145

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DARIFENACIN, A MUSCARINIC RECEPTOR ANTAGONIST WITH SELECTIVITY FOR M3 RECEPTORS, REDUCES INCONTINENCE AND NOCTURIA IN PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study

This study evaluated the effect of darifenacin, a new muscarinic M_3 selective receptor antagonist (M_3 SRA), on the symptoms of overactive bladder (OAB). OAB is a common and often highly debilitating medical complaint, defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia (the need to wake at night one or more times to void).

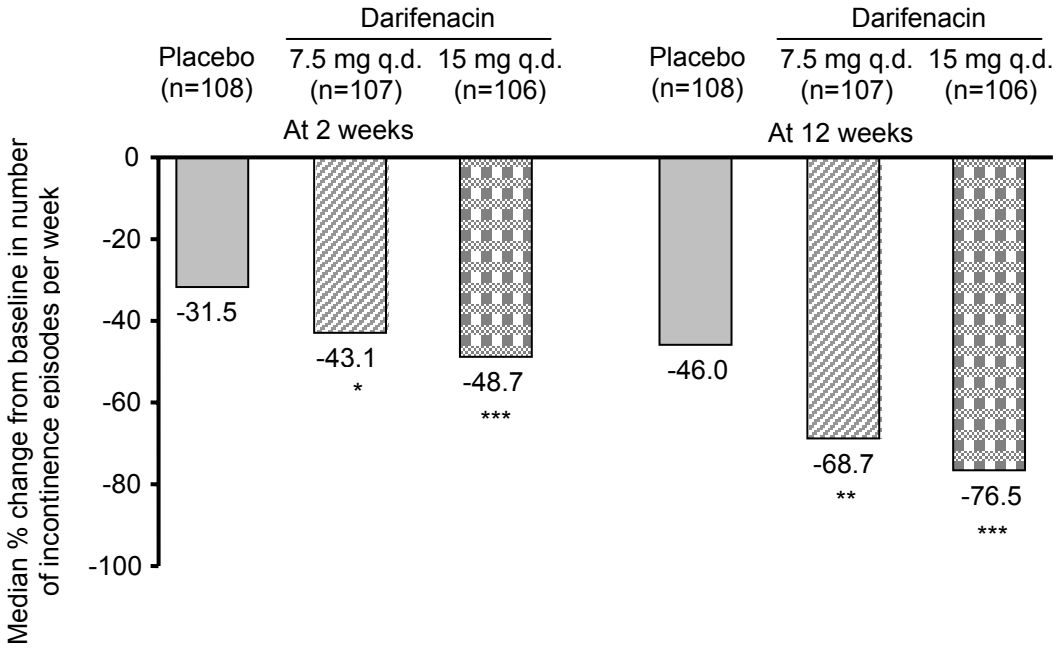
Study design, materials and methods

This multicentre, double-blind, randomised, placebo-controlled study enrolled 439 patients who had suffered from OAB symptoms for ≥6 months. After a 2-week placebo run-in, patients were randomised to receive 12 weeks of treatment with oral darifenacin controlled-release (CR) tablets once daily (q.d.) at doses of 7.5 mg (n=108), 15 mg (n=107), or 30 mg (n=115), or matching placebo (n=109). Efficacy was evaluated from OAB symptoms recorded daily using a validated electronic diary.[1] The primary efficacy variable was the change from baseline in the number of incontinence episodes per week at 12 weeks. Secondary efficacy variables included the number of OAB-related nocturnal awakenings per week. Tolerability and safety were also assessed.

Results

Results are presented for the proposed market doses of darifenacin (7.5 mg and 15 mg). At week 12, treatment with darifenacin was associated with a dose-related reduction from baseline in the number of incontinence episodes per week with a median percentage reduction of 68.7% and 76.5% with darifenacin 7.5 mg and 15 mg, respectively (Figure 1).

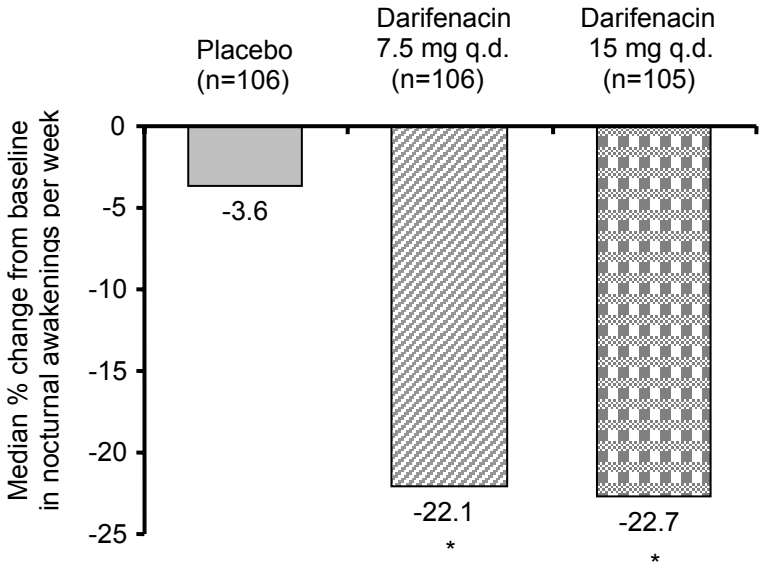
Figure 1. Reduction in frequency of incontinence episodes



*p<0.05, **p<0.01, ***p<0.001 using Wilcoxon rank-sum test stratified by baseline for testing treatment difference versus placebo. n numbers may be lower than randomised numbers because patients were only included in the efficacy analysis if they had a baseline and any post-baseline diary data.

The reduction in incontinence episodes with darifenacin was significantly superior to placebo at all dose levels, and this was noted as early as week 2 of treatment (Figure 1). In addition, there was a significant reduction in the number of nocturnal awakenings due to OAB experienced by patients treated with either darifenacin 7.5 mg or 15 mg compared with placebo (Figure 2).

Figure 2. Reduction in frequency of nocturnal awakenings at week 12



*p<0.05 using Wilcoxon rank-sum test stratified by baseline for testing treatment difference versus placebo. n numbers may be lower than randomised numbers because patients were only included in the efficacy analysis if they had a baseline and any post-baseline diary data.

The overall incidence of all-causality adverse events, the majority of which were mild to moderate in severity, was 57.4%, 68.2% and 49.5% with darifenacin 7.5 mg and 15 mg and placebo, respectively. The most frequent events were dry mouth and constipation. The central nervous system (CNS) and cardiovascular adverse event profile was similar to that of placebo. For all treatment groups there were no clinically relevant changes with regard to laboratory tests or vital signs.

Interpretation of results

Darifenacin at doses of 7.5 mg and 15 mg provided a significant, dose-related improvement in the major symptoms of OAB, including reduced frequency of incontinence episodes, and was well tolerated. Darifenacin also significantly reduced nocturia, a particularly bothersome symptom which is associated with an increased risk of injury due to falls during night-time visits to the bathroom.[2] The CNS and cardiovascular safety profile are suggestive of additional benefits arising from the M_3 selectivity of darifenacin.

Concluding message

The findings in this placebo-controlled study show that the M_3 SRA darifenacin provides an effective and well tolerated new option for OAB therapy.

References

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2. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. Journal of the American Geriatrics Society 2000;48:721-5.

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