

EFFICACY AND TOLERABILITY OF DARIFENACIN, A MUSCARINIC M₃ SELECTIVE RECEPTOR ANTAGONIST, VERSUS OXYBUTYNIN IN THE TREATMENT OF OVERACTIVE BLADDER (OAB)

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INTRODUCTION

- Darifenacin is an M₃ selective receptor antagonist (M₃ SRA) with proven efficacy in the treatment of overactive bladder (OAB)^{1,2} and a reduced propensity for cognitive and cardiac adverse events (AEs).^{3,4}
- The aim of this phase II study was to evaluate the tolerability of darifenacin compared with oxybutynin, which is not selective for the M₃ receptor, in a double-blind, placebo-controlled study in patients with OAB. Although not powered for efficacy some efficacy parameters were assessed.

METHODS

Patients and study design

- This was a phase II multicenter, randomized, double-blind, placebo-controlled, crossover study in patients that had been urodynamically verified within the previous 12 months.
- After screening and a 2-week placebo run-in period, patients received each of the following treatments for 2 weeks according to a randomized sequence
 - darifenacin-controlled release tablets 15 mg once daily (q.d.)
 - oxybutynin 5 mg three-times daily (t.i.d.)
 - matching placebo.
- Each treatment period was separated by a 10-day washout period and blinding was maintained by the double-dummy technique.

Evaluation of tolerability and efficacy

- Tolerability and safety were determined from withdrawal rates, AEs, vital signs, ECG recordings and routine laboratory tests.
- Efficacy was evaluated from paper diaries recording daily incontinence episodes, micturition frequency, frequency of urgency episodes and severity of urgency (mild, moderate or severe).

Statistical analysis

- Statistical analyses of tolerability and efficacy were based on 'complete cases' to provide a precise calculation of treatment differences.
- For tolerability, complete cases were patients who were exposed to all double-blind treatments for at least 7 days (or fewer if antimuscarinic AEs were observed earlier). AEs were compared between treatments using Cochran's Q-test; pair wise treatment comparisons were made using McNemar's test at the 0.05 significance level.
- For efficacy, complete cases were patients who had an efficacy variable value for Week 2 for each treatment period. Efficacy variables were compared between treatments using analysis of variance; pair wise treatment comparisons were made using the least significant difference method.

RESULTS

Study population

- Seventy-six patients (33–84 years, 93% females) were randomized. Baseline characteristics are summarized in Table 1. There were no major differences in demographic or clinical characteristics.

Table 1. Baseline characteristics.

Characteristic	Randomized patients (n=76)*	Efficacy evaluable patients (n=58)
No. of females (%)	71 (93.4)	53 (91.4)
Mean age, years (range)	59.9 (33–84)	60.2 (33–84)
Mean body weight, kg (range)	75.7 (42–157)	76.3 (45–157)
OAB symptoms†		
Mean (SD) no. of incontinence episodes/week	20.4 (17.7)	21.02 (17.84)
Mean (SD) no. of urgency episodes/day	9.3 (3.4)	9.22 (3.11)
Mean (SD) severity of urgency episodes*	2.0 (0.4)	1.96 (0.40)
Mean (SD) no of micturitions/day	10.4 (3.0)	10.47 (2.56)

*Symptom data missing for one patient; †during Week 2 of run-in; *severity of urgency episodes recorded as: 1 = mild; 2 = moderate; 3 = severe. SD = standard deviation.

- Twelve patients withdrew before study end: six during treatment with oxybutynin, two with darifenacin 15 mg q.d., and four with placebo. In most cases (8/12), the reason for discontinuation was unrelated to treatment. The most common treatment-related reason for withdrawal was occurrence of AEs.

Tolerability

Of the patients evaluable for tolerability (n=61) (Table 2)

- Darifenacin was associated with a significantly lower rate of dry mouth compared with oxybutynin (p<0.05). Oxybutynin treatment resulted in significantly higher rates of dry mouth than placebo (p<0.05). Although the incidence of dry mouth was higher with darifenacin than with placebo, the difference was not significant.
 - Constipation rates were comparable between active treatments.
 - Blurred vision and dizziness were only reported during oxybutynin therapy.
- For the overall safety population (n>61)
- The majority of AEs were mild to moderate in severity. Severe treatment-related AEs were reported in three (4.7%) darifenacin-treated patients (one headache, two dry mouth, one constipation), seven (10.1%) oxybutynin-treated patients (six dry mouth, one constipation, one pharyngitis, one rhinitis) and two (2.9%) placebo-treated patients (one headache, one dry mouth).

No serious treatment-related AEs were reported during the study.

- All four treatment-related discontinuations occurred with oxybutynin (all due to dry mouth, with or without rhinitis [n=2], dysphagia [n=1] or dyspepsia [n=1]).
- The incidence of laboratory abnormalities was low for all treatments and there were no clinically relevant treatment-related changes in blood pressure, pulse rate or ECG.

Efficacy

- Fifty-eight patients (complete cases) were eligible for the efficacy analysis. Clinical characteristics were comparable to the total randomized population.
- Darifenacin was as effective as oxybutynin at providing clinical improvement in OAB symptoms (Table 3 and Figure 1). At Week 2, both agents were associated with
 - a significantly lower number of incontinence episodes/week compared with placebo (p<0.05)
 - significantly fewer urgency episodes per week compared with placebo (p<0.05)
 - less severe urgency episodes compared with placebo (p<0.05).

However, neither drug significantly reduced micturition frequency compared with placebo (Table 3 and Figure 1).

Table 2. Incidence (%) of dry mouth, constipation, blurred vision, dizziness and drowsiness in the tolerability evaluable patients.

	Tolerability evaluable patients (n=61)		
	Darifenacin CR 15 mg q.d.	Oxybutynin 5 mg t.i.d.	Placebo
Dry mouth	13.1**	36.1*	4.9
Constipation	9.8	8.2	3.3
Blurred vision	0	3.3	0
Dizziness	0	1.6	0
Drowsiness	0	0	0

*p<0.05 vs placebo. **p<0.05 vs oxybutynin.

Table 3. Mean values for efficacy outcome variables at Week 2 in evaluable patients.

Outcome variables (mean value at Week 2)	Efficacy evaluable patients (n=58)		
	Darifenacin CR 5 mg q.d.	Oxybutynin 5 mg t.i.d.	Placebo
Incontinence episodes/week	10.93*	9.45*	14.64
Urgency episodes/day	7.95*	8.12*	8.71
Severity of urgency episodes (1 = mild; 2 = moderate; 3 = severe)	1.93*	1.89*	2.03
Micturitions/day	9.33	9.24	9.62

Values shown are means adjusted for sequence and period from the crossover analysis of variance. *p<0.05 vs placebo, accounting for multiplicity, by least significant difference method.

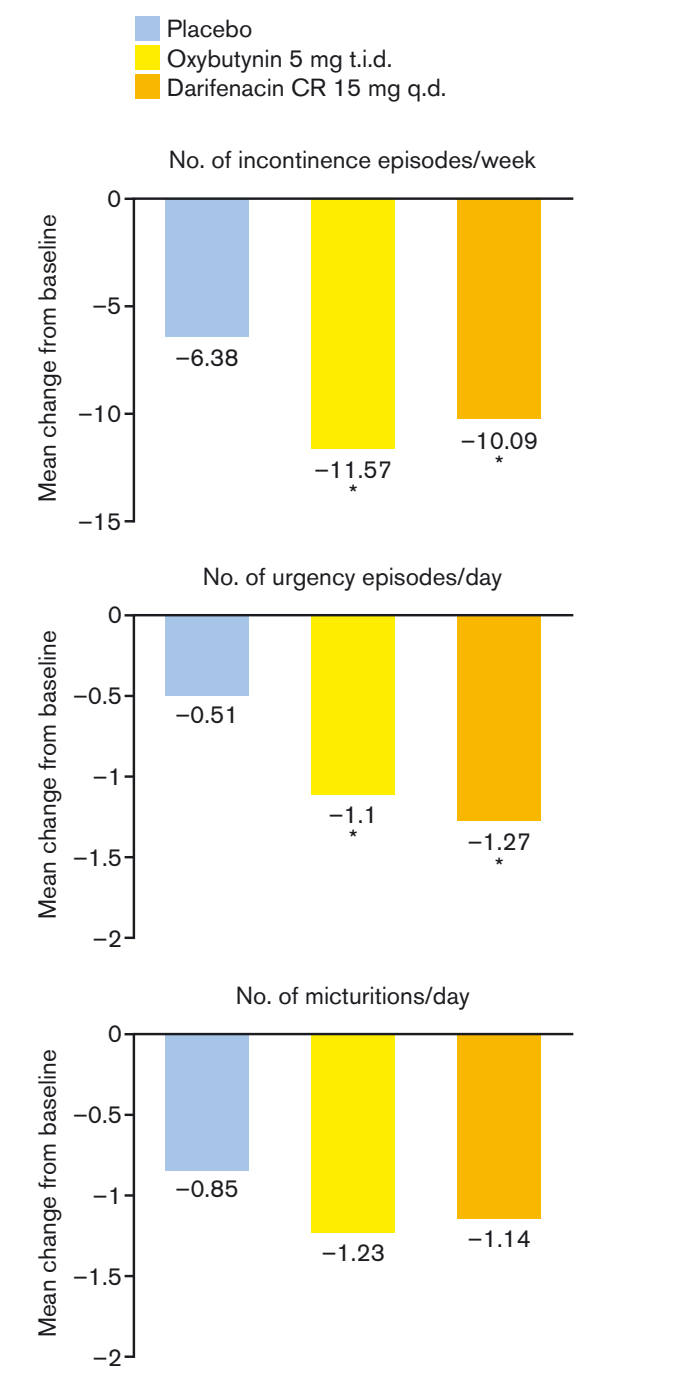


Figure 1. Mean change from baseline in micturition diary variables at Week 2 in evaluable patients (efficacy evaluable population, n=58).

CONCLUSIONS

- Darifenacin was associated with improved tolerability compared with oxybutynin (lower incidence of dry mouth, no blurred vision or dizziness).
- Darifenacin 15 mg q.d. provided comparable efficacy to oxybutynin 5 mg t.i.d. in the treatment of OAB.
- This clinical profile most likely reflects the high selectivity of darifenacin for M₃ receptors whilst sparing M₁ receptors.
- Darifenacin's superior tolerability to oxybutynin and comparable clinical efficacy adds further evidence that this agent is an important novel treatment option for OAB, a chronic condition requiring long-term therapy.

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