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Investigation of the Clinical Efficacy and Safety of Pregabalin Alone or Combined With Tolterodine in Female Subjects With Idiopathic Overactive Bladder

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Aims: To assess the efficacy and safety of pregabalin alone or in combination with tolterodine extended release (ER) in subjects with idiopathic OAB. **Methods:** This 26-week, multicenter, randomized, double-blind, placebo-controlled, three-period crossover study enrolled women aged ≥18 years that were diagnosed with OAB and reported ≥8 micturitions/24 hr and ≥4 urgency episodes/week on 5-day bladder diary at baseline. Subjects were randomized to 1 of 10 treatment sequences and received three of five treatments, each for 4 weeks with 4-week washout periods: standard-dose pregabalin/tolterodine ER (150 mg twice daily [BID]/4 mg once daily [QD], n = 102), pregabalin alone (150 mg BID, n = 105), tolterodine ER alone (4 mg QD, n = 104), low-dose pregabalin/tolterodine ER (75 mg BID/2 mg QD, n = 105), and placebo (n = 103). Subjects completed 5-day diaries at the end of treatment and washout periods. The primary endpoint was change from baseline to week 4 in mean voided volume (MVV) per micturition. The primary comparison was standard-dose pregabalin/tolterodine ER versus tolterodine ER alone; secondary comparisons were pregabalin alone versus tolterodine ER alone and versus placebo. **Results:** Baseline-adjusted changes in MVV were significantly greater after treatment with standard-dose pregabalin/tolterodine ER (39.5 ml) versus tolterodine ER alone (15.5 ml; $P < 0.0001$), and with pregabalin alone (27.4 ml) versus tolterodine ER alone ($P = 0.005$) and placebo (11.9 ml; $P = 0.0006$). Treatments were generally well tolerated; discontinuation rates due to adverse events were 4%, 2%, 5%, 0%, and 1% with standard- and low-dose pregabalin/tolterodine ER, pregabalin, tolterodine ER, and placebo, respectively. **Conclusions:** Pregabalin, alone or with tolterodine ER may offer an alternative treatment option for idiopathic OAB in women. *Neurourol. Urodynam. 30:75–82, 2011.* © 2010 Wiley-Liss, Inc.

Key words: antimuscarinic; efficacy; lower urinary tract symptoms; overactive bladder; pregabalin; safety

INTRODUCTION

Overactive bladder (OAB), a prevalent and chronic condition that negatively affects health-related quality of life (HRQL),[1–3] is defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.[4,5] OAB is commonly attributed to detrusor overactivity.[6] Antimuscarinics, the mainstay of OAB therapy, are widely believed to act on the detrusor muscle and are generally well tolerated and effective in reducing OAB symptoms.[7,8] However, these medications may not alleviate symptoms in some patients, and can be associated with adverse effects (e.g., dry mouth) that limit use.[6,9]

Medications that treat detrusor overactivity via a mechanism of action that differs from that of antimuscarinics may be useful in treating OAB symptoms in subjects refractory to or intolerant of standard antimuscarinic therapy. It has been hypothesized that afferent C- and alpha-delta (αδ)-fiber sensory neurons in the bladder hyperstimulate the spinal reflex center responsible for controlling detrusor activity.[10] Gabapentin, an antiepileptic and analgesic, is a ligand of the α2δ subunit of the voltage-sensitive calcium channels involved in activation of afferent C and αδ fibers.[11] Preliminary clinical studies evaluating subjects with neurogenic detrusor overactivity or refractory idiopathic OAB have shown that gabapentin is effective in reducing OAB symptoms and/or improving urodynamic parameters.[10,12,13] Pregabalin is another antiepileptic and analgesic medication that is similar to gabapentin in its mechanism of action.[14] Although pregabalin and gabapentin have similar efficacy, pregabalin can be administered at considerably lower doses than gabapentin owing to its higher bioavailability, more rapid adsorption, and greater potency.[15] In preclinical OAB studies, pregabalin treatment resulted in marked increases in bladder capacity.[16,17] Moreover, synergism was observed in preclinical studies when pregabalin was combined with tolterodine, an antimuscarinic shown to improve OAB symptoms and HRQL in clinical trials of subjects with OAB,[18–20] suggesting that tolterodine and pregabalin may act independently to improve bladder control at therapeutic doses.[17]

The primary objective of this trial was to assess the efficacy and safety of pregabalin combined with tolterodine extended release (ER) versus tolterodine ER alone for the treatment of idiopathic OAB. Key secondary objectives were to evaluate the efficacy and safety of pregabalin alone versus tolterodine ER alone and placebo, and to assess whether pregabalin and tolterodine ER act synergistically.

MATERIALS AND METHODS

Subjects

Women aged ≥18 years recording urinary frequency of ≥8 micturitions on average per 24 hr, ≥4 episodes of urgency/week

Conflicts of interest: none.
Roger Dmochowski led the review process.
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(defined as a sudden and compelling desire to pass urine that is difficult to defer), and mean voided volume (MVV) <300 ml in a 5-day bladder diary before randomization were eligible to participate. Subjects with OAB symptoms for <6 months before study randomization, significant stress urinary incontinence, documented and untreated urinary tract infection, chronic persistent local lower urinary tract pathology, any relevant neurologic disease with which urinary symptoms could be associated, constipation (<3 bowel movements/week), or cystocele or other clinically significant pelvic prolapse were excluded from the study. Subjects with a mean total voided volume of >3,000 ml within 24 hr or postvoid residual volume of >200 ml were also excluded. Subjects with a history of pelvic radiotherapy, receiving bladder retraining within 3 months of screening, or requiring catheterization or assistance with toileting were excluded.

Study Design

This was a phase II, randomized, double-blind, placebo-controlled, three-period, five-treatment crossover study conducted between December 2005 and November 2006 at 22 sites in six countries (Czech Republic, n = 5 sites; Lithuania, n = 4; Norway, n = 3; Slovakia, n = 4; Sweden, n = 3; United Kingdom, n = 3). The protocol was approved by the appropriate ethics committee or institutional review board at each study site. Subjects provided written informed consent before study enrollment. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and local regulations.

The study comprised seven phases (Fig. 1). After completing a 4-week screening/washout phase, subjects were randomized to 1 of 10 sequences for 3 crossover treatment periods according to a computer-generated, pseudo-random code using the random permuted blocks method (Fig. 1). Each treatment period was separated by a 4-week washout. Following the last treatment period, subjects entered a 2-week follow-up phase for a total study duration of 26 weeks. Each subject received 3 of 5 possible medication regimens: combination standard-dose pregabalin/tolterodine ER (150 mg twice daily [BID]/4 mg once daily [QD]); pregabalin alone (150 mg BID); tolterodine ER alone (4 mg QD); combination low-dose pregabalin/tolterodine ER (75 mg BID/2 mg QD); and placebo. Pregabalin-containing regimens were up-titrated or down-titrated during treatment and subsequent washout periods, respectively; matched placebos were used to ensure blinding.

Efficacy Outcomes

Subjects completed 5-day bladder diaries before Visits 2–7. Diary data collected before Visits 2, 4, and 6 provided pretreatment baseline efficacy data for comparison with post-treatment data collected before Visits 3, 5, and 7, respectively. Data recorded during the last continuous 96 hr of the 5-day diary period were used to derive diary endpoints, including MVV (primary endpoint), urinary incontinence (UI) episodes per 24 hr, urgency episodes per 24 hr, urgency severity (rated on a scale of 1 [no urgency] to 5 [UI]), micturition frequency per 24 hr, and normalized micturition frequency (NMF; calculated by dividing 1,000 ml by the MVV for the 2-day period preceding the study visit).

Subjects completed the patient perception of bladder condition (PPBC), the eight-item overactive bladder questionnaire (OAB-q) Symptom Bother scale, and 13-item HRQL scale of the OAB-q short form (OAB-q SF) at Visits 2–7. The PPBC is a validated single-item measure of bladder-related problems that scores subject responses on a scale from 1 (no problems) to 6 (many severe problems).[21] The OAB-q Symptom Bother scale[22] assesses subject's perception of OAB symptom bother based on a response scale from 1 (no bother) to 6 (a very great deal of bother). The HRQL scale of the OAB-q SF[23] measures subject's perception of OAB symptom impact on HRQL on a response scale from 1 (no impact on HRQL) to 6 (impacts HRQL all of the time).

Safety Outcomes

Safety was assessed via the frequency and severity of all observed or volunteered treatment-emergent adverse events (AEs).

Statistical Analyses

Because the primary study endpoint was diary based and could be incomplete in some subjects, efficacy analyses included data from randomized subjects in the full analysis set who received ≥1 dose of study medication and recorded diary data for ≥2 days (MVV) or for ≥4 days (other diary endpoints) at baseline and Week 4 of ≥1 treatment period. The study was powered only on the primary endpoint (MVV) for the primary treatment comparison (standard-dose pregabalin/tolterodine ER vs. tolterodine ER alone) and secondary treatment comparisons (pregabalin alone vs. tolterodine ER alone and placebo). A 47-subject sample size was estimated to provide 80% power to detect a 15-ml (SD, 29 ml) treatment difference in MVV, at a one-sided 5% significance level. A total sample size of 170 was planned based on an assumed 30% dropout rate and because only 40% of subjects were randomized to receive any given combination of crossover treatments to be compared statistically. Treatment effects on MVV were analyzed as the baseline-adjusted change after 4 weeks of treatment using a mixed-effects model, with subject as a random effect and period and treatment as fixed effects.

Secondary endpoints were analyzed using similar methods as described for the primary endpoint, with nonparametric analyses performed as appropriate. For diary-based secondary endpoints, evaluable subjects were required to provide appropriate diary data for ≥4 days at both baseline and week 4 for ≥1 treatment period. For non-diary-based secondary endpoints, assessments were conducted at baseline and week 4.

The synergistic potential of the pregabalin/tolterodine ER combination was assessed via exploratory treatment comparisons of standard-dose pregabalin/tolterodine ER and low-dose pregabalin/tolterodine ER versus the combined effects of tolterodine ER alone and pregabalin alone. In another exploratory treatment comparison, the efficacy and safety of low-dose pregabalin/tolterodine ER was compared with that of tolterodine ER alone.

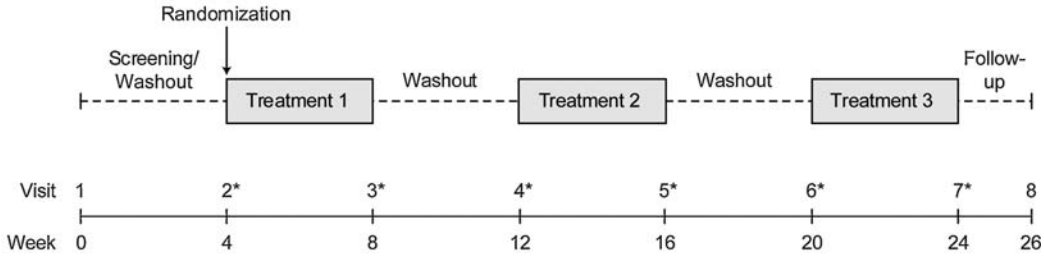
Safety analyses were conducted on all randomized subjects who received ≥1 dose of study medication.

RESULTS

Subjects

Subject disposition is shown in Figure 2. Of the 217 women screened, 188 were randomized and 186 received ≥1 treatment. The mean (SD) age of treated subjects was 52.9 (13.3) years; 54.8% of subjects (n = 102) reported incontinence at baseline.

A Study Design Overview



B Possible Treatment Sequences

Sequence Number	Treatment 1	Treatment 2	Treatment 3
1	Low-dose PGB/TER	TER alone	Standard-dose PGB/TER
2	TER alone	Placebo	PGB alone
3	Placebo	Standard-dose PGB/TER	Low-dose PGB/TER
4	Standard-dose PGB/TER	PGB alone	TER alone
5	PGB alone	Low-dose PGB/TER	Placebo
6	Low-dose PGB/TER	Standard-dose PGB/TER	Placebo
7	TER alone	PGB alone	Standard-dose PGB/TER
8	Placebo	Low-dose PGB/TER	PGB alone
9	Standard-dose PGB/TER	TER alone	Low-dose PGB/TER
10	PGB alone	Placebo	TER alone

Fig. 1. Study design. **A**: Schematic study design overview. Subjects received three of the five possible treatments during 4-week periods separated by 4-week washouts: standard-dose pregabalin/tolterodine extended release (PGB/TER; 150 mg BID/4 mg once-daily); low-dose PGB/TER (75 mg BID/2 mg once daily); PGB alone (150 mg twice daily); TER alone (4 mg once daily); and placebo. **B**: Possible treatment sequences.*Five-day bladder diary assessment.

Of the 186 subjects receiving ≥1 treatment, 164 completed all 3 randomized treatment regimens.

Efficacy

Primary and secondary treatment comparisons. A total of 178 subjects were included in the efficacy analyses. Mean improvement from baseline in MVV was significantly greater following treatment with standard-dose pregabalin/tolterodine ER versus tolterodine ER alone ($P < 0.0001$; Tables I and II). Treatment with pregabalin alone also resulted in a significantly greater improvement in MVV from baseline compared with tolterodine ER alone ($P = 0.005$) and placebo ($P = 0.0006$). These findings were consistent with secondary endpoint results showing significantly greater improvements in micturition frequency ($P = 0.009$), NMF ($P = 0.003$), OAB-q Symptom Bother score ($P = 0.005$), and OAB-q SF HRQL ($P = 0.012$) score with standard-dose pregabalin/tolterodine ER versus tolterodine ER alone. Treatment with pregabalin alone resulted in significantly greater improvements in NMF ($P = 0.028$) and OAB-q Symptom Bother score ($P = 0.002$) versus tolterodine ER alone, and significantly greater improvements in urgency severity ($P = 0.017$), micturition frequency ($P = 0.014$), NMF ($P = 0.006$), OAB-q Symptom Bother score ($P = 0.0003$), OAB-q SF HRQL score ($P < 0.0001$), and PPBC score ($P = 0.038$) versus placebo.

Exploratory treatment comparisons. Exploratory treatment comparisons of standard-dose and low-dose pregabalin/tolterodine ER versus tolterodine ER alone and pregabalin alone showed no significant synergistic effect for either pregabalin/tolterodine ER dose combination (Tables I and II). Treatment with low-dose pregabalin/tolterodine ER did not result in increased efficacy versus tolterodine ER alone for the primary endpoint of MVV ($P = 0.131$; Tables I and II).

Safety

The number of subjects experiencing treatment-emergent AEs was generally similar across treatment groups, with pregabalin-treated subjects reporting the highest number of AEs (Table III). Dry mouth and dizziness were the most frequently reported AEs, with the majority of AEs of mild to moderate severity. No serious AEs were reported during the course of the study. Twelve subjects reported an AE resulting in discontinuation from the study, the majority occurring during treatment with pregabalin alone (n = 5) or standard-dose pregabalin/tolterodine ER (n = 4). AEs most commonly resulting in study discontinuation included dizziness (n = 6) and headache (n = 4), including two subjects reporting both dizziness and headache.

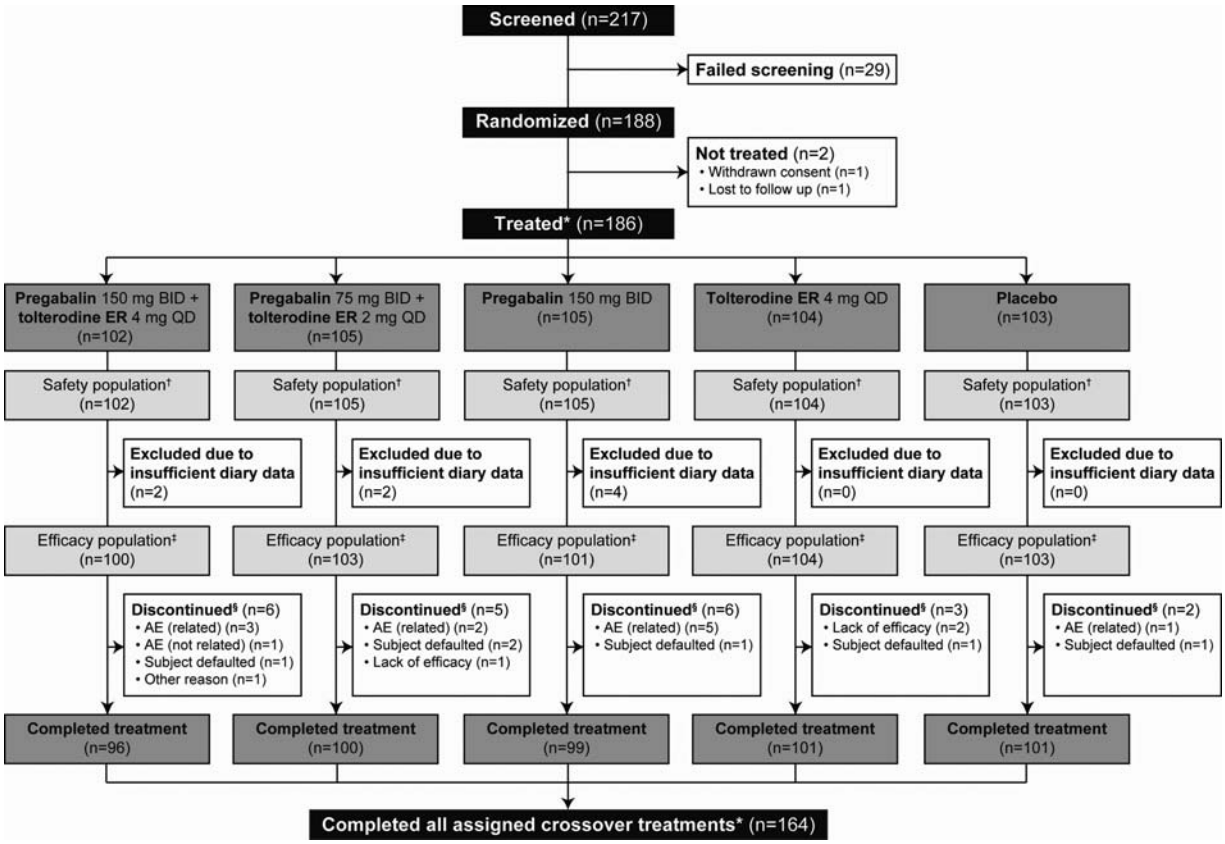


Fig. 2. Subject disposition. AE, adverse event; BID, twice daily; ER, extended release; QD, once daily. *Subjects received three of the five possible treatments. †Safety analyses were conducted on all randomized subjects who received ≥1 dose of study medication. ‡Efficacy analyses included data from all randomized subjects who received ≥1 dose of study medication and recorded diary data for ≥2 days (mean voided volume) or for ≥4 days (other diary endpoints) at baseline and Week 4 of ≥1 treatment period. §Discontinuations in the safety analysis population.

DISCUSSION

This is the first clinical study to our knowledge to assess the efficacy and safety of pregabalin for the treatment of OAB symptoms. The primary analysis showed a significant increase in the change from baseline in MVV for standard-dose pregabalin/tolterodine ER versus tolterodine ER alone after 4 weeks of treatment. Pregabalin alone also showed significantly greater improvement from baseline in MVV versus tolterodine ER alone and placebo. Primary endpoint outcomes were supported by improvements in other OAB symptoms and OAB-specific patient-reported outcomes. All active treatments were generally well tolerated, with no serious AEs reported throughout the study. Reports of dry mouth during all active treatments were not unexpected given that this is one of the most common AEs for both tolterodine ER and pregabalin.[14,24] Rates of dry mouth, dizziness, and total AEs tended to be higher with pregabalin and/or pregabalin/tolterodine ER than with tolterodine ER alone or placebo. It is not clear why the occurrence of dizziness was higher with pregabalin alone (n = 11) versus standard-dose pregabalin/tolterodine ER (n = 6); however, dizziness is a common AE during pregabalin use.[14] Furthermore, the incidence of dizziness in all pregabalin-treated groups was consistent with rates reported in other pregabalin studies.[14] Rates of discontinuation due to adverse events were 4% with standard-dose pregabalin/tolterodine ER treatment, 2% with low-dose pregabalin/tolterodine ER treatment, 5% with pregabalin treatment alone, 0% with tolterodine ER treatment alone, and 1% with placebo. Although discontinuation rates appear higher in pregabalin treatment groups, these rates are comparable to AE-related discontinuation rates reported in previous OAB studies evaluating the safety of antimuscarinic treatment,[18,25,26] and are based on relatively small numbers of patients in this study.

Findings of the present study, that standard-dose pregabalin treatment resulted in significantly greater baseline-adjusted improvements in MVV and micturition frequency relative to placebo, are consistent with results of preclinical OAB studies showing that pregabalin markedly increases bladder capacity[16,17] and clinical studies assessing the efficacy of gabapentin in subjects with OAB or detrusor overactivity.[10,12,13] Significantly greater baseline-adjusted improvements in MVV with standard-dose pregabalin (with or without tolterodine ER) versus tolterodine ER treatment alone further demonstrate the efficacy of pregabalin in this patient population. In addition, treatment with pregabalin also resulted in a significant reduction in urgency severity versus placebo. Although treatment with pregabalin did not result in a significant reduction in UI episodes relative to placebo, it is important to note that only half of the subjects enrolled in this study were incontinent at baseline, which resulted in a relatively low number of subjects being included in this analysis. Furthermore, studies with other agents, such as neurokinin-1 receptor antagonist aprepitant, have similarly demonstrated improvements in some bladder diary variables without improvement in UI episodes.[27] Longer-

TABLE I. Primary and Secondary Efficacy Endpoint Outcomes

	Treatment				
	Standard-dose PGB/TER (150 mg BID/4 mg QD)	Low-dose PGB/TER (75 mg BID/2 mg QD)	PGB alone (150 mg BID)	TER alone (4 mg QD)	Placebo
Primary endpoint					
Mean (SE) voided volume per micturition, ml					
N	95	95	97	101	99
Baseline	163.9 (6.7)	165.7 (6.1)	175.7 (6.7)	168.6 (5.3)	165.7 (5.5)
Change from baseline to week 4	39.5 (5.5)	20.4 (4.3)	27.4 (5.3)	15.5 (4.4)	11.9 (4.6)
Secondary endpoints					
Mean (SE) UI episodes per 24 hr					
N	37	47	41	51	50
Baseline	3.2 (1.2)	1.8 (0.3)	2.2 (0.5)	2.4 (0.4)	2.4 (0.4)
Change from baseline to week 4	−1.1 (0.5)	−0.5 (0.2)	−0.5 (0.4)	−1.1 (0.2)	−0.4 (0.2)
Mean (SE) urgency episodes per 24 hr					
N	96	97	94	101	98
Baseline	8.3 (0.5)	7.7 (0.4)	7.7 (0.4)	7.9 (0.4)	7.3 (0.4)
Change from baseline to week 4	−1.3 (0.4)	−0.9 (0.3)	−1.3 (0.2)	−1.0 (0.3)	−0.8 (0.3)
Mean (SE) severity of urgency episodes					
N	96	97	94	101	98
Baseline	2.5 (0.1)	2.5 (0.1)	2.5 (0.1)	2.5 (0.1)	2.5 (0.1)
Change from baseline to week 4	−0.16 (0.1)	−0.2 (0.05)	−0.2 (0.1)	−0.2 (0.05)	−0.1 (0.05)
Mean (SE) micturition frequency per 24 hr					
N	96	97	94	101	98
Baseline	10.6 (0.4)	10.2 (0.3)	10.2 (0.3)	10.4 (0.3)	10.0 (0.3)
Change from baseline to week 4	−1.3 (0.3)	−0.7 (0.2)	−1.0 (0.2)	−0.7 (0.2)	−0.3 (0.2)
Mean (SE) NMF					
N	95	93	94	101	98
Baseline	7.2 (0.3)	6.9 (0.3)	6.5 (0.3)	6.5 (0.2)	6.8 (0.3)
Change from baseline to week 4	−1.2 (0.2)	−0.7 (0.2)	−1.0 (0.2)	−0.5 (0.2)	−0.5 (0.2)
Mean (SE) OAB-q Symptom Bother scores					
N	96	99	98	101	99
Baseline	40.6 (2.0)	40.3 (1.7)	43.1 (2.1)	41.7 (2.0)	40.7 (2.2)
Change from baseline to week 4	−10.5 (1.6)	−9.4 (1.4)	−11.7 (1.7)	−6.1 (1.5)	−4.7 (1.4)
Mean (SE) OAB-q SF HRQL scores					
N	96	100	98	101	99
Baseline	65.8 (2.2)	65.3 (2.0)	64.3 (1.9)	63.9 (2.1)	66.0 (2.1)
Change from baseline to week 4	9.4 (1.3)	6.0 (1.3)	8.6 (1.4)	6.5 (1.5)	2.0 (1.3)
Mean (SE) PPBC score					
N	96	100	98	101	99
Baseline	4.1 (0.1)	4.1 (0.1)	4.0 (0.1)	4.1 (0.1)	3.9 (0.1)
Change from baseline to week 4	−0.5 (0.1)	−0.4 (0.1)	−0.5 (0.1)	−0.5 (0.1)	−0.3 (0.1)

Standard-dose PGB/TER = pregabalin (150 mg twice daily [BID]) combined with tolterodine extended release (4 mg once daily [QD]); low-dose PGB/TER = pregabalin (75 mg BID) combined with tolterodine extended release (2 mg QD); PGB alone = pregabalin alone (150 mg BID); TER alone = tolterodine extended release (4 mg QD); SE = standard error; UI = urinary incontinence; NMF = normalized micturition frequency; OAB-q = overactive bladder questionnaire; SF HRQL = health-related quality of life scale, short form; PPBC = patient perception of bladder condition.

term studies may be needed to detect a change in the frequency of UI episodes.

Contrary to previously reported preclinical study results,[17] our exploratory analysis of pregabalin/tolterodine ER combinations versus the combination of tolterodine ER alone plus pregabalin alone showed no evidence of synergy. The lack of synergy between these medications was further supported by the limited evidence of clinical benefit in the other exploratory analysis comparing low-dose pregabalin/tolterodine ER with tolterodine ER alone. Additional clinical research is needed to

TABLE II. Treatment Group Differences (*P* Values) in Efficacy Endpoint Outcomes

	Primary comparison	Secondary comparisons		Exploratory comparisons		
	Standard-dose PGB/TER vs. TER alone	PGB alone vs. TER alone	PGB alone vs. placebo	Standard-dose PGB/TER vs. standard-dose TER alone + PGB alone	Low-dose PGB/TER vs. standard-dose TER alone + PGB alone	Low-dose PGB/TER vs. TER alone
Primary endpoint						
Mean voided volume per micturition, ml						
Difference (90% CI)	23.2 (14.1, 32.4)	14.2 (5.1, 23.2)	18.2 (9.1, 27.3)	−6.42 (−19.6, 6.8)	−23.1 (−36.3, −9.9)	6.54 (−3.0, 16.1)
P-value	<0.0001	0.005	0.0006	0.788	0.988	0.131
Secondary endpoints						
Mean UI episodes per 24 hr						
Difference (90% CI)	0.4 (−0.1, 1.0)	0.5 (0.01, 1.0)	−0.2 (−0.7, 0.3)	1.1 (0.4, 1.7)	1.1 (0.4, 1.7)	0.4 (−0.1, 0.9)
P-Value	0.909	0.953	0.225	0.995	0.997	0.926
Mean urgency episodes per 24 hr						
Difference (90% CI)	−0.2 (−0.8, 0.4)	−0.4 (−1.0, 0.2)	−0.4 (−1.0, 0.2)	1.1 (0.3, 1.9)	1.3 (0.5, 2.1)	0.04 (−0.6, 0.7)
P-Value	0.254	0.162	0.137	0.985	0.997	0.537
Mean severity of urgency episodes						
Difference (90% CI)	0.04 (−0.06, 0.1)	−0.01 (−0.1, 0.1)	−0.1 (−0.2, −0.03)	0.3 (0.1, 0.4)	0.2 (0.1, 0.4)	0.0 (−0.1, 0.1)
P-Value	0.737	0.404	0.017	0.999	0.996	0.479
Mean micturition frequency per 24 hr						
Difference (90% CI)	−0.6 (−1.0, −0.2)	−0.4 (−0.8, 0.1)	−0.6 (−1.0, −0.1)	0.4 (−0.2, 0.9)	0.8 (0.3, 1.3)	−0.1 (−0.6, 0.3)
P-Value	0.009	0.082	0.014	0.864	0.994	0.300
Mean NMF						
Difference (90% CI)	−10.0 (−14.8, −5.2)	−5.6 (−10.3, −0.8)	−7.4 (−12.3, −2.6)	1.1 (−5.2, 7.4)	7.5 (1.2, 13.8)	−3.6 (−8.5, 1.4)
P-Value	0.0003	0.028	0.006	0.612	0.975	0.116
Mean OAB-q Symptom Bother score						
Difference (90% CI)	−4.6 (−7.4, −1.7)	−5.1 (−7.9, −2.2)	−6.0 (−8.8, −3.1)	6.4 (2.6, 10.2)	7.4 (3.6, 11.2)	−3.5 (−6.5, −0.6)
P-Value	0.005	0.002	0.0003	0.997	0.999	0.024
Mean OAB-q SF HRQL score						
Difference (90% CI)	3.6 (1.0, 6.3)	2.2 (−0.5, 4.8)	6.2 (3.5, 8.8)	−4.6 (−8.1, −1.0)	−8.3 (−11.8, −4.8)	−0.1 (−2.8, 2.6)
P-Value	0.012	0.089	<0.0001	0.983	1.000	0.531
Mean PPBC score						
Difference (90% CI)	0.0 (−0.2, 0.2)	0.0 (−0.2, 0.2)	−0.2 (−0.4, 0.0)	0.5 (0.3, 0.8)	0.7 (0.4, 0.9)	0.1 (−0.1, 0.3)
P-Value	0.573	0.454	0.038	1.000	1.000	0.886

Standard-dose PGB/TER = pregabalin (150 mg twice daily [BID]) combined with tolterodine extended release (4 mg once daily [QD]); low-dose PGB/TER = pregabalin (75 mg BID) combined with tolterodine extended release (2 mg QD); PGB alone = pregabalin alone (150 mg BID); TER alone = tolterodine extended release (4 mg QD); CI = confidence interval; UI = urinary incontinence; NMF = normalized micturition frequency; OAB-q = overactive bladder questionnaire; SF HRQL = health-related quality of life scale, short form; PPBC = patient perception of bladder condition.
Results based on fitting an analysis of covariance model of change from baseline and including baseline, period and treatment as covariates; one-sided *P* values are presented.

fully assess the potential synergism of this combination in treating idiopathic OAB.

The crossover design of this study was advantageous because subjects acted as their own control, thereby reducing the required number of participants. Confounding treatment-order effects were addressed with a study design that included 10 possible treatment sequences, while carry-over effects were minimized by incorporating 4-week washouts between treatments. MVV, the primary endpoint, is included in the International Continence Society list of signs suggestive of lower urinary tract dysfunction,[4] and is a commonly-used efficacy endpoint in randomized controlled OAB studies.[7] In addition to MVV being an objective and physiologic indicator of treatment efficacy (i.e., that functional bladder capacity is greater at the time of micturition), it is generally less vulnerable to the high placebo response observed with other common OAB efficacy endpoints (e.g., micturition frequency and urgency UI episodes)[28] and thus may be less variable than other endpoints. Accordingly, the selection of MVV as the primary endpoint in this study minimized the number of subjects required to detect treatment differences for the primary and secondary comparisons, and thus minimized the number of subjects exposed to an exploratory treatment regimen.

A limitation of this study is that only women were evaluated; thus, the extent to which our results apply to men with OAB symptoms is unclear. Secondly, crossover treatment periods were of short duration (4 weeks). Lastly, the study was powered only for primary and secondary treatment comparisons of the primary endpoint (MVV).

CONCLUSIONS

Pregabalin 150 mg BID, alone and in combination with tolterodine ER 4 mg QD, is effective in improving MVV compared with tolterodine alone or placebo, in women with idiopathic OAB. Additional studies are needed to evaluate the potential for pregabalin in the treatment of OAB, including demonstration

TABLE III. Treatment-Emergent Adverse Events

	All-causality (treatment-related) treatment-emergent AEs				
	Standard-dose PGB/TER (150 mg BID/4 mg QD) (n = 102)	Low-dose PGB/TER (75 mg BID/2 mg QD) (n = 105)	PGB alone (150 mg BID) (n = 105)	TER alone (4 mg QD) (n = 104)	Placebo (n = 103)
Number of subjects					
Experiencing ≥1 AE	33 (25)	27 (21)	34 (29)	29 (16)	29 (19)
Experiencing ≥1 SAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuing due to AE	4 (3)	2 (2)	5 (5)	0 (0)	1 (1)
Total number of AEs	62 (40)	55 (37)	64 (52)	49 (29)	41 (25)
Number of frequently reported AEs by type					
Dry mouth	14 (14)	8 (8)	11 (11)	9 (9)	9 (9)
Dizziness	6 (6)	5 (5)	11 (11)	2 (2)	0 (0)
Fatigue	2 (1)	2 (2)	5 (1)	4 (4)	2 (2)
Upper abdominal pain	2 (1)	2 (2)	1 (1)	1 (1)	2 (2)
Nausea	2 (2)	1 (1)	2 (2)	0 (0)	1 (1)
Vertigo	2 (2)	2 (2)	2 (2)	0 (0)	1 (1)
Headache	3 (2)	1 (1)	3 (2)	1 (1)	1 (1)
Gastrointestinal disorder	1 (1)	2 (2)	0 (0)	1 (1)	0 (0)
Constipation	5 (3)	1 (1)	1 (1)	1 (1)	1 (1)
Somnolence	1 (1)	0 (0)	2 (2)	0 (0)	1 (1)

AE, adverse event; BID, twice daily; PGB, pregabalin; QD, once daily; SAE, serious adverse event; TER, tolterodine extended release.
Due to the crossover design of the study, ongoing AEs for a subject could be reported in more than 1 treatment period (for up to three different treatments) during the study.

of efficacy over a longer treatment duration and in men with OAB.

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REFERENCES

1. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol 2006;50:1306–15.
2. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760–6.
3. Coyne KS, Sexton CC, Irwin DE, et al. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: Results from the EPIC study. BJU Int 2008;101:1388–95.
4. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167–78.
5. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29:4–20.
6. Semins MJ, Chancellor MB. Diagnosis and management of patients with overactive bladder syndrome and abnormal detrusor activity. Nat Clin Pract Urol 2004;1:78–84, quiz 109.
7. Chapple CR, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. Eur Urol 2008;54:543–62.
8. Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. BJU Int 2007;100:987–1006.
9. Drake MJ. Emerging drugs for treatment of overactive bladder and detrusor overactivity. Expert Opin Emerg Drugs 2008;13:431–46.
10. Carbone A, Palleschi G, Conte A, et al. Gabapentin treatment of neurogenic overactive bladder. Clin Neuropharmacol 2006;29:206–14.
11. Marais E, Klugbauer N, Hofmann F. Calcium channel alpha(2)delta subunits-structure and Gabapentin binding. Mol Pharmacol 2001;59:1243–8.
12. Carbone A, Parascani R, Morello P, et al. The use of gabapentine in the treatment of neurogenic detrusor overactivity: Preliminary urodynamic and clinical results. Neurourol Urodyn 2002;21:336–7 (abstract).
13. Kim YT, Kwon DD, Kim J, et al. Gabapentin for overactive bladder and nocturia after anticholinergic failure. Int Braz J Urol 2004;30:275–8.
14. Lyrica® (pregabalin). Full prescribing information. New York, NY: Parke-Davis; 2009.
15. Wesche D, Bockbrader H. A pharmacokinetic comparison of pregabalin and gabapentin [abstract]. J Pain 2005;6:S29.
16. Fraser MO, Chien C, Burgard EC, et al. Modulators of the α2δ subunit of neuronal calcium channels inhibit bladder sensory pathways: In vitro patch clamp and in vivo cystometry in rats and cats. Neurourol Urodyn 2005;24:190–1 (abstract).
17. Fraser MO, Chien C, Thor KB, et al. Remarkable synergy of neurotropic agents, gabalin and pregabalin, with antimuscarinics: Inhibition of bladder overactivity in the rat and cat. Neurourol Urodyn 2005;24:192 (abstract).
18. van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: Superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001;57:414–21.
19. Homma Y, Kawabe K. Health-related quality of life of Japanese patients with overactive bladder treated with extended-release tolterodine or immediate-

release oxybutynin: A randomized, placebo-controlled trial. World J Urol 2004;22:251–6.
20. Herschorn S, Heesakkers J, Castro-Diaz D, et al. Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms. Curr Med Res Opin 2008;24:3513–21.
21. Coyne KS, Matza LS, Kopp Z, et al. The validation of the Patient Perception of Bladder Condition (PPBC): A single-item global measure for patients with overactive bladder. Eur Urol 2006;49:1079–86.
22. Coyne K, Revicki D, Hunt T, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. Qual Life Res 2002;11:563–74.
23. Overactive Bladder Questionnaires. The OAB-q Short Form (OAB-q SF). 2009 [cited 2009 September 10]; Available from: www.oabq.com/oab-science.html #OAB-qSF.
24. Detrol® LA (tolterodine tartrate). Full prescribing information. Pfizer, Inc.; New York, NY: 2008.
25. Chapple CR, Van Kerrebroeck PE, Junemann KP, et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. BJU Int 2008;102:1128–32.
26. Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol 2007;52:1204–12.
27. Green SA, Alon A, Ianus J, et al. Efficacy and safety of a neurokinin-1 receptor antagonist in postmenopausal women with overactive bladder with urge urinary incontinence. J Urol 2006;176:2535–40.
28. van Leeuwen JHS, Castro R, Busse M, et al. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. Eur Urol 2006;50:440–53.