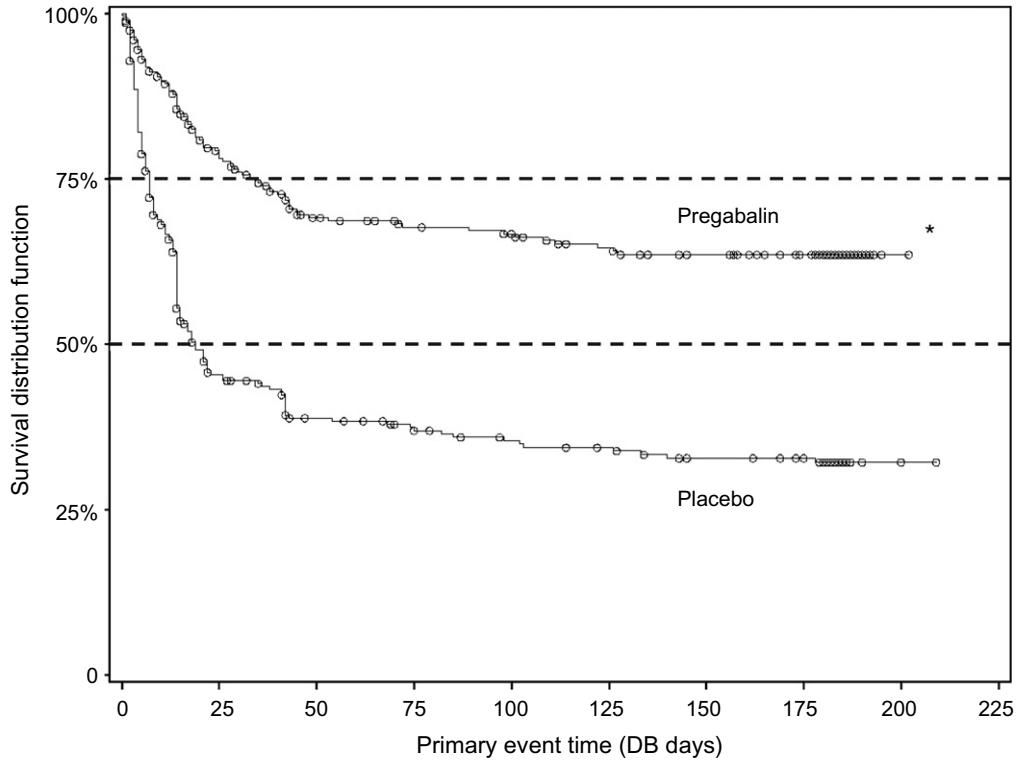


Fig. 2. Kaplan–Meier plot of time (in days) to loss of therapeutic effect. Open circles [O] indicate censored patients. *Comparison (log-rank test) with placebo, $P < .0001$.

Table 3
Summary of Kaplan–Meier estimates of time to loss of therapeutic response: six sensitivity analyses

Secondary definition	N	Time to LTR (days)		P-value (all pregabalin versus placebo)	Patients with LTR by end of DB, n	Censored, ^a n (%)
		1st quartile (95% CI)	Median (95% CI)			
(1) All patients who withdrew early had an LTR						
Placebo	287	6 (4–7)	14 (14–18)	<.0001	235	52 (18.1)
Pregabalin	279	18 (14–25)	71 (45–114)		180	99 (35.5)
(2) All patients who withdrew early maintained pain relief						
Placebo	287	7 (5–10)	22 (17–42)	<.0001	174	113 (39.4)
Pregabalin	279	38 (25–101)	NA		90	189 (67.7)
(3) All patients who withdrew due to an AE had an LTR						
Placebo	287	6 (5–8)	17 (14–22)	<.0001	191	96 (33.5)
Pregabalin	279	24 (18–35)	158 (101–NUL)		132	147 (52.7)
(4) All patients with <30% reduction in pain VAS in reference to V2 had an LTR at first such visit (i.e., no confirmatory finding required)						
Placebo	287	7 (6–10)	15 (14–20)	<.0001	194	93 (32.4)
Pregabalin	279	21 (15–34)	192 (126–NUL)		125	154 (55.2)
(5) All patients who withdrew before Day 8 were censored						
Placebo	287	15 (14–19)	85 (42–NUL)	<.0001	97	190 (66.2)
Pregabalin	279	71 (38–NUL)	NA		66	213 (76.3)
(6) All patients who withdrew because of worsening of FMS were censored <i>unless</i> confirmed by pain VAS						
Placebo	287	14 (14–41)	NA (178–NUL)	<.0001	83	204 (71.1)
Pregabalin	279	NA	NA		28	251 (90.0)

Abbreviations: NUL, no upper limit; CI, confidence interval.

^a An LTR event was not recorded.

Table 4
Summary of Kaplan–Meier estimates of time to loss of therapeutic response (lack of improvement or worsening) in secondary endpoints

Secondary efficacy parameter	Time to LTR (days)		P-value comparison with placebo	Patients with LTR by end of DB, n	Censored, ^a n (%)
	1st quartile (95% CI)	Median (95% CI)			
PGIC					
Placebo, N = 287	14 (NA)	20 (15–35)	<.0001	177	110 (38.3)
Pregabalin, N = 279	25 (17–42)	126 (77–NUL)		128	151 (54.1)
FIQ Total score ^b					
Placebo, N = 287	14 (13–14)	14 (NA)	<.0001	248	39 (13.6)
Pregabalin, N = 279	14 (NA)	19 (15–41)		214	65 (23.3)
MOS-Sleep scale Overall Sleep Problems Index ^c					
Placebo, N = 287	14 (13–14)	14 (NA)	<.0001	235	52 (18.1)
Pregabalin, N = 279	14 (14–15)	42 (41–43)		191	88 (31.5)
MAF					
Placebo, N = 287	14 (NA)	27 (16–42)	<.0001	161	126 (43.9)
Pregabalin, N = 279	19 (14–37)	119 (69–155)		137	142 (50.9)
SF-36 Physical component ^d					
Placebo, N = 287	14 (NA)	15 (14–19)	<.0001	201	86 (30.0)
Pregabalin, N = 279	14 (14–16)	49 (42–71)		160	119 (42.7)
SF-36 Mental component ^d					
Placebo, N = 287	14 (13–14)	14 (14–15)	<.0001	219	68 (23.7)
Pregabalin, N = 279	14 (NA)	42 (41–43)		191	88 (31.5)

^a An LTR event not reported.

^b Analysis of each of the 10 subscales of the FIQ showed significant benefit ($P < .0001$) for pregabalin treatment over placebo.

^c Analysis of 5 additional subscales of the MOS-Sleep Scale showed significant benefit for pregabalin treatment over placebo (all $P \leq .0003$) for 4 of these subscales, including Sleep Disturbance.

^d The Physical and Mental components of the SF-36 are derived values from the instrument's 8 subscales. The Physical component includes the Physical Functioning, Role-Physical, Bodily Pain, and General Health subscales, while the Mental component includes the Vitality, Social Functioning, Role-Emotional, and Mental Health subscales. Analysis of each of the 8 subscales showed significant benefit ($P < .0001$) for pregabalin treatment over placebo.

cebo-treated patients was seen in the 300 mg/d pregabalin group.

3.3. Secondary evaluations

As with the primary analysis, evaluations of secondary endpoints were based on comparisons between all pregabalin patients and all placebo patients. All secondary efficacy endpoints demonstrated statistically significantly greater time to LTR for pregabalin compared with placebo (Table 4). On the PGIC, half of all placebo patients were no longer reporting improvements of “much improved” or “very much improved” by Day 20, while half of pregabalin patients showed a similar loss of response on Day 126 ($P < .0001$). Median time to worsening of FIQ total score was significantly longer for pregabalin (Day 19) versus placebo (Day 14, $P < .0001$). Similarly, half of placebo patients showed worsening in the Overall Sleep Problems Index of the

MOS-Sleep Scale by Day 14 compared with by Day 42 for pregabalin patients ($P < .0001$). On the MAF, worsening occurred by Day 27 in half the placebo patients compared with by Day 119 in half the pregabalin patients ($P < .0001$). Compared with those receiving placebo, patients treated with pregabalin showed significantly longer times to worsening of the SF-36 Health Survey's Physical and Mental component scores: Day 49 and Day 42 for the pregabalin group versus Day 15 and Day 14 for the placebo group ($P < .0001$ for each comparison).

3.4. Acetaminophen use

Acetaminophen was permitted as a rescue medication, and use of acetaminophen was recorded during the trial. Mean (standard deviation) daily acetaminophen dose was numerically but not statistically significantly greater in subjects who received placebo during

Table 5
Most common^a treatment-emergent adverse events, all causality

Open-label phase					
Adverse event	Pregabalin, N = 1051 (%)				
Dizziness	378 (36)				
Somnolence	230 (22)				
Headache	148 (14)				
Weight increase	113 (11)				
Dry mouth	83 (8)				
Peripheral edema	82 (8)				
Fatigue	74 (7)				
Vision blurred	74 (7)				
Balance disorder	68 (7)				
Disturbance in attention	67 (6)				
Nausea	66 (6)				
Euphoric mood	65 (6)				
Constipation	56 (5)				
Increased appetite	43 (4)				
Double-blind phase ^b					
Adverse event	Placebo, n = 287 (%)	Pregabalin 300 mg/d, n = 63 (%)	Pregabalin 450 mg/d, n = 73 (%)	Pregabalin 600 mg/d, n = 143 (%)	All pregabalin, n = 279 (%)
Insomnia	18 (6)	5 (8)	2 (3)	9 (6)	16 (6)
Nausea	13 (5)	4 (6)	5 (7)	5 (4)	14 (5)
Anxiety	5 (2)	3 (5)	3 (4)	8 (6)	14 (5)
Arthralgia	5 (2)	3 (5)	5 (7)	6 (4)	14 (5)
Sinusitis	8 (3)	1 (2)	4 (6)	9 (6)	14 (5)
Influenza	3 (1)	3 (5)	3 (4)	7 (5)	13 (5)
URTI	7 (3)	4 (6)	1 (1)	6 (4)	11 (4)
Weight increase	1 (<1)	1 (2)	3 (4)	6 (4)	10 (4)
Headache	9 (3)	3 (5)	1 (1)	5 (4)	9 (3)
Peripheral edema	2 (1)	2 (3)	3 (4)	3 (2)	8 (3)
Fatigue	3 (1)	3 (5)	2 (3)	3 (2)	8 (3)
Diarrhea	15 (5)	3 (5)	2 (3)	2 (1)	7 (3)
Nasopharyngitis	11 (4)	2 (3)	1 (1)	4 (3)	7 (3)
Bronchitis	3 (1)	3 (5)	0	2 (1)	5 (2)
Vomiting	4 (1)	3 (5)	0	1 (1)	4 (1)
Migraine	1 (<1)	1 (2)	3 (4)	0	4 (1)

^a Occurring in at least 4% of patients.

^b AE reports in the DB period represent new onset or change in intensity of previously reported AEs as of randomization.

DB treatment compared with those who received pregabalin: 243 (513) mg/d versus 165 (498) mg/d.

3.5. Safety

All 1051 patients who met inclusion criteria and were assigned to OL treatment received at least one dose of study drug and were analyzed for safety. Of these, 863 (82%) reported one or more AE. The most frequently reported AEs during the OL treatment phase were dizziness (36%), somnolence (22%), headache (14%), and weight increased (11%, Table 5). Most (93%) of the 2923 treatment-emergent AEs reported during OL treatment were mild or moderate in intensity, as determined by the investigators. A total of 196 patients (19%) withdrew from the OL phase due to AEs, and, of these, the AEs leading to withdrawal were considered severe in 70 patients.

Of 566 patients randomized into the DB treatment phase, 129 (45%), 37 (59%), 46 (63%), and 89 (62%) in the placebo, 300, 450, and 600 mg/d pregabalin groups, respectively, experienced a treatment-emergent AE, with 82% of these events having maximum intensity of mild or moderate. AEs led to withdrawal in the DB phase for 20 (7%), 12 (19%), 13 (18%), and 22 (15%) of the placebo, 300, 450, and 600 mg/d groups. The most common AEs in the pregabalin treatment group were insomnia (6%), sinusitis, nausea, arthralgia, anxiety, and influenza (each 5%), upper respiratory tract infection (URTI, 4%), and weight increased (4%, Table 5). Placebo rates for these AEs were insomnia, 6%; sinusitis, 3%; nausea, 5%; arthralgia, 2%; anxiety, 2%; influenza, 1%; URTI, 3%; and weight increased, <1%.

During the OL phase, treatment-emergent serious AEs (SAEs) were experienced by 8 (0.8%) patients. In the DB phase, 11 patients had SAEs, of which 3 (1%) had been receiving placebo and 8 (2.9%) pregabalin (one patient received 300 mg/d and 7 received 600 mg/d). Two patients in the trial died. One patient who had been receiving placebo died on Day 47 of DB treatment because of a severe pulmonary embolism. One patient treated with pregabalin died due to severe acute lobar pneumonia 28 days after the DB phase ended. None of the SAEs, including these deaths, were considered associated with study drug.

3.6. Clinical laboratory tests and other safety measures

Median changes from OL baseline to end of OL treatment did not indicate clinically important changes in clinical laboratory values. Three patients were withdrawn during OL treatment for laboratory AEs (MedDRA preferred terms: hemoglobin decreased, hepatic enzyme increased, CL_{cr} decreased). No patient was withdrawn for laboratory AEs during the DB treatment phase. There were few clinically significant changes in

vital signs from OL baseline to end of OL treatment. These included 2 patients (0.2%) with decreases in sitting systolic blood pressure (<90 and decrease from baseline ≥ 30 mm Hg), 6 patients (0.6%) with weight decrease ($\geq 7\%$ less than baseline), and 59 patients (6.3%) with weight increase ($\geq 7\%$ greater than baseline). There were no clinically significant physical examination findings or neurologic examination findings.

4. Discussion

Fibromyalgia is an important cause of pain, fatigue, reduced quality of life, and disability. Treatment is challenging. This trial, which encompassed up to 32 weeks of treatment, incorporated a novel design as applied to trials in fibromyalgia to evaluate the durability or maintenance of response with pregabalin treatment relative to placebo. A trial enriched for responders with placebo-controlled discontinuation has been used in many studies of long-duration where retention of patients was of high priority to the question being posed, and high dropout rates for the placebo arm were of concern (such a design is commonly used in patients with juvenile arthritis). In this case, the hypothesis to be tested was that therapeutic response would persist longer in patients taking an individually-determined optimal dose of pregabalin compared with patients receiving placebo. Long-duration, placebo-controlled, parallel-group studies of patients with chronic pain are not commonly performed, and it was determined that the present study design had a higher likelihood of determining durability of therapeutic response while allowing a reasonable sample size and maintaining power to determine differences between groups. Survival analysis as an analytical method has been applied to multiple therapeutic indications, and this approach lends itself well to evaluating the durability of a predetermined level of response to treatment.

In the OL treatment phase, our findings demonstrate that more than half of patients (566/1051) completed 6 weeks of treatment with pregabalin and realized at least a 50% improvement in their pain VAS scores coupled with an overall impression (as evaluated by the PGIC) of their health as having been “much” or “very much” improved. It should be noted that a significant number of FM patients entering the OL treatment phase either did not tolerate or did not respond (according to the predefined criteria) to treatment with pregabalin. However, the baseline pain scores of patients in this monotherapy trial could be described as severe: mean OL baseline pain VAS score was 78 mm (out of 100), a value corresponding with cutpoints established for a similarly valid 0–10 numeric pain rating scale (0–3, mild pain; 4–6, moderate pain; 7–10, severe pain) [8,35].

In pregabalin responders, the data addressing the durability of beneficial response were highly positive.

Patients treated with pregabalin had significantly delayed time to LTR versus those receiving placebo. The robustness of this primary finding was confirmed by each of 8 sensitivity analyses, 2 of which were post hoc analyses to account for possible unblinding as patients transitioned from open-label to double-blind treatment, demonstrating significant superiority of pregabalin over placebo. Using the strictest definition of LTR – that every patient who discontinued for any reason was considered to have an LTR event – pregabalin remained statistically significantly superior to placebo. Additionally, though the primary analysis evaluated all pregabalin-treated patients as a single dosage group, supplemental analyses by fixed-dosage group (300, 450, 600 mg/d) demonstrated significantly longer time to LTR for each pregabalin dosage compared with placebo. Comparison of the pregabalin dosage groups was not undertaken, as this was not a dose-response trial and as patients were randomized to receive their optimal pregabalin dosage (as established during OL treatment) rather than being randomized to a predetermined fixed dosage.

Fibromyalgia encompasses a constellation of symptoms, which includes sleep disturbance and fatigue in addition to pain and impairment of HRQoL [21]. As secondary efficacy measures, the current trial included LTR on the PGIC, FIQ, MOS-Sleep scale, MAF, and SF-36 Health Survey. On each of these measures, pregabalin was associated with a significantly longer time to worsening than was placebo. These data demonstrate that, in addition to the durability of effect for maintaining improvement in pain, the effect of pregabalin to improve multiple important symptom domains of FM, including sleep, fatigue, functioning, and sense of overall health, is durable over time.

Pregabalin was generally well tolerated during both OL and DB treatment phases, and the AE profile of the OL phase is consistent with that observed in previous randomized, placebo-controlled trials of pregabalin in neuropathic pain syndromes and in FM [4,7,11,17,23–25,28,31]. However, as with many other therapies in this condition, a sizeable number of FM patients do not tolerate pregabalin. In the OL treatment phase, 19% discontinued due to AEs, and during the DB phase, 16% of pregabalin compared with only 7% of patients receiving placebo discontinued due to AEs. Patients who completed the 6-week OL treatment and responded to pregabalin were tolerating the drug well and thus did not have a high incidence, during DB treatment, of AEs typically observed in *de novo* pregabalin patients.

4.1. Study limitations

This trial was conducted largely at institutional centers. It excluded patients with medical (including psychiatric) conditions that could interfere with the assessment

of FM-associated pain, and it excluded patients with conditions that could make their participation in a clinical trial a risk to them. It also prohibited a large number of medications. Finally, it excluded individuals with pending or settled disability or legal claims related to FM. These factors could compromise the generalizability of these findings to typical clinical practice.

By design, this was an enrichment trial, such that only responders to OL pregabalin treatment were randomized. Inherent in such a trial design, as described by Leber and Davis [16], is the possibility of carryover effects from, in this case, the 6-week OL treatment phase, that could “unblind” patients to the treatment they were receiving when converted to placebo. The OL treatment phase was 42 days long, and patients assigned to placebo were tapered off pregabalin during the first week of DB treatment. In the one FM trial of pregabalin that has been published [4], the median times to onset of dizziness and somnolence – the 2 AEs most commonly associated with pregabalin – were 1 day or less, while the median durations of dizziness were 4 days (150 mg/d), 6 days (300 mg/d), and 15 days (450 mg/d) and of somnolence 31 days (150 mg/d), 21 days (300 mg/d), and 18 days (450 mg/d). It is not unreasonable to surmise that most patients treated with pregabalin for 6 weeks would not have had meaningful carryover AEs that may have effectively unblinded them on entering double-blind. Prespecified sensitivity analysis 5 (see above), which assumed all early withdrawals (by Day 8) represented unblinding as patients tapered to placebo, confirmed the statistical significance of the superiority of pregabalin to placebo for delaying time to LTR, despite the possibility of unblinding. Further, the 6 prespecified sensitivity analyses were supplemented by 2 additional sensitivity analyses performed post hoc to account for possible unblinding due to the AE profile of pregabalin. In the first of these analyses, patients who withdrew by Day 15 were considered censored. In the second, all patients who experienced dizziness or somnolence (the 2 most commonly reported AEs associated with pregabalin) during open-label treatment that did not resolve prior to entry into double-blind treatment were censored. Both these analyses confirmed the superiority of pregabalin to placebo.

The issue of placebo response is important in all randomized-controlled trials, as trials provide a powerful context surrounding treatment [15]. Placebo responses may be particularly important in studies where pain is a primary outcome, as chronic pain is among the symptoms most influenced by the placebo effect [15]. As reviewed by Koshi and Short, plausible hypotheses to explain placebo responses in studies of chronic pain include engagement of endogenous opioid systems due to expectation of benefit and activation of dopaminergic neurons related to expectation of reward [15]. The placebo effect can also be quite durable, lasting years in

some studies [18,19]. In this study, there was clearly a durable placebo effect, with 55 patients who received placebo completing the DB treatment phase. Still, the difference in durable response significantly favored pregabalin in all sensitivity analyses. Regarding the other cause of unblinding in an enrichment trial design, namely, loss of efficacy, the objective of this trial was to determine the durability of patients' response to pregabalin, and time to loss of therapeutic response, i.e., of efficacy, was the primary outcome measure.

Finally, as the non-responder rate was 15% and the rate of discontinuations attributable to AEs was 19% in the OL treatment phase, findings from this enriched population may not be generalizable to the broader FM population. However, this study may provide an estimate of the durability of response in those patients in whom clinical efficacy and tolerability is provided by pregabalin.

4.2. Conclusions

Pregabalin, dosed at 300, 450, and 600 mg/d (BID), demonstrated a durable effect for maintaining patients' improvement in pain associated with FM as well as in measures of global assessment, sleep, fatigue, and functional status in those who respond to this treatment. Together with its demonstrated safety and tolerability, these long-term efficacy findings strongly suggest pregabalin represents an important new option for the treatment of FM.

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