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# Efficacy of Darifenacin in Patients with Varying Baseline Symptom Severity

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## ABSTRACT

**INTRODUCTION:** The severity of overactive bladder (OAB) symptoms such as incontinence episodes (IEs), urgency episodes, and micturition frequency varies between patients. It is therefore of interest to determine if patients respond differently to OAB antimuscarinic therapy according to symptom severity.

The objective of the present study was to evaluate data on symptom reduction and time of onset of action for patients in a pooled analysis of three phase III darifenacin studies. These data were analyzed in relation to darifenacin dose received and OAB symptom severity at baseline, as defined by IE frequency at randomization.

**METHODS:** The investigation was a retrospective analysis of pooled data from three 12-week, fixed-dose, double-blind studies involving 1053 adults (19–88 years old) who received darifenacin 7.5 mg or 15 mg once daily and matched patients who received placebos. Patients with mild/moderate OAB (defined as < 21 IEs/week at baseline) or severe OAB (≥ 21 IEs/week) were analyzed at 2, 6, and 12 weeks or the end of the study. Measurements included the absolute and percentage change from baseline in IEs/week, urgency episodes/day, micturitions/day, and mean volume/void.

**RESULTS:** There was a statistically significant improvement in OAB symptoms at week 12 or the last visit for patients with mild/moderate OAB taking darifenacin 7.5 mg and 15 mg, when compared with patients taking the placebo. There was also a statistically significant improvement in OAB symptoms at week 12 for patients with severe OAB taking darifenacin 15 mg, when compared with patients taking the placebo. Patients taking darifenacin 15 mg had statistically significant improvements in as few as 2 weeks for all OAB symptoms measured when compared with patients taking the placebo, regardless of baseline severity.

**CONCLUSION:** Both darifenacin 7.5 mg and 15 mg effectively relieved OAB symptoms, with statistically significant reductions in symptoms seen in as few as 2 weeks. For patients with mild/moderate OAB, 7.5 mg was sufficient to achieve a statistically significant effect; for patients with severe OAB, 15 mg was the most effective dose. These findings highlight the importance of dose titration according to individual patient needs.

**KEYWORDS:** Antimuscarinic; Darifenacin; Detrusor overactivity; Symptom severity; OAB

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original study

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## INTRODUCTION

Overactive bladder (OAB) syndrome is a highly prevalent and debilitating condition. It is characterized by a complex of symptoms including urinary urgency with or without urinary incontinence episodes, often with frequency and nocturia [1]. Symptoms and symptom severity may vary considerably between individual patients with OAB, which may affect patient responses to pharmacotherapy. If there is a positive correlation between symptom severity and treatment response, then severity may be a predictor of response and OAB management could be more individualized to a patient's needs.

The first-line pharmacotherapeutic agents for OAB are antimuscarinics, such as darifenacin, solifenacin, tolterodine, and oxybutynin. Clinical studies have shown that these agents can exert significant effect in patients with a spectrum of OAB symptoms, including those with severe symptoms [2–6]. There is also clinical evidence showing that the ability to up-titrate the therapeutic dose (in accordance with approved labelling) can benefit patients [7–9]. However, more evidence is needed to understand if patients with differing symptom severity respond differently to therapy.

Although there is no generally agreed-upon standard definition of OAB severity, in clinical studies and practice the most commonly used measure is frequency of urinary incontinence episodes (IEs) [10–12]. For example, in one post hoc analysis, severity of baseline urinary incontinence was defined by the number of IEs/week; another defined symptom severity by number of IEs and micturitions per 24 hours [11,12]. The relevance of IEs as a meaningful measure of severity is supported by evidence of significant correlations between improvements in IEs and subjective patient-reported outcomes, such as the Patient's Perception of Bladder Condition (PPBC) and health related quality of life (HRQoL) [13,14]. In post hoc analyses designed to validate the PPBC questionnaire used in two studies, patients rating their bladder problems as severe reported an average of 3.3 IEs/day (> 21/week) [15]. These studies formed the basis for defining OAB severity by IE frequency in the present analysis.

The authors of the present investigation evaluated efficacy data from patients included in a pooled analysis of three phase III darifenacin studies in relation to their OAB symptom severity at baseline, as defined by IE frequency. Darifenacin is a muscarinic receptor antagonist with higher relative affinity for $M_3$ over the other muscarinic receptors. Darifenacin has demonstrated significant efficacy in symptom improvement with once-daily 7.5 mg and 15 mg doses [2]. However, patient response to this agent has not been assessed previously according to differing OAB severity.

The present retrospective analysis focuses on treatment efficacy and onset of action across different levels of OAB severity. In addition, HRQoL data from patients with differing OAB severity are analyzed to characterize the gains in quality of life associated with improvements in OAB symptoms across the two OAB severity subgroups.

## METHODS

### *Study Design*

The present analysis was conducted on pooled efficacy and tolerability data for marketed darifenacin doses (7.5 mg and 15 mg once daily) from three fixed dose, multicenter, randomized, double-blind, placebo-controlled, 12-week studies. The analysis is a post hoc assessment of previously reported data.

Consistent methodology, inclusion/exclusion criteria, efficacy, and safety assessments between the three individual studies allowed data to be pooled and have been reported in full previously [2]. In brief, each study was preceded by a screening visit, 2-week washout (if required) and a 2-week treatment-free or placebo run-in period after which patients were randomized to 12 weeks of double-blind treatment with study medication. Study visits were performed after 2, 6, and 12 weeks of treatment (Figure 1). The main inclusion criteria were: men and women aged ≥ 18 years with symptoms of OAB for ≥ 6 months; 5–50 IEs/week; an average of ≥ 8 micturitions/day; and at least one urgency episode/day.

Data on patient characteristics at baseline were assessed to determine whether there were any natural cutoff points for defining different degrees of severity of OAB. Because no cutoff points were seen, categories of OAB severity were defined by frequency of baseline IEs based on published literature. In the PPBC validation analyses previously mentioned, patients with severe bladder problems had on average 3.3 IEs/day, whereas those with moderate symptoms had on average 2.4 IEs/day [15]. Authors of another study found that patients requiring a dose increase with an antimuscarinic agent had a higher mean number of IEs/day when compared with patients not requiring a dose increase (3.06 versus 2.32, respectively) [11]. Hence, in the analyses reported here, mild/moderate OAB was defined as < 21 IEs/week at baseline and severe OAB as ≥ 21 IEs/week at baseline.

### *Assessments*

Efficacy was determined from electronic daily bladder diaries completed by the patients. They recorded IEs, episodes of urgency (ie, strong desire to void), severity of urgency (recorded


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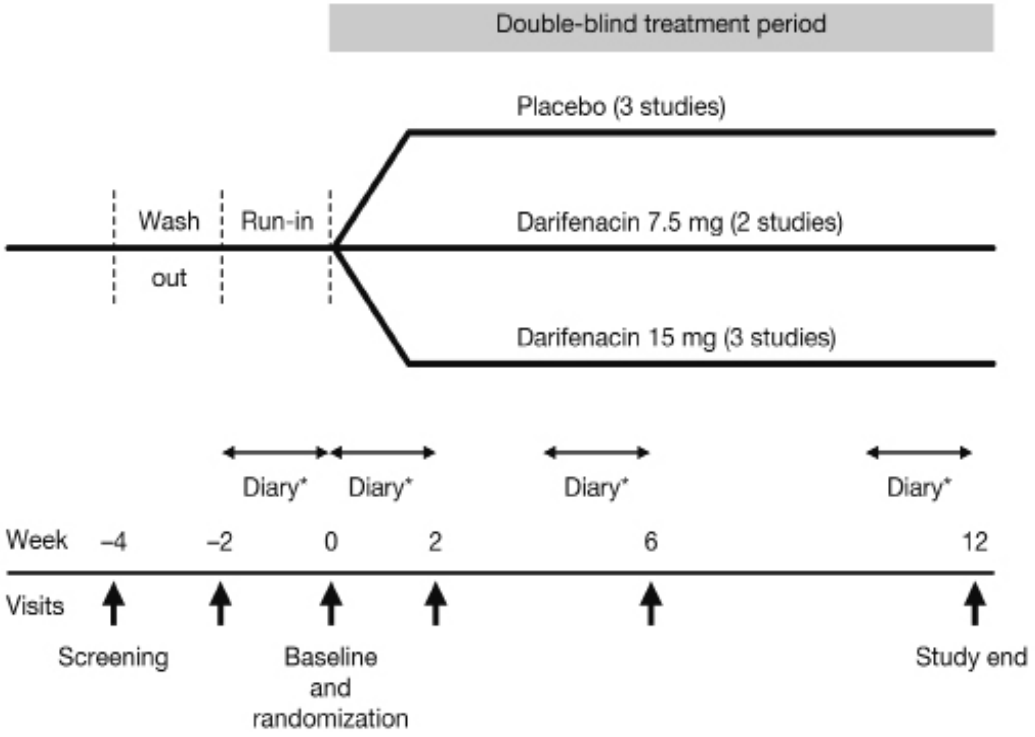
Figure 1. Study Design for Three Pooled Phase III Studies doi: 10.3834/uij.1944-5784.2009.06.16f1




*Diaries were completed for 2 weeks (in two studies) or 1 week (one study)

on a 100 mm visual analog scale, where 0 = mild, 100 = severe), micturitions, bladder capacity (volume voided), and IEs/week leading to change in pads or clothing (ie, significant leaks). The incidence of urinary urgency incontinence episodes (UUIEs) per week was derived from the number of IEs recorded, together with urgency.

In the present retrospective analysis, efficacy outcomes were analyzed for patients with mild/moderate OAB (< 21 IEs/week) or severe OAB (≥ 21 IEs/week) at baseline. The absolute and percentage change from baseline at each study visit and at the end of the study were assessed for the efficacy parameters recorded in patient diaries and for the derived OAB variable UUIE. Response rates were analyzed by the number of patients with reductions from baseline of > 3, > 5, and > 10 IEs/week. Shifts in patient OAB severity from baseline to the last observation were determined through changes in the number of IEs/week. The numbers of patients with improvements in OAB severity (change from ≥ 21 to < 21 IEs/week) and no change or worsening in OAB severity (change from < 21 to ≥ 21 IEs/week) were presented as a percentage of the total study population.

Improvements in HRQoL for each OAB severity category were assessed using the validated King's Health Questionnaire (KHQ) [16]. This multidimensional questionnaire measures HRQoL in both women and men with lower urinary tract dysfunction including OAB. HRQoL is assessed in 9 separate domains of the KHQ: Incontinence Impact, Severity Measures, Role Limitations, Social Limitations, Emotions, Physical Limitations, Personal Relationships, Sleep/Energy, and General Health Perception. The first 6 domains listed address concerns of particular relevance to OAB patients. All 9 domains of the KHQ are scored on a scale from 0 (best) to 100 (worst). Results are presented as mean changes in domain scores from baseline to study end, with decreasing scores representing improvement in HRQoL.

Finally, tolerability and safety were evaluated from withdrawal rates and adverse events (AEs).

### *Statistical Analysis*

The median differences between the baseline and the end of treatment were calculated for all bladder diary variables, and the patient groups receiving darifenacin and placebo treatments were compared. The median differences were

Table 1. Baseline Characteristics (N = 1053). doi: 10.3834/uij.1944-5784.2009.06.16t1

| Characteristic | Placebo Group for Darifenacin 7.5 mg | | Group Taking Darfenacin 7.5 mg | | Placebo Group for Darifenacin 15 mg | | Group Taking Darifenacin 15 mg | |
|---|---|---|---|---|---|---|---|---|
| | M/M[a] | Severe[b] | M/M[a] | Severe[b] | M/M[a] | Severe[b] | M/M[a] | Severe[b] |
| **N** | 173 | 99 | 216 | 121 | 244 | 142 | 199 | 131 |
| **Mean Age in Years (Range in Years)** | 55.7 (19-85) | 55.1 (29–84) | 55.3 (22–88) | 60.6 (26–88) | 56.1 (19-88) | 56.9 (29–85) | 56.5 (24–83) | 59.1 (25–85) |
| **Women, n (% of N)** | 141 (81.5) | 86 (86.9) | 183 (84.7) | 105 (86.8) | 204 (83.6) | 125 (88) | 164 (82.4) | 115 (87.8) |
| **Median Incontinence Episodes/Week, n** | 12 | 28.4 | 11.9 | 28.6 | 11.3 | 29 | 11.7 | 29.5 |
| **Median Urgency Episodes/Day, n** | 7.6 | 9.1 | 7.4 | 8.6 | 7.6 | 9.1 | 7.9 | 9.7 |
| **Median Urinary Urge Incontinence Episodes/Week, n** | 10.3 | 25.3 | 10.4 | 25.5 | 10.4 | 25.3 | 10.5 | 26 |
| **Median Micturitions/Day, n** | 9.9 | 10.6 | 10.1 | 10.3 | 10 | 10.5 | 10.5 | 10.9 |
| **Median Volume Voided/Day, mL** | 166.3 | 154.7 | 159.9 | 162.9 | 160.9 | 152.2 | 156.5 | 152.1 |
| **Incontinence Episodes/Week Resulting in Change of Pads or Clothing, n** | 6 | 16.3 | 6 | 18.4 | 5.4 | 15.5 | 5 | 18.5 |

[a] Patients with mild/moderate OAB baseline symptoms (< 21 incontinence episodes/week)
[b] Patients with severe OAB baseline symptoms (≥ 21 incontinence episodes per week)

statistically tested to see if they were different from zero using the Wilcoxon rank-sum test. Because the 7.5 mg dose was not used in all three studies, the relevant placebo comparison for each dose used only the placebo response from the matching studies (ie, the 7.5 mg darifenacin dose was compared with pooled placebo data from two studies; the 15 mg dose was compared with pooled placebo data from all three studies). The Hodges-Lehmann estimate, along with its associated 95% confidence interval, was derived for the median of the difference between the groups receiving darifenacin and the groups receiving the placebo.

Shift tables are presented showing the number and proportion of patients who changed their severity category from baseline to the last visit (last-observation-carried-forward [LOCF]). In addition, cumulative logistic regression was used to test for differences between darifenacin and placebo treatments with regards to the proportion of patients who had ≥ 21 IEs/week (severe OAB category), 5–21 IEs/week, or < 5 IEs/week at last visit (LOCF). Because the inclusion criteria for the original studies stated that patients should have > 5 IEs/week, < 5 IEs/week at LOCF was considered an important improvement. The covariate terms in the cumulative logistic regression were treatment, baseline severity of IEs, and study protocol.

The proportions of patients who had a reduction of > 3, > 5, and > 10 IEs/week from baseline to week 2, 6, 12, and last visit (LOCF) were analyzed for the two severity subgroups. For each severity subgroup, logistic regression (adjusted for baseline IEs/week, study, age, and gender) was used to compare the proportions of patients receiving darifenacin and placebo treatments who had each categorical reduction.

The KHQ scores of patients receiving 7.5 mg and 15 mg darifenacin were compared with the scores of patients receiving the placebo using an analysis of covariance model. The response variable was the absolute change from baseline in the KHQ domain and the covariates were study, baseline values, and treatment.

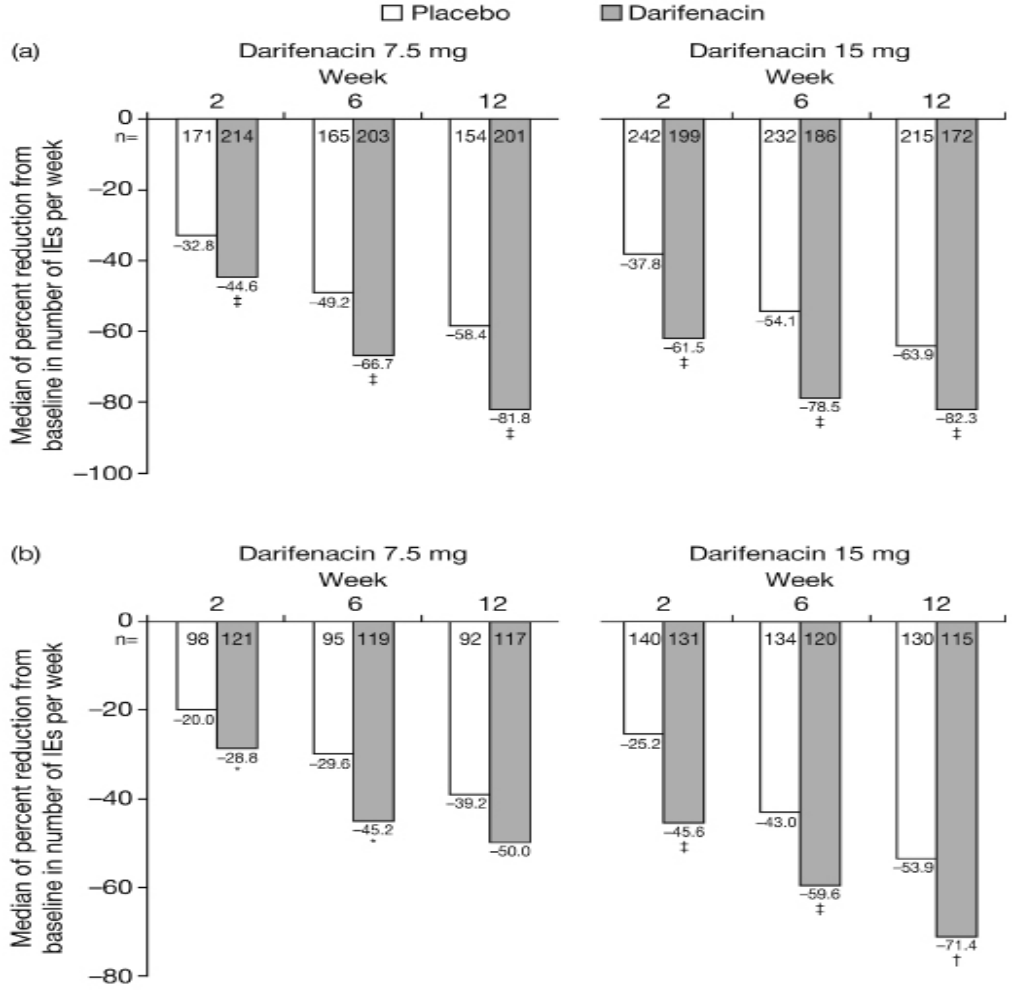
The efficacy parameters were analyzed for patients who received at least 1 dose of randomized study medication and had both a baseline and post-baseline efficacy assessment (full analysis population). Data were analyzed for the three study visits (at weeks 2, 6, and 12) or at the end of the study utilizing the LOCF method when week 12 data were missing. All statistical tests were performed using a 2-sided test at a 5% significance level without adjustment for multiple comparisons.

## RESULTS

### *Study Population*

Of the 1059 patients randomized to receive darifenacin 7.5 mg, 15 mg, or placebo, 1053 comprised the full analysis population evaluated in the present study. Six patients were not included

Figure 2. Efficacy of Darifenacin on Urinary Incontinence Episodes (IEs) per Week Over Time in Patients With OAB According to Baseline Symptom Severity: (a) Patients With Mild/Moderate Baseline Symptoms (< 21 IEs/Week) and (b) Patients with Severe Baseline Symptoms (≥ 21 IEs/Week). doi: 10.3834/uij.1944-5784.2009.06.16f2




*p<.05; †p≤.01; ‡p≤.001 vs placebo (Wilcoxon Rank Sum test)

due to incomplete data in the electronic diaries (2 patients receiving darifenacin 7.5 mg; 4 patients receiving darifenacin 15 mg).

In the full analysis population, the age of the patients ranged from 19 to 88 years and 85% were women. All patients were incontinent at baseline and 37% had severe symptoms as defined by this analysis (≥ 21 IEs/week). Baseline demographics were comparable across the patient OAB categories and are shown in Table 1. As expected, the median number of urgency episodes/day, UUIEs, and number of significant leaks/week were numerically lower for patients with mild/moderate OAB when compared with patients with severe OAB. However, micturition frequency and mean volume voided/day were comparable across the baseline OAB severity categories.

### *Efficacy Findings*

*Improvement in OAB Symptoms*

Patients with mild/moderate OAB who were taking both doses of darifenacin experienced improvement in all OAB symptoms analyzed (IEs and UUIEs/ week, urgency episodes/ day, severity of urgency, number of micturitions/day, bladder capacity, and significant leaks) when compared with patients taking the placebo. The median absolute and percent changes from baseline to each time point for these efficacy outcomes are shown in Table 2a. Also shown are the treatment effects (median differences between darifenacin and placebo) as absolute and percentage changes to each time point.

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Table 2a. Effects of Darifenacin and Placebo Treatment on OAB Symptoms, Shown as Absolute Change and (% Change) From Baseline to Each Time Point for Patients with Mild/Moderate Baseline Symptoms (< 21 Incontinence Episodes per Week) (N = 1053). doi: 10.3834/uij.1944-5784.2009.06.16t2a

| OAB Symptom | Week | Placebo Group for Darifenacin 7.5 mg | Group Taking Darfenacin 7.5 mg | Median Treatment Difference from Placebo | | | | Placebo Group for Darifenacin 15 mg | Group Taking Darfenacin 15 mg | Median Treatment Difference from Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Change | P[a] | % | P[a] | | | Change | P[a] | % | P[a] |
| Incontinence Episodes per Week, n | 2 | –3.6 (–32.8) | – 4.9 (–44.6) | -1.6 | ≤.01 | -15.1 | ≤.001 | –3.8 (–37.8) | –6 (–61.5) | -2.5 | ≤.001 | -22.5 | ≤.001 |
| | 6 | –5 (–49.2) | –6.1 (–66.7) | -1.7 | ≤.01 | -15 | ≤.001 | –5.1 (–54.1) | –7.7 (–78.5) | -2.6 | ≤.001 | -18.2 | ≤.001 |
| | 12 | –6 (–58.4) | –7 (–81.8) | -2 | ≤.01 | -16.1 | ≤.001 | –6.3 (–63.9) | –9 (–82.3) | -2.4 | ≤.001 | -14.1 | ≤.001 |
| | LOCF | –5.7 (–57.7) | –7 (–78.3) | -2 | ≤.001 | -16.3 | ≤.001 | –6 (–61.4) | –8.1 (–81.2) | -2.2 | ≤.001 | -13.8 | ≤.001 |
| Urgency Episodes per Day, n | 2 | –0.5 (–6.5) | –1.1 (–15.9) | -0.7 | ≤.001 | -11.2 | ≤.001 | –0.6 (–7) | –1 (–14.7) | -0.7 | ≤.001 | -9.7 | ≤.001 |
| | 6 | –1.1 (–14.3) | –1.7 (–25.7) | -0.7 | ≤.01 | -11.2 | ≤.01 | –1.2 (–14.5) | –2 (–26.3) | -0.9 | ≤.001 | -12.5 | ≤.001 |
| | 12 | –1.1 (–16) | –2.1 (–32.7) | -0.9 | ≤.01 | -13.5 | ≤.01 | –1.2 (–19.1) | –2.3 (–33.8) | -0.8 | ≤.01 | -12.3 | ≤.01 |
| | LOCF | –1 (–15.4) | –2 (–31.9) | -0.9 | ≤.001 | -13.9 | ≤.001 | –1.2 (–17.1) | –2.1 (–31.3) | -0.8 | ≤.01 | -11.8 | ≤.01 |
| Urinary Urge Incontinence Episodes per Week, n | 2 | –3 (–33.3) | –4.3 (–45.5) | -1.5 | ≤.01 | -14.9 | ≤.001 | –3.2 (–38) | –5.7 (–64.1) | -2.4 | ≤.001 | -24.6 | ≤.001 |
| | 6 | –4.9 (–52.9) | –6 (–66.7) | -1.4 | <.05 | -12.4 | ≤.01 | –5 (–56.7) | –7 (–81.7) | -2.1 | ≤.001 | -19.2 | ≤.001 |
| | 12 | –5.6 (–61.1) | –7 (–82.4) | -1.5 | <.05 | -13.8 | ≤.001 | –5.9 (–66.5) | –7.5 (–84.4) | -1.7 | ≤.001 | -14.7 | ≤.001 |
| | LOCF | –5.3 (–60.9) | –6.5 (–81.4) | -1.7 | ≤.01 | -14 | ≤.001 | –5.5 (–63.9) | –7 (–82.9) | -1.7 | ≤.001 | -14 | ≤.001 |
| Severity of Urgency on Visual Analog Scale, mm | 2 | –1 (–2) | –3.8 (–7.2) | -2.7 | ≤.01 | -5.2 | ≤.01 | –1.4 (–2.1) | –6.1 (–11) | -4 | ≤.001 | -7.7 | ≤.001 |
| | 6 | –4 (–6.2) | –7.8 (–15.3) | -4.3 | ≤.01 | -7.9 | ≤.01 | –3.8 (–6.6) | –7.9 (–14.8) | -4.2 | ≤.01 | -8.3 | ≤.001 |
| | 12 | –4.8 (–9.3) | –9.7 (–16.2) | -4.8 | ≤.01 | -9.1 | ≤.01 | –4.7 (–8.4) | –9.5 (–17.4) | -4.3 | ≤.01 | -8.7 | ≤.001 |
| | LOCF | –4.7 (–8.1) | –9 (–15.6) | -4.6 | ≤.01 | -9 | ≤.001 | –4.7 (–8) | – 8.7 (–15.5) | -4 | ≤.01 | -8 | ≤.001 |
| Micturitions per Day, n | 2 | –0.3 (–2.8) | –0.8 (–7.5) | -0.6 | ≤.001 | -5.8 | ≤.001 | –0.3 (–2.8) | –0.8 (–6.8) | -0.5 | ≤.01 | -4.5 | ≤.001 |
| | 6 | –1 (–9.3) | –1.4 (–14.4) | -0.6 | ≤.001 | -6.2 | ≤.001 | –1 (–9.1) | –1.6 (–15.2) | -0.6 | ≤.001 | -6.2 | ≤.001 |
| | 12 | –0.9 (–9.3) | –1.9 (–18.5) | -1 | ≤.001 | -9.7 | ≤.001 | –1 (–10.2) | –1.6 (–15.4) | -0.6 | ≤.01 | -6.1 | ≤.001 |
| | LOCF | –0.9 (–9) | –1.8 (–17.8) | -1 | ≤.001 | -9.4 | ≤.001 | –1 (–9.9) | –1.6 (–15.3) | -0.6 | ≤.001 | -6 | ≤.001 |
| Median Volume per Void, mL | 2 | 1.2 (0.6) | 8.3 (6.7) | 11.2 | ≤.001 | 6.9 | ≤.001 | 1.1 (0.7) | 14.9 (9.3) | 13.1 | ≤.001 | 8.3 | ≤.001 |
| | 6 | 10.9 (6.8) | 18.3 (10.7) | 10.3 | ≤.01 | 6.5 | ≤.01 | 6.9 (4.7) | 28.6 (18.6) | 21 | ≤.001 | 13.5 | ≤.001 |
| | 12 | 9.8 (6.2) | 13.8 (9.9) | 7.8 | ns | 4.5 | ns | 8.3 (5.7) | 35.2 (22.2) | 25.4 | ≤.001 | 16.6 | ≤.001 |
| | LOCF | 8.3 (5.5) | 14.3 (10.3) | 10.4 | <.05 | 6.2 | <.05 | 6.8 (4.7) | 29.4 (18.8) | 20.9 | ≤.001 | 13.4 | ≤.001 |
| IE per Week Resulting in Pad/Clothing Change, n | 2 | –1.2 (–25.9) | –3 (–50.3) | -1.7 | ≤.001 | -25 | ≤.001 | –1.4 (–30) | –3.3 (–69.3) | -1.6 | ≤.001 | -30.7 | ≤.001 |
| | 6 | –2.2 (–50.6) | –3.8 (–74) | -1.6 | ≤.001 | -16.7 | ≤.001 | –2.2 (–57) | –3.8 (–81) | -1.4 | ≤.01 | -16.7 | ≤.001 |
| | 12 | –2.2 (–60) | –4.3 (–84.6) | -1.8 | ≤.001 | -13.1 | ≤.001 | –2.7 (–68.5) | –4 (–83.3) | -1.4 | ≤.01 | -8.7 | ≤.01 |
| | LOCF | –2.1 (–55.2) | –4.3 (–83.2) | -2.1 | ≤.001 | -17.2 | ≤.001 | –2.2 (–66.7) | –3.8 (–82.7) | -1.4 | ≤.001 | -11.5 | ≤.001 |

Abbreviations: IE, incontinence episodes; LOCF, last observation carried forward; ns, not statistically significant ($p \geq .05$)

[a]Wilcoxon Rank Sum test

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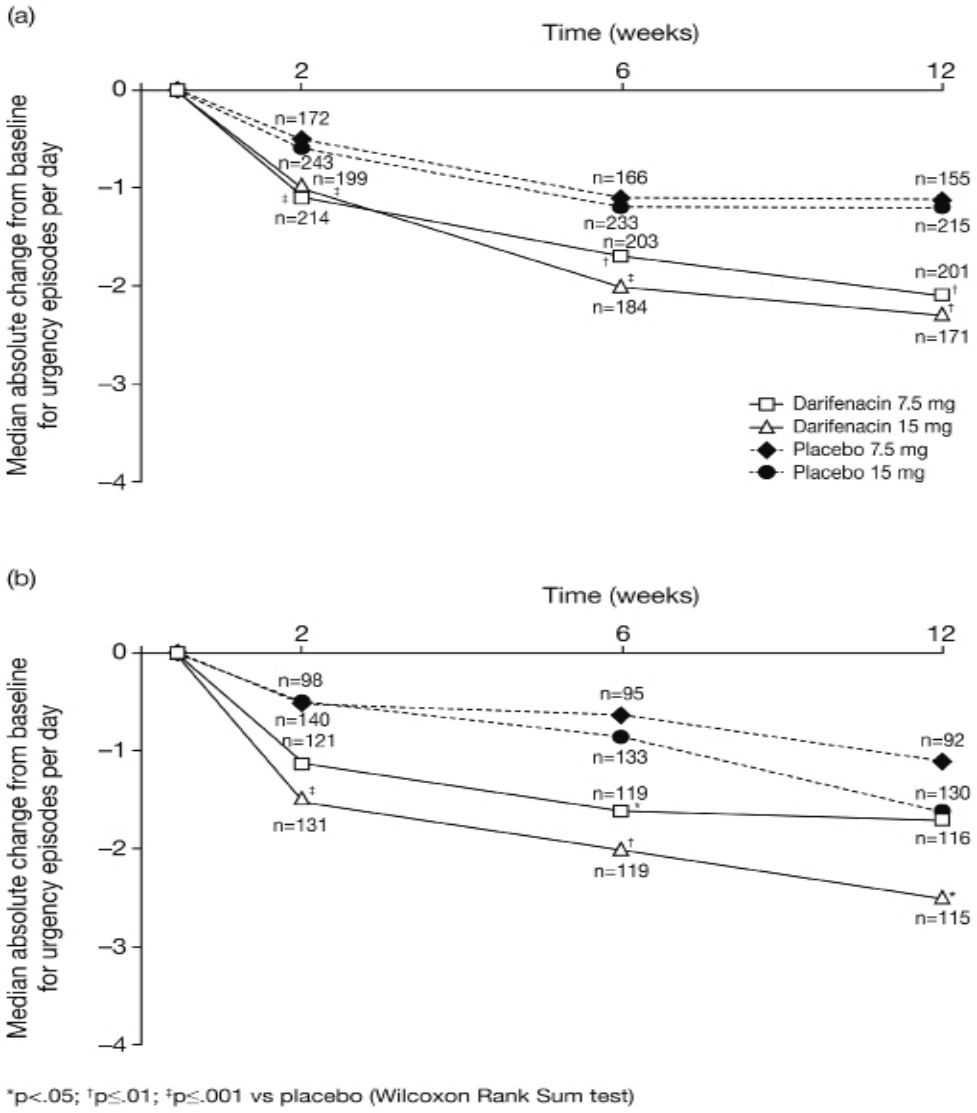
Table 2b. Effects of Darifenacin and Placebo Treatment on OAB Symptoms, Shown as Absolute Change and (% Change) From Baseline to Each Time Point for Patients with Severe Baseline Symptoms (≥ 21 Incontinence Episodes per Week) (N = 1053). doi: 10.3834/uij.1944-5784.2009.06.16t2b

| OAB Symptom | Week | Placebo Group for Darifenacin 7.5 mg | Group Taking Darfenacin 7.5 mg | Median Treatment Difference from Placebo | | | | Placebo Group for Darifenacin 15 mg | Group Taking Darfenacin 15 mg | Median Treatment Difference from Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Change | P[a] | % | P[a] | | | Change | P[a] | % | P[a] |
| Incontinence Episodes per Week, n | 2 | –5 (–20) | –9.1 (–28.6) | -3.7 | <.05 | -12.1 | <.05 | –7.7 (–25.2) | –13.4 (–45.6) | -5.8 | ≤.001 | -19.8 | ≤.001 |
| | 6 | –8 (–29.6) | –13.5 (–45.2) | -5.1 | ≤.01 | -14.7 | <.05 | –11.3 (–43) | –17 (–59.6) | -6.5 | ≤.001 | -21 | ≤.001 |
| | 12 | –11(–39.2) | –15 (–50) | -3 | ns | -7.2 | ns | –13.7 (–53.9) | –18.5 (–71.4) | -4.7 | ≤.01 | -14.1 | ≤.01 |
| | LOCF | –11 (–36.8) | –15 (–50) | -3 | ns | -7.3 | ns | –13.5 (–53.3) | –18.5 (–70.7) | -4.7 | ≤.001 | -13.6 | ≤.01 |
| Urgency Episodes per Day, n | 2 | –0.5 (–5.8) | –1.1 (–11.4) | -0.4 | ns | -4.8 | ns | –0.5 (–5.7) | –1.5 (–16.4) | -1 | ≤.001 | -11.6 | ≤.001 |
| | 6 | –0.6 (–6.7) | –1.6 (–19.5) | -0.9 | <.05 | -10.5 | <.05 | –0.8 (–8.8) | –1.9 (–19.3) | -1.1 | ≤.01 | -12.7 | ≤.001 |
| | 12 | –1.1 (–11.1) | –1.7 (–20.9) | -0.4 | ns | -5.8 | ns | –1.6 (–17.5) | –2.5 (–27.7) | -1 | <.05 | -12.4 | ≤.01 |
| | LOCF | –0.9 (–10.2) | –1.7 (–21.4) | -0.5 | ns | -7.9 | ns | –1.4 (–14) | –2.4 (–27.3) | -1.1 | ≤.01 | -12.9 | ≤.01 |
| Urinary Urge Incontinence Episodes per Week, n | 2 | –5.5 (–25.5) | –9 (–32.2) | -3.8 | <.05 | -11.5 | ns | –7.2 (–28.5) | –12.2 (–46.8) | -5.4 | ≤.001 | -19.8 | ≤.001 |
| | 6 | –5.8 (–29.6) | –12.3 (–46.5) | -5.3 | ≤.01 | -14.4 | <.05 | –9.5 (–45.5) | –15 (–65.5) | -5.7 | ≤.001 | -18.7 | ≤.001 |
| | 12 | –9 (–48.1) | –14.5 (–51.3) | -4 | <.05 | -5.9 | ns | –11.8 (–57.8) | –17.2 (–70.8) | -4.3 | ≤.01 | -11 | <.05 |
| | LOCF | –9 (–48.1) | –14 (–51.3) | -3.7 | <.05 | -5.3 | ns | –11.8 (–57.2) | –17.2 (–70.8) | -4.3 | ≤.01 | -11 | <.05 |
| Severity of Urgency on Visual Analog Scale, mm | 2 | –0.9 (–1.3) | –5.3 (–8.5) | -3.1 | <.05 | -5.4 | <.05 | –1.6(–2.6) | –7.2 (–11.2) | -4.8 | ≤.001 | -8 | ≤.001 |
| | 6 | –0.7 (–1.5) | –6.4 (–10.2) | -4.8 | <.05 | -8.2 | <.05 | –2.6 (–4.4) | –9.4 (–14.9) | -7.4 | ≤.001 | -12.3 | ≤.001 |
| | 12 | –3.1 (–6.2) | –4.9 (–6.7) | -2.5 | ns | -4.3 | ns | –4.1 (–7.3) | –9.7 (–15.8) | -5.7 | ≤.01 | -9.7 | ≤.01 |
| | LOCF | –3.1 (–6.2) | –5.3 (–9.2) | -2.8 | ns | -4.6 | ns | –3.9 (–7.3) | –10.4 (–17) | -6.4 | ≤.001 | -10.7 | ≤.001 |
| Micturitions per Day, n | 2 | –0.5 (–4) | –1.1 (–8.7) | -0.4 | ns | -3.1 | ns | –0.5 (–4.2) | –1.2 (–9.8) | -0.5 | <.05 | -4.8 | <.05 |
| | 6 | –0.7 (–7.3) | –1.4 (–13.6) | -0.5 | ns | -4.4 | ns | –0.9 (–8) | –1.6 (–12.7) | -0.9 | ≤.001 | -8.3 | ≤.001 |
| | 12 | –1.1 (–10) | –1.5 (–14.2) | -0.3 | ns | -1.9 | ns | –1.3 (–11.3) | –2.3 (–19.7) | -0.9 | ≤.01 | -8.3 | ≤.01 |
| | LOCF | –1 (–9.1) | –1.4 (–14) | -0.3 | ns | -2 | ns | –1.2 (–10.1) | –2.2 (–19.5) | -0.9 | ≤.001 | -8.3 | ≤.01 |
| Median Volume per Void, mL | 2 | 4.6 (3.5) | 7.4 (4.8) | 6.4 | ns | 4.3 | ns | 5.2 (4.1) | 11.8 (9.2) | 8.4 | <.05 | 6.6 | <.05 |
| | 6 | 5.6 (4.3) | 19 (9.9) | 8.4 | ns | 5.7 | ns | 5.7 (4.3) | 26.5 (17.7) | 17.2 | ≤.01 | 13.4 | ≤.001 |
| | 12 | 7.1 (5.2) | 15.7 (8) | 8.2 | ns | 3.8 | ns | 6.5 (4.3) | 26.6 (17.5) | 19.9 | ≤.01 | 13.8 | ≤.01 |
| | LOCF | 6.4 (4.7) | 15.7 (8) | 8.9 | ns | 4.4 | ns | 5.3 (3.4) | 25.1 (16.4) | 18.3 | ≤.001 | 12.6 | ≤.001 |
| IE per Week Resulting in Pad/Clothing Change, n | 2 | –2 (–22.7) | –4 (–30.8) | -2.3 | <.05 | -12.7 | ns | –2.2 (–26.6) | –6.5 (–45.5) | -4.2 | ≤.001 | -21.3 | ≤.001 |
| | 6 | – 3.4 (–39.2) | –6 (–50.3) | -3.8 | ≤.01 | -15.8 | <.05 | –4 (–50) | –9 (–63.2) | -4.9 | ≤.001 | -19.6 | ≤.001 |
| | 12 | –3.5 (–42.9) | –6.9 (–51.7) | -2.1 | ns | -10.4 | ns | –5 (–45) | –9.9 (–73) | -4.3 | ≤.001 | -21.3 | ≤.001 |
| | LOCF | –3.9 (–42.9) | –7 (–53.7) | -2.4 | ns | -11.3 | ns | –4.6 (–43.2) | –9.8 (–73.3) | -4.9 | ≤.001 | -22.5 | ≤.001 |

Abbreviations: IE, incontinence episodes; LOCF, last observation carried forward; ns, not statistically significant (p ≥ .05)
[a]Wilcoxon Rank Sum test

Figure 3. Efficacy of Darifenacin on Urinary Urgency Episodes per Day Over Time in Patients With OAB According to Baseline Symptom Severity: (a) Patients With Mild/Moderate Baseline Symptoms (< 21 Incontinence Episodes [IEs] per Week) and (b) Patients with Severe Baseline Symptoms (≥ 21 IEs/Week). doi: 10.3834/uij.1944-5784.2009.06.16f3




*p<.05; †p≤.01; ‡p≤.001 vs placebo (Wilcoxon Rank Sum test)

Patients with mild/moderate OAB who were taking darifenacin doses of 7.5 mg and 15 mg had statistically significant improvements in all efficacy parameters from baseline to week 12 and/or last visit (LOCF), when compared with patients taking the placebo (Table 2a; Figure 2; Figure 3). Symptom improvements were similar for patients taking darifenacin 7.5 mg and 15 mg. For example, at week 12 the median percent reduction in number of *IEs/week* was 81.8% and 82.3% with 7.5 mg and 15 mg darifenacin, respectively, compared with 58.4% and 63.9% median percent reduction in the corresponding placebo groups ($P \leq .001$ for both darifenacin doses) (Figure 2). These results were paralleled by statistically significant reductions in *significant leaks* from baseline to week 12 (84.6% [$P \leq .001$] and 83.3% [$P \leq .01$] for patients receiving darifenacin 7.5 mg and 15 mg, respectively, versus 60% and 68.5% for patients receiving the placebo) and *severity of urgency* (16.2% [$P \leq .01$] and 17.4% [$P \leq .001$] for patients receiving darifenacin 7.5mg and 15 mg, respectively, versus 9.3% and 8.4% for patients receiving the placebo).

Patients with severe OAB who were taking 15 mg of darifenacin had statistically significant improvement in all efficacy parameters from baseline to week 12 or LOCF when compared with patients taking the placebo (Table 2b; Figure 2; Figure 3).

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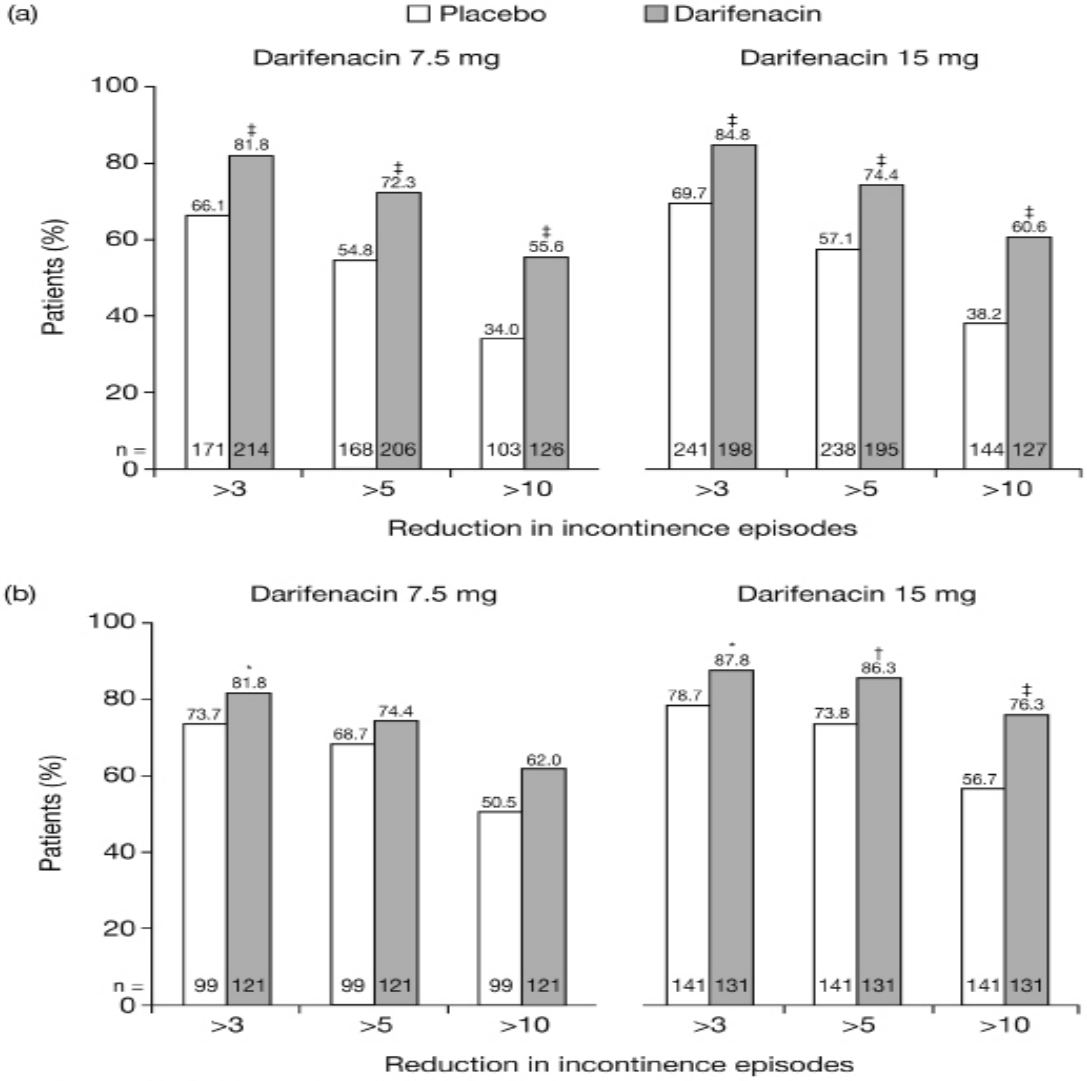
Figure 4. Proportion of Patients at Last Observation Responding With Different Levels of Reduction in Incontinence Episodes (IEs) per Week According to Baseline Symptom Severity: (a) Patients with Mild/Moderate Baseline Symptoms (< 21 IEs/Week) and (b) Patients with Severe Baseline Symptoms (≥ 21 IEs/Week). doi: 10.3834/uij.1944-5784.2009.06.16f4

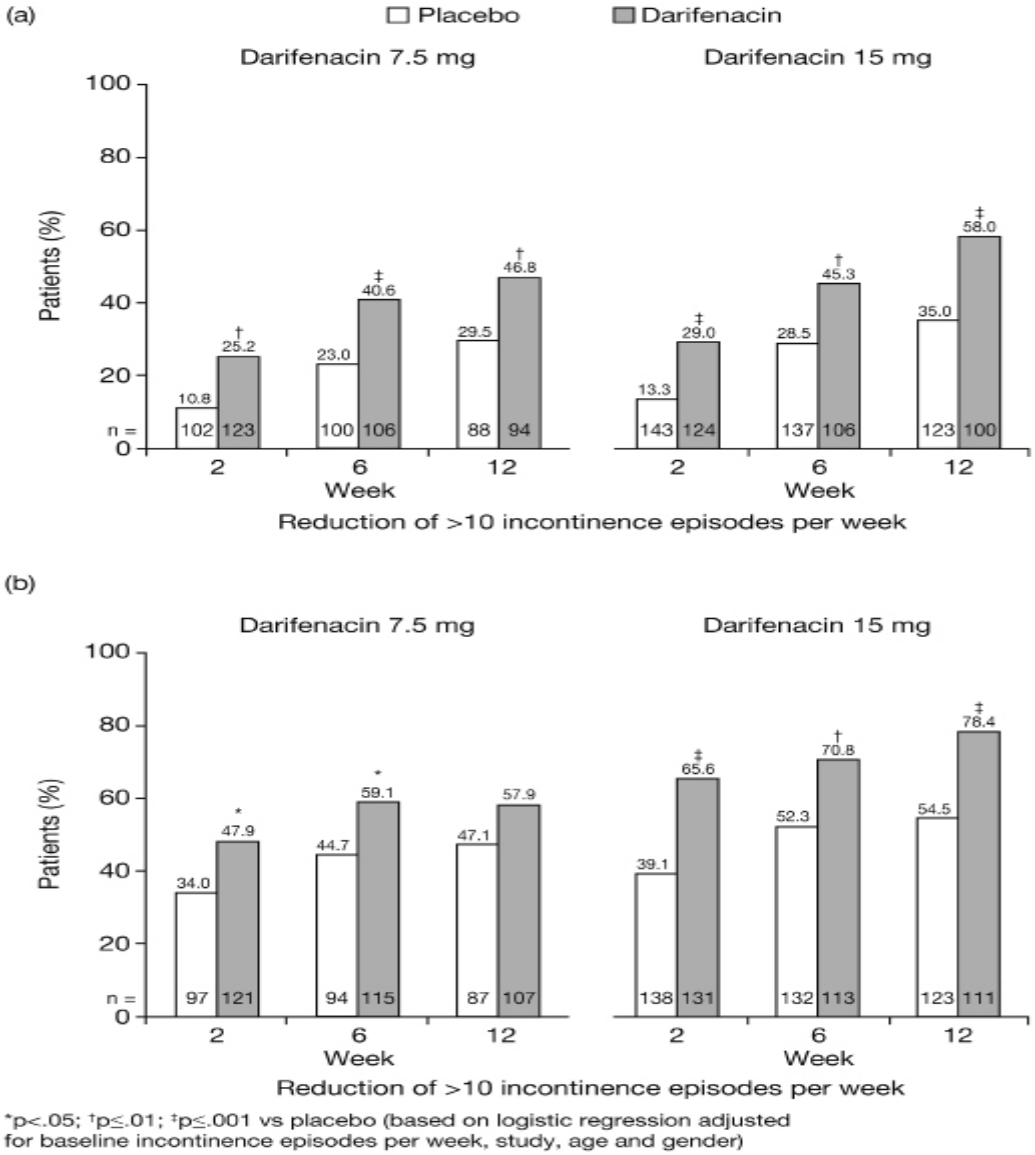



*p<.05; †p≤.01; ‡p≤.001 vs placebo (based on logistic regression adjusted for baseline incontinence episodes per week, study, age and gender)

The lower dose of darifenacin was associated with less marked improvements in this patient category. For example, at week 12 the median percent reduction in number of *IEs/week* was 50% (not statistically significant [NS]) and 71.4% ($P \leq .01$) for patients receiving 7.5 mg and 15 mg of darifenacin, respectively, compared with 39.2% and 53.9% for patients receiving the placebo (Figure 2). Again, these results were paralleled by reductions in other OAB parameters, such as *significant leaks* (51.7% [NS] and 73% [$P \leq .001$] for patients taking darifenacin 7.5 mg and 15 mg, respectively, versus 42.9% and 45% for patients taking the placebo), *severity of urgency* (6.7% [NS] and 15.8% [$P \leq .01$] for patients taking darifenacin 7.5 mg and 15 mg, respectively, versus 6.2% and 7.3% for patients taking the placebo) and *bladder capacity* (8% [NS] and 17.5% [$P \leq .01$] for patients taking darifenacin 7.5 mg and 15 mg, respectively, versus 5.2% and 4.3% for patients taking the placebo).

Statistically significant symptom improvements were observed for all micturition parameters at the earliest time point (week 2) in patients with mild/moderate OAB receiving both darifenacin doses and in patients with severe OAB treated with 15 mg. These improvements were sustained throughout the study until the last visit (LOCF) (Table 2a; Table 2b; Figure 2; Figure 3).

Figure 5. Proportion of Patients Over Time With a Reduction of > 10 Incontinence Episodes per Week According to Baseline Symptom Severity: (a) Patients With Mild/Moderate Baseline Symptoms (< 21 Incontinence Episodes (IEs) per Week) and (b) Patients with Severe Baseline Symptoms (≥ 21 IEs/Week). doi: 10.3834/uij.1944-5784.2009.06.16f5




*p<.05; †p≤.01; ‡p≤.001 vs placebo (based on logistic regression adjusted for baseline incontinence episodes per week, study, age and gender)

*Response Rates*

By the last observation, patients had responded to taking darifenacin doses of 7.5 mg and 15 mg with reductions from baseline of > 3, > 5 and > 10 IEs/week, when compared with patients taking the placebo (Figure 4). These reductions reached statistical significance for patients with mild/moderate OAB taking darifenacin doses of 7.5 mg and 15 mg and for patients with severe OAB taking darifenacin 15 mg. More than 55% of patients with mild/moderate OAB taking either darifenacin dosage achieved a reduction of > 10 IEs/week when compared with patients taking the placebo ($P < .01$). A total of 76.3% of patients with severe OAB taking darifenacin 15 mg dosage achieved a reduction of > 10 IEs/week when compared with patients taking the placebo ($P < .001$).

The percentage of patients responding to 7.5 mg and 15 mg darifenacin treatment with a reduction in IEs of > 10 was statistically significant at the earliest time point (week 2), regardless of baseline severity (Figure 5).

Table 3. Change in the Severity of Patient Incontinence Episodes (IE) Between Baseline and the Last Observation (N = 1053). doi: 10.3834/uij.1944-5784.2009.06.16t3

| Treatment Group | Baseline IE | Total n | IE at Last Observation n (%)[a] | | |
|---|---|---|---|---|---|
| | | | < 5 | ≥ 5-21 | ≥ 21[b] |
| Placebo Group for Darifenacin 7.5 mg | < 5 | 1 | 1 (100) | – | – |
| | ≥ 5-21 | 171 | 86 (50.3) | 76 (44.4) | 9 (5.3) |
| | ≥ 21 | 99 | 19 (19.2) | 41 (41.4) | 39 (39.4) |
| Group Taking Darifenacin 7.5 mg | < 5 | 1 | 1 (100) | – | – |
| | ≥ 5-21 | 213 | 141 (66.2) | 66 (31) | 6 (2.8) |
| | ≥ 21 | 121 | 26 (21.5) | 54 (44.6) | 41 (33.9) |
| Placebo Group for Darifenacin 15 mg | < 5 | 2 | 2 (100) | – | – |
| | ≥ 5-21 | 241 | 134 (55.6) | 95 (39.4) | 12 (5) |
| | ≥ 21 | 141 | 30 (21.3) | 60 (42.6) | 51 (36.2) |
| Group Taking Darifenacin 15 mg | < 5 | 2 | 1 (50) | 1 (50) | – |
| | ≥ 5-21 | 197 | 140 (71.1) | 54 (27.4) | 3 (1.5) |
| | ≥ 21 | 131 | 42 (32.1) | 66 (50.4) | 23 (17.6) |

[a] Based on number of patients in each baseline severity category for each treatment group
[b] Defined as severe OAB

*Incontinence Severity at Study End*

A total of 66% of patients with severe incontinence at baseline (≥ 21 IEs/week) taking 7.5 mg of darifenacin improved to mild/moderate incontinence at the last observation; 82.4% of patients with severe incontinence at baseline taking 15 mg of darifenacin had similar improvement. Only 2.2% (n=9) of patients with mild/moderate incontinence at baseline taking darifenacin 7.5 or 15 mg had developed severe OAB at the last observation.

A total of 21.5% of patients with severe incontinence at baseline receiving 7.5 mg of darifenacin had < 5 IEs/week at the end of the study, compared with 19.2% of patients taking the placebo; 44.6% of patients with severe incontinence receiving 7.5 mg of darifenacin had 5-20 IEs/week at the study end, compared with 41.4% of patients taking the placebo (Table 3). In contrast, 32.1% of patients with severe incontinence at baseline receiving 15 mg of darfenacin had < 5 IEs/week at the end of the study, compared with 21.3% of patients taking the placebo; 50.4% of patients with severe incontinence receiving 15 mg of darfenacin had 5-20 IEs/week at the end of the study, compared with 42.6% of patients taking the placebo. After adjusting for baseline severity and study protocol, the treatment effect for darifenacin at each dose was significantly superior to the placebo ($P < .002$) at the last visit (LOCF).

*Improvements in HRQoL*

Patients with mild/moderate OAB taking both doses of darifenacin had statistically significant improvements in KHQ scores at the last observation for 7 out of the 9 domains ($P < .05$) when compared with patients taking the placebo (Table 4). Six of the 7 domains are considered particularly relevant for OAB symptoms (Incontinence Impact, Severity Measures, Role Limitations, Social Limitations, Emotions, and Physical Limitations).

Patients with severe OAB taking 15 mg of darifenacin had statistically significant improvements in KHQ scores at the last observation for 5 of the 9 domains ($P < .05$) when compared with patients taking the placebo (Table 4). All 5 domains are considered relevant for OAB symptoms (Incontinence Impact, Severity Measures, Role Limitations, Social Limitations, Emotions).

### *Tolerability and Safety*

In a previous study by Chapple et al [2], darifenacin was well tolerated at both 7.5 and 15 mg doses. The overall incidence of all-causality AEs (as analyzed for the population as a whole) was 54% and 65.6% for patients taking darifenacin 7.5 mg and 15 mg, respectively, and 48.7% for patients taking the placebo.

Table 4. Mean Absolute Change from Baseline to the Last Study Visit (LOCF) and Least Squares (LS) Mean Difference Between Treatments in the King's Health Questionnaire Domains (N = 1053). doi: 10.3834/uij.1944-5784.2009.06.16t4

| King's Health Questionnaire Domain | Placebo Group for Darifenacin 7.5 mg | Group Taking Darfenacin 7.5 mg | LS Mean Difference Between Treatments | *P*[a] | Placebo Group for Darifenacin 15 mg | Group Taking Darfenacin 15 mg | LS Mean Difference Between Treatments | *P*[a] |
|---|---|---|---|---|---|---|---|---|
| **Patients with Mild/Moderate Baseline Symptoms (< 21 Incontinence Episodes per Week)** | | | | | | | | |
| **Incontinence Impact** | –12.3 | –26.7 | –13.1 | ≤.001 | –10.8 | –20.4 | –9.7 | ≤.001 |
| **Severity Measures** | –4.1 | –12.8 | –8.4 | ≤.001 | –5 | –12.3 | –7.9 | ≤.001 |
| **Role Limitations** | –14.8 | –27.8 | –13 | ≤.001 | –14 | –23.4 | –11.2 | ≤.01 |
| **Social Limitations** | –4.9 | –15.4 | –9.2 | ≤.001 | –5.9 | –14.4 | –8.6 | ≤.001 |
| **Emotions** | –7.9 | –15.6 | –8.4 | ≤.001 | –8.1 | –12.3 | –5.6 | <.05 |
| **Physical Limitations** | –17 | –24.1 | –8.1 | ≤.01 | –16.9 | –22.7 | –8 | ≤.01 |
| **Personal Relationships** | –4.7 | –6.6 | –1.8 | ns | –4 | –5.8 | –2.5 | ns |
| **Sleep/Energy** | –7.5 | –12.8 | –6.4 | ≤.01 | –7 | –9.7 | –4 | <.05 |
| **General Health Perception** | –1.7 | –1.9 | –1.6 | ns | –0.2 | –1 | –1.4 | ns |
| **Patients with Severe Baseline Symptoms (≥ 21 Incontinence Episodes per Week)** | | | | | | | | |
| **Incontinence Impact** | –9.3 | –17 | –6.6 | ns | –8.6 | –21.6 | –11.9 | ≤.001 |
| **Severity Measures** | –2.5 | –9.1 | –5.9 | <.05 | –2.4 | –14.6 | –10.8 | ≤.001 |
| **Role Limitations** | –16.2 | –18.7 | –3.2 | ns | –13.8 | –23.7 | –10.6 | ≤.01 |
| **Social Limitations** | –4.2 | –12.1 | –5.8 | ns | –5.7 | –13.3 | –7.4 | ≤.01 |
| **Emotions** | –9.5 | –12 | –1.9 | ns | –9 | –16.5 | –6.7 | <.05 |
| **Physical Limitations** | –14.9 | –13.5 | –2.2 | ns | –13.7 | –18.2 | –7 | ns |
| **Personal Relationships** | –4.2 | –8.3 | –7.5 | ns | –5.6 | –5.2 | –1.3 | ns |
| **Sleep/Energy** | –7.9 | –2.3 | 4.2 | ns | –8.5 | –10.6 | –2.2 | ns |
| **General Health Perception** | –5.9 | –1.1 | 2.7 | ns | –3.9 | –0.4 | 1 | ns |

Abbreviation: ns, not statistically significant (p ≥ .05)
[a]Treatment difference vs placebo (analysis of covariance)

As expected, the incidence of AEs reported was not affected by baseline severity but increased with the dosage level. The most common AEs were *dry mouth* and *constipation*. These AEs resulted in treatment discontinuation for 0.6%, 2.1%, and 0.3% of patients taking darifenacin 7.5 mg, 15 mg, and the placebo, respectively.

In the present study, *dry mouth* was reported by 21.3% and 35.7% of patients with mild/moderate OAB receiving darifenacin 7.5 mg and 15 mg, respectively, compared with 11.6% and 10.7% for matched patients receiving the placebo. For patients with severe OAB, 18.2% and 35.9% of those treated with darifenacin 7.5 mg and 15 mg, respectively, reported *dry mouth* compared with 1% and 4.2% for matched patients treated with the placebo. *Constipation* was reported by 15.3% and 20.1% of patients with mild/moderate OAB receiving darifenacin 7.5 mg and 15 mg, respectively, compared with 9.2% and 7.4% for matched patients receiving the placebo. For patients with severe OAB, 14% and 23.7% of patients treated with darifenacin 7.5 mg and 15 mg, respectively, reported *constipation* compared with 1.0% and 4.2% of matched patients treated with the placebo.

## DISCUSSION

The present retrospective analysis demonstrated that darifenacin treatment effectively relieved the symptoms of OAB regardless of baseline severity, defined by the frequency of IEs. In patients with mild/moderate OAB, darifenacin 7.5 mg once

daily was sufficient to achieve a statistically significant effect for all efficacy parameters analyzed at the end of the study. In patients with severe OAB, darifenacin 15 mg once daily was more effective, with statistically significant improvements achieved in all parameters at the end of the study.

Statistically significant improvements in OAB symptoms were seen after as few as 2 weeks of treatment and were sustained over time. Improvements across all time points were seen for patients with mild/moderate OAB receiving both darifenacin doses when compared with the placebo and for patients with severe OAB receiving darifenacin 15 mg. By the last observation, the analysis showed that over two-thirds of patients with severe OAB at baseline improved to mild/moderate OAB following darifenacin treatment. This improvement was greatest for patients receiving darifenacin 15 mg, where the difference reached statistical significance when compared with patients receiving the placebo.

Patients taking 7.5 mg and 15 mg of darifenacin also had statistically significant improvements in HRQoL parameters at the last observation, when compared with patients taking the placebo. Improvements in KHQ scores reached statistical significance with darifenacin 7.5 mg for patients with mild/moderate OAB severity, whereas darifenacin 15 mg produced statistically significant improvements in patients with both mild/moderate and severe OAB.

The large patient population obtained by pooling studies for the present analysis is considered a strength of the study. This pooling allowed patients with different OAB severities to be categorized for comparison. However, the smaller number of patients in some subsets should be taken into account when interpreting the data.

Overall, the present results are consistent with post hoc analyses of treatment response data for patients with severe OAB from clinical studies of other antimuscarinic agents, such as solifenacin, tolterodine, and fesoterodine [3,6,17,18]. However, differences in the definitions of severe OAB do not allow direct comparisons across studies. In a retrospective analysis of data from a randomized, placebo-controlled study of tolterodine extended-release, baseline severity of the patient population was stratified (1–6, 7–13, 14–20, and ≥ 21 IEs/week) [12]. Mean reductions in weekly IEs were sustained across the study duration for each level of baseline symptom severity. However, the results did not show whether patients with severe OAB would benefit from dose titration, because this analysis only evaluated one dose of tolterodine. In contrast, an analysis of pooled data from patients receiving solifenacin 5 mg or 10 mg in clinical studies showed that 10 mg was more effective than a placebo or 5 mg at improving symptoms in patients with severe OAB [3]. The authors defined severe OAB as patients having at least one of the following: > 3 IEs/24 hours; > 8 urgency episodes/24 hours; or > 13 micturition episodes/24 hours. Another analysis of patient symptom severity in a clinical study of solifenacin concluded that patients with more severe OAB symptoms at baseline (based on IEs, urgency episodes, and micturitions/24 hours) were more likely to request a dose increase (in accordance with approved labelling) [11]. The data for both darifenacin in the present study and solifenacin in the previous study highlight the value of offering dose titration to patients.

A previous study has shown that the two licensed darifenacin treatment doses allowed for individualized dosing according to patient needs [9]. Results of this prior study are supported by the present retrospective analysis, which demonstrated that the higher darifenacin dose was well tolerated and provided increased efficacy for patients with more severe OAB. However, the present findings are limited by the use of fixed darifenacin doses that did not allow for patients to select their optimum dose, as may be done in clinical practice. The assessment of dose titration in clinical studies provides more information about patient response to treatment [9] and would be useful for evaluation of response in relation to baseline severity of OAB. The option to up-titrate in a flexible-dosing study would allow patients to individualize their treatment according to their OAB severity and drug sensitivity.

In summary, the analysis reported here has demonstrated that darifenacin 7.5 mg and 15 mg effectively relieved OAB symptoms, with an onset of action as early as 2 weeks. Patients with severe OAB benefit from the higher darifenacin dose of 15 mg. The results also highlight the importance of analyzing OAB severity when selecting appropriate pharmacotherapy and doses for patients with OAB, both in clinical studies and clinical practice. Adequate consideration needs to be given to symptom severity in treatment algorithms and management.

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**CONFLICT OF INTEREST**:
Dmochowski: Consultant to the sponsors
Larson-Peters: Employed by a sponsor (Procter & Gamble)
Aronstein: Employed by a sponsor (Procter & Gamble)
Seifu: Employed by a sponsor (Novartis Pharmaceuticals Corp)

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