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# RESPONDER RATES, A BETTER WAY TO EXPRESS DRUG EFFICACY: DATA FROM DARIFENACIN POOLED PHASE III STUDIES

## Hypothesis / aims of study

Overactive bladder (OAB) is a highly prevalent and chronic disease, for which currently available treatments have been described as of questionable value [1]. There is considerable debate on the value of expressing efficacy as whole group mean/median changes. An alternative is to express efficacy in terms of responders and non-responders. However, the optimum cut point in order to define responders remains to be confirmed. Darifenacin is a new muscarinic $M_3$ selective receptor antagonist for the treatment of OAB. Pooled results of three phase III clinical trials of darifenacin versus placebo in patients with OAB have been evaluated for clinical relevance in terms of responder rates at different levels of efficacy.

## Study design, materials and methods

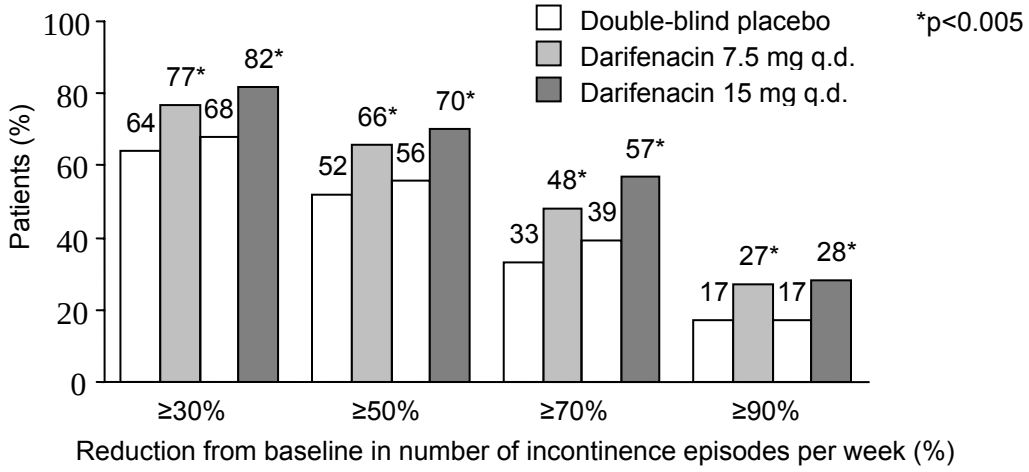
This analysis is based on the pooled results of three multicentre, randomised, double-blind, placebo-controlled 12-week studies with darifenacin controlled-release tablets. A pooled analysis of these trials is possible due to the near-identical design and patient enrolment criteria (patients aged ≥18 years with symptoms of OAB for ≥6 months, 5–50 episodes of incontinence/week during the run-in period, an average frequency of micturition of ≥8 voids/24 hours, and ≥1 episode of urgency/24 hours, on average). After a 2-week washout (if required) and a 2-week run-in period, 1,059 patients (19–88 years, 85% females) were randomised to 12 weeks' once daily (qd) double-blind treatment with darifenacin 7.5 mg (two studies), 15 mg (all three studies) or placebo. Efficacy was determined from electronic daily diaries used to record the number of incontinence episodes per week and a range of secondary efficacy parameters; normalisation of micturition frequency (<8 voids/day, on average); and patients achieving 3 dry days per week and 7 consecutive dry days by study end.

## Results

In the full analysis set, 665 patients were treated with darifenacin 7.5 mg (n=335) or 15 mg (n=330), while the remainder received matching placebo (n=383). Baseline demographics and clinical characteristics were comparable between treatment groups.

A range of responder rates after 12 weeks of treatment are shown below for reduction in incontinence episodes (Figure 1).

**Figure 1. Percentage of patients who achieved increasing degrees of improvement**



As with incontinence episodes, reductions of at least 30%, 50%, 70% and 90% in the frequency of urgency episodes were achieved significantly more frequently with darifenacin than placebo, for both doses (all $p<0.005$). Furthermore, normal micturition frequency (<8 voids/day) was achieved by significantly more patients given darifenacin 7.5 mg qd (34% vs placebo 27%, $p<0.05$) or darifenacin 15 mg qd (35% vs placebo 28%, $p<0.01$).
In addition, treatment with 7.5 or 15 mg darifenacin for 12 weeks resulted in 3 dry days achieved by 55.4% and 61.2% of patients, respectively (both $p\leq0.001$ versus placebo); and 7 consecutive dry days by 19% ($p=0.108$) and 24% of patients ($p=0.011$ versus placebo), respectively.
Darifenacin was well tolerated. Dry mouth (7.5 mg 20%; 15 mg 35%; placebo 8%) and constipation (7.5 mg 15%; 15 mg 21%; placebo 6%) were the most common adverse events, but together resulted in low rates of discontinuation (darifenacin 7.5 mg 0.6%; darifenacin 15 mg 2.1%; placebo 0.3%). CNS and cardiovascular (CV) safety was comparable to placebo.

**Interpretation of results**

After 12 weeks of treatment,

- More than a quarter of darifenacin-treated patients achieved ≥90% reduction in the frequency of incontinence episodes (Figure 1)
- More than one third of darifenacin-treated patients achieved normalisation of micturition frequency (<8 micturitions per day, on average)
- More than 20% of darifenacin-treated patients achieved ≥70% reduction in urgency episodes (21% with 7.5 mg and 23% with 15 mg darifenacin qd)
- Significantly more patients achieved 3 dry days per week with darifenacin treatment than with placebo (55.4% vs 43.2%; $p=0.001$, for darifenacin 7.5 mg qd vs placebo; 61.2% vs 48.3%; $p<0.001$, for darifenacin 15 mg qd vs placebo).
- Significantly more patients in the darifenacin 15 mg qd group achieved 7 consecutive dry days than in the placebo group (24% vs 16%, respectively; $p=0.011$).
- The large placebo response is thought to be due to the use of electronic rather than paper diaries.

**Concluding message**

Many patients achieve near-normalisation in their symptoms of OAB, including substantial reductions in frequency of incontinence episodes, normalisation of micturition frequency, and a substantial portion of patients achieving 3 or 7 dry days, with 12 weeks' darifenacin treatment. By using various cut points for responder analysis, a more complete picture is given of darifenacin's efficacy, enabling a more informed doctor–patient discussion regarding likely benefits of therapy.

**References**

1. British Medical Journal. 2003;326(7394):841-4.

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