

Efficacy and Safety of Solifenacin Succinate 10 mg Once Daily: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial in Patients With Overactive Bladder

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ABSTRACT

BACKGROUND: Solifenacin succinate is an antimuscarinic drug with reported efficacy and tolerability at a recommended starting dose of 5 mg QD in patients with overactive bladder (OAB).

OBJECTIVE: The objective of this trial was to investigate the efficacy, safety, and tolerability of solifenacin 10 mg QD in patients with OAB.

METHODS: In this multicenter, Phase III, double-blind, placebo-controlled, parallel-group trial, patients aged ≥ 18 years with OAB were randomized at a 1:1 ratio to receive solifenacin 10 mg or placebo QD for 12 weeks. The patients were instructed to complete a micturition diary for the 3 days preceding each scheduled visit (weeks 4, 8, and 12). The primary end point was the change from baseline in the mean number of micturitions per 24 hours; secondary end points included the mean change from baseline in the number of episodes per 24 hours of urgency, incontinence, nocturnal voiding, and nocturia and the mean volume voided per micturition. Tolerability was monitored through adverse events (AEs), vital sign measurements, ECGs, laboratory assessments, and physical examination.

RESULTS: A total of 672 patients were randomized and received ≥ 1 dose of study drug (solifenacin, $n = 340$; placebo, $n = 332$). The mean (SE) decrease from baseline to study end in the number of micturitions per 24 hours was significantly greater in the solifenacin group compared with the placebo group ($-3.0 [0.2]$ vs $-1.5 [0.2]$, respectively; $P < 0.001$). The mean decrease in the number of episodes of incontinence was significantly greater in the solifenacin group compared with the placebo group ($-2.0 [0.2]$ vs $-1.1 [0.2]$; $P < 0.001$), as was the mean decrease in the number of episodes of urgency ($-4.1 [0.2]$ vs $-2.1 [0.2]$; $P < 0.001$). Of the patients with ≥ 1 incontinence episode per 24 hours at baseline, significantly more patients in the solifenacin group achieved complete continence at study end than did patients in the placebo

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group (119/225 [52.9%] vs 80/237 [33.8%]; $P < 0.001$). The change from baseline to study end in the mean volume voided per micturition increased significantly in the solifenacin group compared with the placebo group (47.2 vs 2.7 mL; $P < 0.001$). Most AEs were mild or moderate in intensity. The AEs that were most commonly reported in the solifenacin-treated group were anticholinergic in nature: dry mouth (91 [26.8%] vs 13 patients [3.9%] in the placebo group; $P < 0.001$); constipation (58 [17.1%] vs 11 [3.3%]; $P < 0.001$); and blurred vision (12 [3.5%] vs 4 [1.2%]; $P < 0.05$). Serious AEs (SAEs) were reported for 5 patients in the solifenacin group and 3 patients in the placebo group. In the solifenacin group, 2 patients experienced chest pain, 1 had cellulitis, 1 had dehydration, and 1 had colonic obstruction; only 1 SAE (colonic obstruction) was judged to be possibly related to the study drug. In the placebo group, 1 patient had chest pain, 1 had bacterial meningitis, and 1 had hemopericardium.

CONCLUSIONS: This study found that solifenacin 10 mg QD for 12 weeks was associated with significantly reduced symptoms of OAB, including the frequency of micturition, and episodes of urgency and of incontinence. With solifenacin, the volume voided per micturition increased by 47.2 mL, and 53% of patients with ≥ 1 incontinence episode per 24 hours at baseline achieved complete continence. This efficacy was accompanied by a favorable safety and tolerability profile. (*Curr Ther Res Clin Exp.* 2009;70:405–420) © 2009 Excerpta Medica Inc.

KEY WORDS: anticholinergic, incontinence, overactive bladder, solifenacin, urgency.

INTRODUCTION

Overactive bladder (OAB) is a symptom syndrome suffered by many individuals^{1,2} and is defined by the International Continence Society as “urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of pathologic or metabolic conditions that might explain these symptoms.”³ OAB syndrome is a highly prevalent condition with serious quality of life (QoL) and socioeconomic consequences.⁴ The US-based National Overactive Bladder Evaluation (NOBLE) program has estimated that, overall, 16.2% of men and 16.9% of women have symptoms of OAB, representing 33 million sufferers in the United States.⁵ These figures concur with a European population-based survey, which found an OAB prevalence of 15.6% in men and 17.4% in women. The study also confirmed age as a risk factor, with the prevalence of an urgency–frequency syndrome rising to 41.9% of men and 31.3% of women in those aged ≥ 75 years.⁴

OAB syndrome is associated with a range of complications and comorbidities, including urinary tract infection, skin ulceration in patients with *wet* OAB (defined as urgency and frequency with urinary incontinence) and an increased risk of falls in the elderly.^{6,7} Further effects of OAB on QoL include diminished physical, psychosocial, occupational, and sexual function,⁸ which may be seen in OAB patients both with and without incontinence.⁹ This is an important aspect of the syndrome, as the majority of patients (66%) have *dry* OAB (defined as urgency and frequency without urinary

incontinence).¹⁰ A lack of understanding of the severity of the impact of dry OAB on QoL may play a role in the undertreatment of this condition.¹¹ In addition to the debilitating effects on the physical, social, and emotional functioning of patients, OAB may have a large financial impact. In 2000, the estimated total cost associated with OAB in the United States was >\$12 billion, an amount comparable to that of gynecologic and breast cancers (\$11.1 billion) and osteoporosis (\$13.8 billion).¹²

For patients with OAB, antimuscarinic therapy remains the primary pharmacotherapeutic option.^{13,14} However, while antimuscarinic drugs are effective, they are often associated with unwanted adverse events (AEs).^{15,16} Therefore, effective antimuscarinic treatments with improved tolerability profiles are required. Solifenacin succinate is an antimuscarinic drug that has reported good efficacy and tolerability in a Phase III clinical development program.^{17,18} It is recommended (and approved) at a dose of 5 mg QD, which may be increased to 10 mg QD if required and if the 5-mg dose is well tolerated.¹⁹ The findings of 2 randomized, double-blind, placebo-controlled trials indicated that treatment with solifenacin 5 and 10 mg QD was significantly better than placebo in improving all symptoms of OAB, including frequency, urgency, incontinence, and volume voided.^{17,18} In a separate Phase IIIb study,²⁰ solifenacin was found to be significantly more effective ($P = 0.035$) at reducing episodes of urgency than tolterodine extended release (ER). In addition, solifenacin was significantly more effective than tolterodine ER on a range of other efficacy variables, including overall incontinence ($P = 0.006$), urge incontinence ($P = 0.001$), pad use ($P = 0.023$), and volume voided per micturition ($P = 0.010$). Solifenacin treatment was also found to be noninferior to tolterodine for the frequency of micturitions ($P = 0.004$ for noninferiority).²⁰ All 3 studies reported an acceptable tolerability profile for solifenacin.^{17,18,20}

Although the recommended starting dose of solifenacin is 5 mg QD, the ability to improve efficacy while maintaining a good tolerability profile at the higher 10-mg dose suggests that there is considerable scope for flexible dosing.^{17,18,20}

The aim of this study was to assess the efficacy, safety, and tolerability of solifenacin 10 mg* QD in patients with OAB.

PATIENTS AND METHODS

STUDY DESIGN

This multicenter, Phase III, randomized, double-blind, placebo-controlled, parallel-group trial was designed to determine the efficacy, safety, and tolerability of solifenacin 10 mg in the treatment of OAB. The study consisted of a 2-week screening/washout period, a 12-week double-blind treatment period, and a 2-week posttreatment follow-up assessment for those patients who did not enter an open-label extension study.

Men and women aged ≥ 18 years with a diagnosis of OAB made by an investigator based on symptoms (urinary frequency, urgency, or urge incontinence) were eligible to enter the 2-week screening phase. Patients were required to keep micturition diaries for 3 days during the screening period. To be eligible for inclusion in the randomization phase, patients had to have recorded a mean of ≥ 8 micturitions per 24 hours

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plus a mean of ≥ 1 incontinence episode per 24 hours and/or a mean of ≥ 1 urgency episode per 24 hours during the screening period.

Exclusion criteria included stress urinary incontinence or mixed urinary incontinence in which stress was predominant (mixed incontinence was otherwise allowed), a neurologic cause of detrusor overactivity, urinary retention, grade III/IV prolapse with cystocele, and recurrent or active urinary tract infection. Patients with abnormal findings on 12-lead ECG or abnormal laboratory findings were also excluded. Women of childbearing potential were required to have a negative serum pregnancy test at screening and to use a medically acceptable form of contraception during study participation.

The study was conducted in 33 centers across the United States between February 2001 and October 2001. Participants were recruited from existing patients in the centers' databases and also through advertisements and a national call center. The screening process yielded patients who were eligible for entry into the 12-week, double-blind treatment period. Patients were randomized at a ratio of 1:1 to receive either solifenacin 10 mg or placebo orally QD, supplied in identical blister packs to maintain blinding. The solifenacin and placebo tablets were also identical in appearance. Each pack had a blinded tear-off label containing the name of the product and the dose, which was to be used only if it became necessary to unblind the patient. Randomization was performed at the center level to provide a balance of treatment groups within a center. PROC PLAN (SAS Institute Inc., Cary, North Carolina) was used to generate the randomization codes.²¹ In addition, sealed copies of the randomization code were kept by Covance Drug Safety Coordination United States (Nashville, Tennessee).

Both solifenacin and the placebo were manufactured by Yamanouchi Pharmaceutical Co., Ltd. (Takahagi, Japan) and were formulated as tablets by Yamanouchi Technologies, Inc. (Palo Alto, California).

The patients were instructed to complete a micturition diary for the 3 days preceding each scheduled visit (weeks 4, 8, and 12). The patients recorded the date and time of micturitions and episodes of incontinence and urgency. The mean volume voided per micturition was recorded on any 2 of the 3 days. The patients also recorded the time they went to bed and the time they awoke. When recording micturitions, patients also filled out a check box indicating whether or not the micturition awakened them. Nocturnal voids were captured as all micturitions that occurred between the time the patient reported going to bed and the reported time of awakening. Episodes of nocturia were captured as micturitions that woke the patient from sleep between the time the patient reported going to bed and the time he or she reported awakening.

The study was performed in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol, informed-consent form, and investigator's brochure were reviewed by a central institutional review board (IRB) (Schulman Associates Institutional Review Board, Cincinnati, Ohio) and by the IRB at each study site. All patients were informed of the nature and purpose of the study, and written informed consent was obtained from all study participants before screening.

EFFICACY ASSESSMENTS

The primary end point was the change in the mean number of micturitions per 24 hours from baseline to *study end*, defined as the last available on-treatment visit on or before week 12. Secondary end points included the change from baseline to study end in the mean number of episodes of urgency, incontinence, nocturnal voiding, and nocturia per 24 hours and the mean volume voided per micturition.

SAFETY ASSESSMENTS

Tolerability was assessed throughout the trial by the investigators by monitoring AEs. The Medical Dictionary for Regulatory Activities was used to code AEs.²² The investigators categorized the AEs by severity according to standard definitions and assessed the causal relationship to study medication based on predetermined definitions of *unrelated*, *possibly related*, or *probably related*. *Serious AEs* were defined as those resulting in death, life-threatening AEs, AEs requiring inpatient hospitalization or prolongation of existing hospitalization, and AEs resulting in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event or intervention. Vital signs and ECGs were recorded at screening (week -2), baseline (week 0), and at weeks 4, 8, and 12. Laboratory assessments (hematology, clinical chemistry, and urinalysis) were also carried out at these times. Physical examinations were performed at screening, baseline, week 12, and at posttreatment follow-up. Postvoid residual volume was measured by bladder scan at screening and at week 12.

STATISTICAL ANALYSIS

Based on the detection of an active–placebo difference of 1 micturition per 24 hours between the treatment group and the placebo group, with an SD of 3, a significance level of $\alpha = 0.05$ (2-sided), and a power of 90%, it was estimated that a sample size of 250 patients per treatment arm would be required to complete the study. Assuming a dropout rate of 20%, ~630 patients needed to be randomized.

The safety population included all patients who were randomized and received ≥ 1 dose of double-blind treatment. This population was used for the summaries of demographic and baseline characteristics and the safety analyses. The full analysis set (FAS) included all patients who were randomized, received ≥ 1 dose of double-blind study medication, and had baseline (from the 3-day diary of the screening/washout period) and on-treatment diary data available. The efficacy analyses were performed using the FAS.

All end points and analyses were determined a priori. All statistical comparisons were made using 2-sided tests at a significance level of $\alpha = 0.05$. Continuous variables were summarized using descriptive statistics, and frequencies and percentages were used to report categorical data. The efficacy analysis was performed on the mean change from baseline to study end. The last on-treatment assessment method was used as the end point assessment in the analysis. Study groups were compared using ANOVA, with terms for *center* and *treatment*, if normality assumptions warranted. A Shapiro-Wilks test was performed to test the normality of the residuals; if the normality

assumption was not met, a Van Elteren analysis was to be conducted using *center* as a blocking variable.²³ As normality was not met, the nonparametric analysis using the Van Elteren method was performed for treatment comparisons.

Study group comparisons of the percentage of patients with incontinence at baseline who became continent (ie, did not report incontinence in the 3-day diary at study end) were based on the Mantel-Haenszel test. Additional analyses were performed on the percentage of patients meeting a set of criteria with respect to the number of micturitions and episodes of incontinence, nocturnal voiding, and nocturia. The incidence estimates were compared between study groups at each visit and at the study end, also using the Mantel-Haenszel test.

RESULTS

PATIENTS

Figure 1 shows the disposition of patients throughout the study. A total of 672 patients (549 women, 123 men) were randomized to receive solifenacin 10 mg (272 women, 68 men; mean [SD] age, 59 [14] years; weight, 82 [21.3] kg; white race, 287 [84.4%]) or placebo (277 women, 55 men; mean age, 58 [13] years; weight, 81 [20.5] kg; white race, 272 [81.9%]) (Table I). Each patient received ≥ 1 dose of study drug. The safety population comprised all randomized patients, while 57 patients (8.5%) (solifenacin group, 34/340 patients [10.0%]; placebo group, 23/332 patients [6.9%]) were excluded from the efficacy analysis due to the lack of baseline or on-treatment diary data, leaving 306 solifenacin-treated patients and 309 patients in the placebo group in the FAS. The 2 groups were comparable with respect to baseline demographic and clinical characteristics.

A total of 128 patients (19.0%) discontinued prematurely; discontinuation rates were comparable between groups (70/340 [20.6%] in the solifenacin group vs 58/332 [17.5%] in the placebo group). Discontinuations due to AEs occurred in 37 [10.9%] and 18 patients [5.4%] in the solifenacin and placebo groups, respectively.

EFFICACY

The mean (SE) decrease from baseline to study end in the number of micturitions per 24 hours was significantly greater in the solifenacin group compared with the placebo group (-3.0 [0.2] vs -1.5 [0.2]; $P < 0.001$) (Figure 2). At baseline, the mean number of micturitions per 24 hours was 11.7 (0.2) in the solifenacin group and 11.5 (0.2) in the placebo group. At study end, the mean number of micturitions per 24 hours was decreased to 8.7 (0.2) in the solifenacin group and 10.0 (0.2) in the placebo group. Solifenacin was associated with a significantly greater decrease in the frequency of micturitions per 24 hours compared with placebo at all time points from week 4 to study end (all, $P < 0.001$) (Table II). In addition, a significantly greater proportion of patients in the solifenacin group compared with the placebo group achieved normalization of micturition (mean no. of micturitions per 24 hours < 8) at study end (136/306 [44%] vs 83/309 [27%]), respectively; $P < 0.001$).

The mean (SE) decrease from baseline to study end in the number of episodes of incontinence per 24 hours was significantly greater in the solifenacin group compared

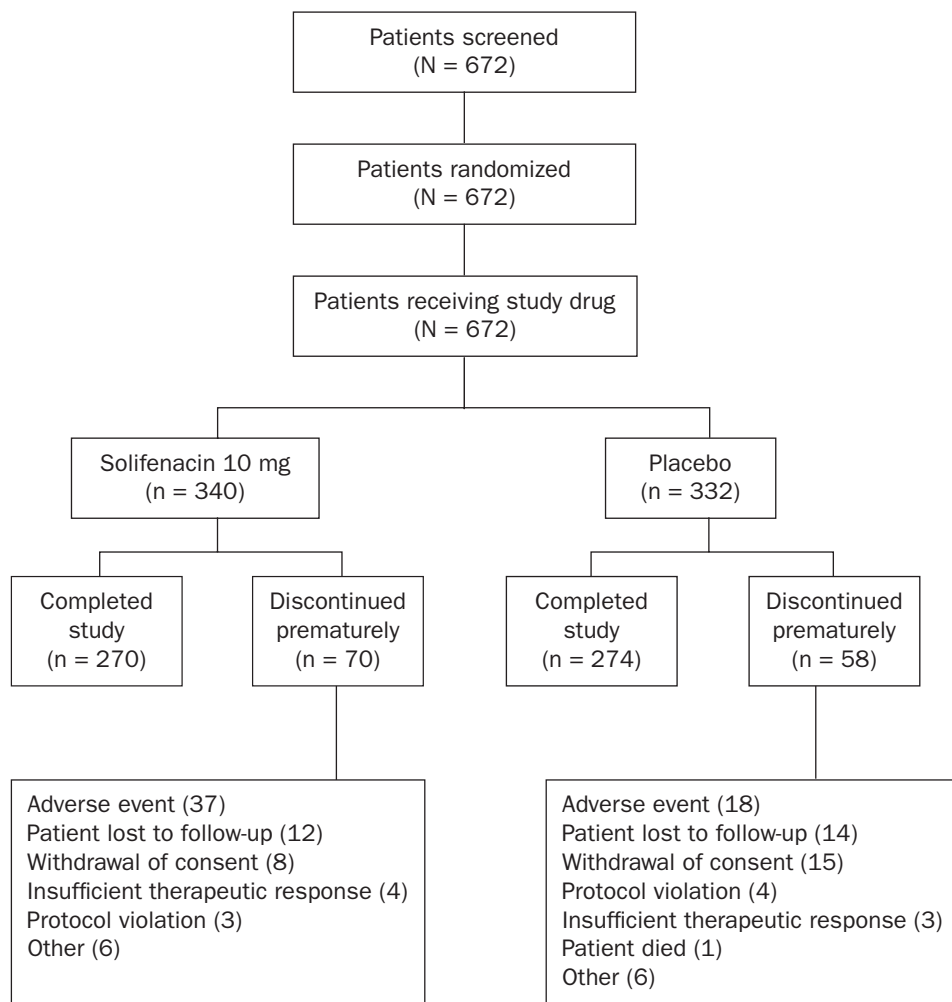


Figure 1. Patient disposition throughout the study.

with the placebo group (-2.0 [0.2] vs -1.1 [0.2], respectively; $P < 0.001$) (Figure 2). At baseline, the mean number of episodes of incontinence per 24 hours in the solifenacin group ($n = 225$) was 3.1 (0.2) compared with the 3.0 (0.2) episodes in the placebo group ($n = 237$). At study end, the number of episodes was 1.1 (0.2) and 1.8 (0.2), respectively. As with the primary efficacy end point, solifenacin was associated with a significantly greater decrease in the number of episodes of incontinence per 24 hours compared with placebo at all time points from week 4 to the study end (all, $P < 0.001$) (Table II).

Similarly, the mean (SE) decrease from baseline to study end in the number of episodes of urgency per 24 hours was significantly greater in the solifenacin group com-

Table I. Baseline demographic and clinical characteristics of the safety population (N = 672).

Characteristic	Solifenacin (n = 340)	Placebo (n = 332)
Age, mean (SD), y	59 (14)	58 (13)
Sex, no. (%)		
Women	272 (80.0)	277 (83.4)
Men	68 (20.0)	55 (16.6)
Race, no. (%)		
White	287 (84.4)	272 (81.9)
African American	28 (8.2)	42 (12.7)
Hispanic	17 (5.0)	13 (3.9)
Asian	4 (1.2)	3 (0.9)
Other	4 (1.2)	2 (0.6)
Weight, mean (SD), kg	82 (21.3)	81 (20.5)
Time since start of OAB symptoms, mean (SD), y	9 (10.3)	9 (10.2)
Urge incontinence only, no. (%)	161 (47.4)	163 (49.1)
Mixed stress/urge incontinence with urge as predominant factor, no. (%)	178 (52.4)	165 (49.7)
Prior anticholinergic drug therapy, no. (%)	142 (41.8)	111 (33.4)
History of nondrug treatment of OAB, no. (%)	80 (23.5)	80 (24.1)

OAB = overactive bladder.

pared with the placebo group (-4.1 [0.2] vs -2.5 [0.2]; $P < 0.001$). The mean number of episodes of urgency per 24 hours in the solifenacin group ($n = 305$) and the placebo group ($n = 306$) was 6.9 (0.2) and 7.2 (0.2), respectively, at baseline. At study end, these values were reduced to 2.8 (0.2) and 4.7 (0.2) episodes per 24 hours, respectively. Again, solifenacin was associated with a significantly greater decrease in the number of episodes of urgency per 24 hours compared with placebo at all time points from week 4 to the study end (all, $P < 0.001$) (Table II).

Of the patients who reported ≥ 1 incontinence episode per 24 hours at baseline in the solifenacin ($n = 225$) and the placebo ($n = 237$) groups, significantly more patients in the solifenacin group than the placebo group achieved complete continence at study end (119/225 [52.9%] vs 80/237 [33.8%], respectively; $P < 0.001$).

The change from baseline to study end in the mean volume voided per micturition increased significantly in the solifenacin group ($n = 308$) compared with the placebo group ($n = 305$) (47.2 vs 2.7 mL, respectively; $P < 0.001$) (Figure 3).

The number of nocturnal voiding episodes per 24 hours and the number of nocturia episodes per 24 hours were both significantly reduced in the solifenacin group compared with the placebo group at week 4 (nocturnal voiding episodes: solifenacin,

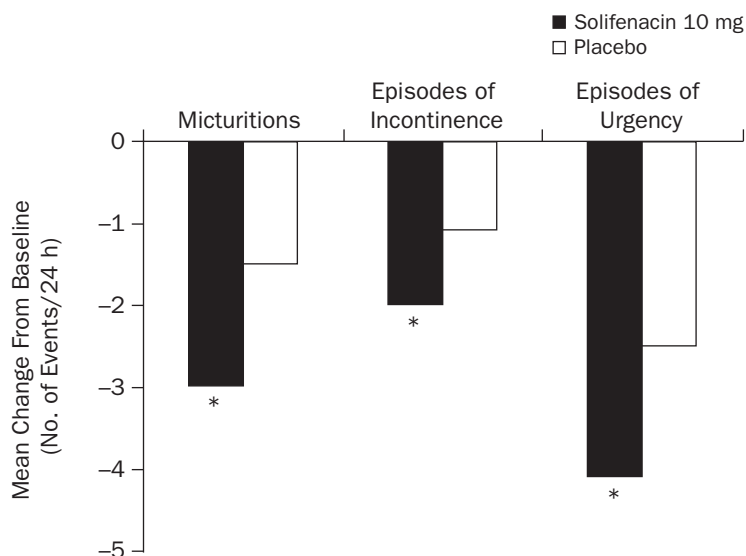


Figure 2. Mean change in the number of overactive bladder symptoms per 24 hours from baseline to study end in adult patients with overactive bladder. * $P < 0.001$ versus placebo.

–0.5 [n = 282] and placebo –0.4 [291], $P < 0.05$; nocturia episodes: solifenacin, –0.5 [266] and placebo, –0.3 [278], $P < 0.05$); however, these differences were not statistically significant at study end (number of nocturnal voiding episodes: solifenacin, –0.7 [n = 283] and placebo, –0.5 [292]; nocturia episodes: solifenacin, –0.6 [267] and placebo, –0.4 [279]).

SAFETY

AEs were reported by 236 (69.4%) and 197 patients (59.3%) in the solifenacin and placebo groups, respectively. Most of the patients experienced AEs that were mild or moderate in intensity; 44 patients (12.9%) in the solifenacin group and 24 patients (7.2%) in the placebo group experienced AEs that were judged to be severe in intensity. The majority of AEs that were most commonly reported in the solifenacin-treated group were anticholinergic in nature: dry mouth (91 [26.8%] vs 13 [3.9%] patients in the placebo group; $P < 0.001$); constipation (58 [17.1%] vs 11 [3.3%]; $P < 0.001$); and blurred vision (12 [3.5%] vs 4 [1.2%]; $P < 0.05$) (Table III).

Frequently reported AEs experienced by the study patients, other than the common anticholinergic AEs reported previously, are shown in Table IV. The most frequently occurring of these AEs in the solifenacin and placebo group, respectively, were found in the following system organ classes: gastrointestinal disorders (154 [45.3%] vs 77 [23.2%] patients); infections and infestations (55 [16.2%] vs 52 [15.7%]); and nervous system disorders (41 [12.1%] vs 45 [13.6%]).

Serious AEs (SAEs) were reported for 5 patients in the solifenacin group and 3 patients in the placebo group. In the solifenacin group, 2 patients experienced chest

Table II. Change from baseline in the number of overactive bladder symptoms per 24 hours, by visit. Data are mean (SE).

Variable	Week 4		Week 8		Week 12		Study End	
	Solifenacin	Placebo	Solifenacin	Placebo	Solifenacin	Placebo	Solifenacin	Placebo
Micturitions per 24 hours	-2.5 (0.14)*	-1.3 (0.14)	-2.7 (0.16)*	-1.4 (0.14)	-2.9 (0.16)*	-1.5 (0.16)	-3.0 (0.15)*	-1.5 (0.15)
Incontinence episodes per 24 hours	-1.8 (0.19)*	-1.0 (0.14)	-2.0 (0.17)*	-1.2 (0.16)	-2.2 (0.19)*	-1.2 (0.18)	-2.0 (0.19)*	-1.1 (0.16)
Urgency episodes per 24 hours	-3.5 (0.20)*	-1.9 (0.19)	-3.7 (0.21)*	-2.4 (0.20)	-4.0 (0.21)*	-2.4 (0.22)	-4.1 (0.20)*	-2.5 (0.20)

*P < 0.001 versus placebo.

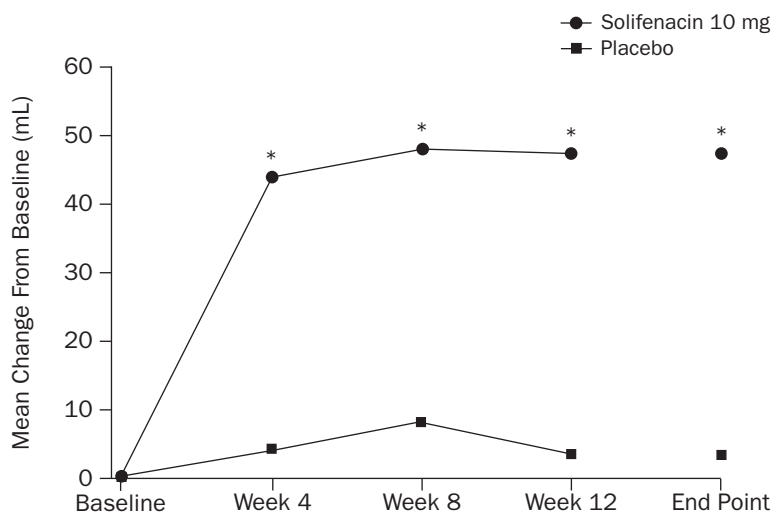


Figure 3. Mean change from baseline in volume voided (mL)/micturition by visit in adult patients with overactive bladder. * $P < 0.001$ versus placebo.

pain, 1 had cellulitis, 1 had dehydration, and 1 had colonic obstruction. In the placebo group, 1 patient had chest pain, 1 had bacterial meningitis, and 1 had hemopericardium. Only 1 SAE (colonic obstruction) was judged to be possibly related to the study drug and occurred in the solifenacin group.

Thirty-seven patients (10.9%) in the solifenacin group and 23 patients (6.9%) in the placebo group discontinued study medication due to an AE. The anticholinergic AEs of dry mouth, constipation, blurred vision, and nausea were the most common AEs leading to discontinuation. The discontinuation rates in the solifenacin and placebo groups due to these AEs were as follows: dry mouth (12 [3.5%] vs 1 [0.3%], respectively); constipation (12 [3.5%] vs 0 [0%]); blurred vision (5 [1.5%] vs 0 [0%]); and nausea (7 [2.1%] vs 3 [0.9%]). No other AE led to discontinuation for >1% of the patients in either treatment group.

Solifenacin had no influence on clinical laboratory parameters or vital signs. Mean baseline QTc was 422.5 and 421.2 msec in the solifenacin ($n = 220$) and placebo ($n = 227$) groups, respectively; mean (SE) change from baseline was 4.9 (1.29) and 1.3 (1.24) msec, respectively. The small increase of 3.6 msec in the mean QTc change from baseline in the solifenacin group was statistically significant ($P = 0.018$), but not deemed clinically significant.

DISCUSSION

OAB syndrome can have a major impact on patient health-related QoL. Solifenacin is a once-daily oral antimuscarinic drug that is indicated for the treatment of OAB at doses of 5 and 10 mg; this provides flexibility of dosing, particularly for patients who require the greater clinical efficacy of solifenacin 10 mg.

Table III. Common antimuscarinic adverse events (AEs) by treatment group (N = 672). Data are number (%) of patients.

AE	Solifenacin 10 mg (n = 340)				Placebo (n = 332)			
	Mild	Moderate	Severe	Overall	Mild	Moderate	Severe	Overall
Dry mouth	48 (14.1)	35 (10.3)	8 (2.4)	91 (26.8)*	9 (2.7)	4 (1.2)	0	13 (3.9)
Constipation	26 (7.6)	25 (7.4)	7 (2.1)	58 (17.1)*	7 (2.1)	4 (1.2)	0	11 (3.3)
Blurred vision	7 (2.1)	3 (0.9)	2 (0.6)	12 (3.5)†	4 (1.2)	0 (0.0)	0	4 (1.2)

*P < 0.001 versus placebo.

† P < 0.05 versus placebo.

Table IV. Adverse events (AEs), excluding common antimuscarinic events, occurring in $\geq 2\%$ of study patients (N = 672). Data are number (%) of patients.

AE	Solifenacin (n = 340)	Placebo (n = 332)
Gastrointestinal disorders	154 (45.3)	77 (23.2)
Nausea	19 (5.6)	13 (3.9)
Dyspepsia	16 (4.7)	3 (0.9)
Diarrhea	7 (2.1)	15 (4.5)
Infections and infestations	55 (16.2)	52 (15.7)
Urinary tract infection (not otherwise specified)	21 (6.2)	11 (3.3)
Nasopharyngitis	3 (0.9)	11 (3.3)
Upper respiratory tract infection	6 (1.8)	7 (2.1)
Nervous system disorders	41 (12.1)	45 (13.6)
Headache	16 (4.7)	24 (7.2)
Dizziness (excluding vertigo)	10 (2.9)	8 (2.4)
Musculoskeletal, connective tissue, and bone disorders	33 (9.7)	37 (11.1)
Arthralgia	6 (1.8)	11 (3.3)
Back pain	6 (1.8)	7 (2.1)
Eye disorders (all, including blurred vision)	24 (7.1)	14 (4.2)
Renal and urinary disorders	16 (4.7)	11 (3.3)
Urinary retention	7 (2.1)	3 (0.9)

In the current study, treatment with solifenacin suggested a significant reduction in the primary end point, the number of micturitions per 24 hours, compared with placebo ($P < 0.001$). Analysis of the secondary end point, urgency, showed that the number of urgency episodes per 24 hours was reduced by 60% from baseline following treatment with solifenacin, whereas the reduction was 35% in the placebo arm ($P < 0.001$). Similarly, the number of incontinence episodes during a 24-hour period was significantly reduced in the solifenacin group compared with the placebo group ($P < 0.001$). Of the patients who reported ≥ 1 incontinence episode at baseline, 53% of those treated with solifenacin 10 mg achieved complete continence at study end, compared with 34% in the placebo group ($P < 0.001$). The percentage of patients achieving total dryness is not only an important variable in clinical trials of OAB treatments, it is one of the most significant factors in the clinician's choice of therapeutic agents and the patient's perception of benefits. Furthermore, reductions in the episodes of micturition, incontinence, and urgency with solifenacin were observed at the first assessment at week 4 and were maintained throughout the study period.

The efficacy findings reported here are consistent with those from previous studies.^{17,18,20} Two randomized, double-blind, placebo-controlled, 12-week trials^{17,18} found that solifenacin at doses of 5 and 10 mg QD was associated with significantly greater decreases in the number of micturitions, urgency episodes, and urge incontinence episodes compared with placebo. In addition, a recent study comparing the efficacy of solifenacin (5 or 10 mg QD) with tolterodine ER (4 mg QD) in OAB patients found that, with a flexible-dosing regimen, solifenacin was associated with greater efficacy than tolterodine in decreasing urgency episodes, incontinence, urge incontinence, and pad use and increasing the volume voided per micturition; solifenacin also demonstrated noninferiority to tolterodine in improving micturition frequency.²⁰

Mean voided volume, a secondary end point in the present study, increased significantly in the solifenacin group compared with the placebo group. As mean voided volume is the most objective parameter in measuring treatment efficacy, the large increase in the present study and previous studies supports the efficacy of solifenacin 10 mg QD.

Episodes of nocturia and nocturnal voiding were also decreased significantly in patients treated with solifenacin compared with placebo at week 4. However, these differences were not statistically significant at study end. In a previous study, episodes of nocturia were significantly decreased in patients treated with solifenacin 10 mg versus placebo ($P = 0.036$).¹⁷ In general, few studies have assessed the effects of antimuscarinic treatment on nocturia, and none have reported any statistically significant efficacy. This is largely due to the multifactorial nature of nocturia. In addition, it is difficult to design trials to investigate the effects of antimuscarinic drugs on nocturia due to the lower incidence of symptoms and the requirement of large numbers of patients to detect statistically significant beneficial effects.²⁴

The results of any clinical trial must always be considered in the context of the limitations of that particular study. The limitations of this study may include the use of the FAS for the analysis of the efficacy variables. However, this set represents the population that is as close as possible to the ideal implied by the intention-to-treat principle and conforms to the International Conference on Harmonisation E9 guidelines.²⁵ The decision to use the FAS was made a priori. Furthermore, a similar small number of patients was excluded from each treatment arm in the FAS (23 patients in the placebo group and 34 patients in the solifenacin group). Another potential limitation of this study was the relatively high patient-withdrawal rates (solifenacin group, 70/340 [20.6%] vs placebo group, 58/332 [17.5%]). These percentages were similar in the 2 treatment groups, although an AE as a reason for discontinuation was reported in 37 patients in the solifenacin group and 18 patients in the placebo group; the difference was not significant. The discontinuations would not have been expected to affect the outcome of the study.

Solifenacin was well tolerated in the current study; the majority of AEs most commonly reported for solifenacin were anticholinergic in nature, as anticipated. Reasons for study withdrawal were similar in both treatment groups. The anticipated anticholinergic AEs of dry mouth, constipation, blurred vision, and nausea were the most common AEs leading to discontinuation in the active-treatment arm.

CONCLUSIONS

This study found that solifenacin 10 mg QD for 12 weeks was associated with significantly reducing symptoms of OAB, including the frequency of micturition and of episodes of urgency and incontinence per 24 hours, compared with placebo. With solifenacin, the volume voided per micturition increased by 47.2 mL, and 53% of patients with ≥ 1 incontinence episode per 24 hours achieved total continence. This efficacy was accompanied by a favorable tolerability profile, as the AEs experienced by the solifenacin recipients were mostly mild and anticholinergic in nature. This study supports the efficacy and safety profile of solifenacin 10 mg in this population of OAB patients.

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