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EFFICACY OF DARIFENACIN IN A 2-YEAR LONG-TERM EXTENSION STUDY IN PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study

Overactive bladder (OAB) is a prevalent and chronic condition, with antimuscarinic agents the most common treatment. Darifenacin is a recently approved muscarinic M_3 selective receptor antagonist for the treatment of OAB, with proven efficacy in phase III clinical trials (1). This study examined the long-term efficacy, tolerability and safety of darifenacin controlled-release (CR) in patients with OAB who had completed 12 weeks' treatment in one of two randomised, double-blind, placebo-controlled studies (2,3). This represents the first 24-month extension study to be reported with an extended release formulation of any antimuscarinic OAB therapy, the efficacy findings of which are reported here.

Study design, materials and methods

This multicentre, open-label, 2-year extension study enrolled patients from two 12-week, placebo-controlled, double-blind studies (feeder studies) of darifenacin CR 3.75, 7.5 or 15 mg once daily (qd) in patients with OAB symptoms for ≥6 months (2,3). Regardless of previous treatment, all patients entering the extension study received darifenacin 7.5 mg qd for two weeks. Thereafter, doses were individualized (7.5 or 15 mg qd) as needed following discussion with the investigator. Efficacy was evaluated from OAB symptoms recorded in a paper diary. The primary efficacy variable was the median change from baseline (of the feeder study) in the number of urge incontinence episodes/week, assessed at the end of the feeder study and after 3, 6, 12 and 24 months of the extension period (or end of study). Secondary efficacy variables, tolerability and safety were also assessed.

Results

716 patients entered (mean age 57.3 years [range 19–89], 609 [85.1%] female) and 475 patients (66.3%) completed the study; 9.5% discontinued treatment due to lack of effect, 8.9% due to an adverse event, 8.9% due to withdrawal of consent and 6.3% due to other reasons. More than 85% of patients complied with therapy (taking 80–120% of doses).

Darifenacin treatment resulted in significant improvements ($p<0.001$) in primary and secondary efficacy endpoints at the end of the feeder studies, which were sustained throughout the extension study (see Table). The number of urge incontinence episodes/week (median baseline value 16.67), decreased from baseline by a median of 80–86% at each time point in the extension phase (see Table). Improvements in efficacy endpoints were associated with 34.9% of patients achieving a micturition frequency of <8 voids/day by study end.

Darifenacin was well tolerated. The most common all-causality adverse events were dry mouth and constipation, reported by 23.3% and 20.9% of patients during the extension study, respectively, but these infrequently resulted in treatment discontinuation (less than 2% and 3%, respectively).

Table. Median (and percentage) change from baseline (of the feeder studies) in primary and secondary efficacy endpoints during 2-year open-label extension study

	Duration of open-label treatment in extension study (months)				
Efficacy measure	**0**[†]	**3**	**6**	**12**	**24**
Incontinence episodes/week	-8.4* (-63)	-10.5* (-80)	-11.0* (-84)	-11.0* (-86)	-11.0* (-84)
Micturitions/day	-1.5* (-14)	-1.3* (-13)	-1.4* (-14)	-1.6* (-14)	-1.4* (-14)
Volume urine passed/void, mL	14.1*(10)	19.1* (12)	21.2* (14)	20.9* (13)	19.0* (12)
Urgency episodes/day	-1.9* (-24)	-3.7* (-55)	-3.6* (-55)	-3.5* (-55)	-3.9* (-56)
Severity of urgency	-8.3* (-15)	-15.1* (-29)	-15.7* (-27)	-14.4* (-27)	-15.4* (-29)
Nocturnal awakenings due to OAB	-1.4* (-14)	-1.0* (-10)	-1.0* (-14)	-1.8* (-15)	-1.5* (-14)
Incontinence episodes/week requiring change in clothes or pads	-3.0* (-74)	-5.0* (-88)	-5.0* (-91)	-5.0* (-100)	-4.7* (-100)

[†]Differences from baseline to end of 12-week double-blind feeder studies in the extension study population
*p<0.001 using Wilcoxon signed rank test compared with baseline

Interpretation of results

Darifenacin 7.5 and 15 mg provided significant and sustained improvements in OAB symptoms, with a median reduction from baseline in the number of urge incontinence episodes/week of 80–86% at all timepoints over the 2-year extension period. This was paralleled by significant and sustained improvements in secondary efficacy variables, including urgency episodes (median reduction ≥55%), consistent improvements in micturition frequency, allowing more than one in three patients to achieve normal frequency, and a median 100% reduction in the number of incontinence episodes requiring a change in clothing or pads.

Long-term treatment with darifenacin was also well tolerated, with the most common events (dry mouth and constipation) seen at similar or lower rates than previously reported (1–3) and associated with low discontinuation rates.

The significant and sustained efficacy of long-term darifenacin treatment, coupled with a good tolerability profile, translated into patient confidence in their treatment, as seen by few discontinuations due to either lack of effect or adverse events (both ≤9%), and high rates of treatment compliance (>85%) and persistence (>66%) over 2 years.

Concluding message

This 2-year open-label study, the longest reported with any extended-release formulation of an antimuscarinic OAB therapy; indicates that darifenacin provides efficacious, sustained and well-tolerated treatment for OAB. Significant efficacy findings and good tolerability resulted in few discontinuations and high patient confidence in treatment, as shown by high rates of compliance and persistence with treatment over the 2-year duration, making darifenacin a prudent choice of treatment for OAB.

References

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