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Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial

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Objective

To assess the superiority of fesoterodine 8 mg vs 4 mg for improvement in urgency urinary incontinence (UUI) episodes and other diary variables, diary-dry rate (proportion of patients with >0 UUI episodes on baseline diary and 0 UUI episodes on post-baseline diary), and improvements in measures of symptom bother, health-related quality of life (HRQL), and other patient-reported outcomes (PROs).

Patients and Methods

This was a 12-week, randomised, double-blind, placebo-controlled, multinational trial of men and women aged ≥18 years with overactive bladder (OAB) symptoms including UUI (ClinicalTrials.gov ID NCT01302067). Patients were randomised (2:2:1) to receive fesoterodine 8 mg, fesoterodine 4 mg, or placebo once daily; those randomised to fesoterodine 8 mg started with fesoterodine 4 mg once daily for 1 week, then 8 mg once daily for the remaining 11 weeks. Patients completed bladder diaries at baseline and weeks 4 and 12 and the Patient Perception of Bladder Condition (PPBC), Urgency Perception Scale (UPS), and Overactive Bladder Questionnaire (OAB-q) at baseline and week 12. The primary endpoint was change from baseline to week 12 in UUI episodes per 24 h.

Results

At week 12, patients receiving fesoterodine 8 mg (779 patients) had significantly greater reductions from baseline in UUI episodes, micturitions, and urgency episodes than patients receiving fesoterodine 4 mg (790) or placebo (386); diary-dry rate was significantly higher in the fesoterodine 8-mg group vs the fesoterodine 4-mg and placebo groups (all $P < 0.05$). At week 12, patients receiving fesoterodine 8 mg also had significantly greater improvements in scores on the PPBC, UPS, and all OAB-q scales and domains than patients receiving fesoterodine 4 mg or placebo (all $P < 0.01$). Patients receiving fesoterodine 4 mg had significantly greater improvements in UUI episodes, urgency episodes, and micturitions; significantly higher diary-dry rates; and significantly greater improvement in PPBC scores and OAB-q scores than patients receiving placebo (all $P < 0.05$). Dry mouth was the most commonly reported adverse event (AE) in the fesoterodine groups (placebo group, 3.4%; fesoterodine 4-mg group, 12.9%; fesoterodine 8-mg group, 26.1%); most cases were mild or moderate in all treatment groups. Rates of serious AEs and discontinuations due to AEs were low in all groups.

Conclusions

In a 12-week, prospectively designed, superiority trial, fesoterodine 8 mg showed statistically significantly superior efficacy vs fesoterodine 4 mg and placebo, as measured by reductions in UUI episodes and other diary variables, diary-dry dry rate, and improvements in measures of symptom bother, HRQL, and other PROs; clear evidence of dose-dependent efficacy is unique to fesoterodine among antimuscarinics and other oral agents for the treatment of OAB. Fesoterodine 4 mg was significantly more effective than placebo on all outcomes except for improvements in UPS scores. These data support the benefit of having two doses of fesoterodine in clinical practice, with the recommended starting dose of 4 mg for all patients and the fesoterodine 8-mg dose available for patients who require a higher dose to achieve optimal symptom relief.

Keywords

fesoterodine, dose comparison, urgency urinary incontinence, overactive bladder, dose response, dose titration

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Introduction

While urinary urgency is the defining symptom of overactive bladder (OAB) syndrome, urgency urinary incontinence (UUI) episodes may be the OAB symptom that causes the greatest personal and economic burden [1,2]. Fesoterodine, an antimuscarinic for the treatment of OAB symptoms, was developed in two once-daily doses, 4 and 8 mg, thus offering dose flexibility for treatment individualisation [3,4]. Based on each patient's treatment response, the dosage can be adjusted to optimise the therapeutic balance between efficacy and tolerability [5].

Flexible-dosing strategies are based on the assumption that increasing dosage will result in increased efficacy [5]. However, fixed-dose studies of various pharmacological OAB treatments have typically not shown a statistically significant dose-response effect for the reduction of OAB symptoms [6–8] or have shown a dose-response effect only over a short (4-week) period [9]. In two phase III pivotal trials, fesoterodine 4 and 8 mg demonstrated significant improvements in OAB symptoms and health-related quality of life (HRQL) compared with placebo in patients with OAB [10,11]. A *post hoc* analysis of data pooled from these phase III trials showed that fesoterodine 8 mg significantly reduced UUI episodes and significantly increased the number of continent days/week and mean voided volume/micturition compared with fesoterodine 4 mg, suggesting significant additional benefit of the higher dose [12]. A significantly higher percentage of patients receiving fesoterodine 8 mg self-reported a treatment response vs patients receiving fesoterodine 4 mg [12]. Models based on phase II and phase III data also support a fesoterodine dose response [13].

The objective of the present double-blind, placebo-controlled study was to prospectively assess the superiority of fesoterodine 8 mg compared with fesoterodine 4 mg and placebo in improving UUI episodes and other bladder diary endpoints and measures of symptom bother, HRQL, and other patient-reported outcomes (PROs) after 12 weeks of treatment in patients with OAB.

Patients and Methods

Study Design

The EIGHT (**E**valuation of urinary urge **I**ncontinence patients **G**iven fesoterodine 8 mg vs fesoterodine 4 mg in a **H**ead-to-head efficacy **T**rial) trial was a 12-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre study of treatment with fesoterodine 8 mg, fesoterodine 4 mg, or placebo (ClinicalTrials.gov ID: NCT01302067). The proportion of patients in the study was monitored to ensure that a maximum of ≈65% were antimuscarinic naive. The EIGHT trial was conducted at 241 centres in 27 countries between May 2011 and November 2012. The trial was approved by the appropriate Institutional Review Boards and Independent Ethics Committees and conducted in accordance with the protocol, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines, and applicable local regulatory requirements and laws. All patients provided written informed consent.

At the end of a 2-week, single-blind, placebo run-in phase, eligible patients were randomised (2:2:1) to receive double-blind fesoterodine 8 mg, fesoterodine 4 mg, or placebo once daily via a centralised randomisation system. In accordance with labelling, a starting dose of 4 mg was used in the fesoterodine groups; patients randomised to fesoterodine 8 mg started with fesoterodine 4 mg for 1 week, followed by a dose increase to 8 mg for the remaining 11 weeks of the study. The study medications and placebo were identical in appearance to preserve blinding.

Patients

Eligible patients were men and women aged ≥18 years with self-reported OAB symptoms for ≥6 months before screening and a mean of ≥8 micturitions and ≥2 and ≤15 UUI episodes/24 h (Urinary Sensation Scale [USS] rating of 5 [14]) captured in a 3-day diary at baseline who reported that their bladder caused at least some moderate problems on the Patient Perception of Bladder Condition (PPBC) [15]. Patients were required to be able to complete micturition diaries and study related questionnaires and comply with study procedures. Female patients who were pregnant, nursing, or had a positive urine pregnancy test or intended to become pregnant during the trial or within 3 months after the completion of the trial were not eligible, and female patients of childbearing potential who were heterosexually active were required to use an adequate form of contraception. Other exclusion criteria were: any condition that would contraindicate use of fesoterodine; conditions that may affect bladder function, including predominant stress UI, significant pelvic organ prolapse, clinically significant BOO (evidenced by previous history of acute urinary retention requiring catheterisation, use of an indwelling catheter or an intermittent self-catheterisation programme, urodynamic evidence of obstruction, or severe voiding symptoms including a previously measured post-void residual urine volume of ≥200 mL) that was not being appropriately managed, and neurological conditions that are known or suspected of influencing bladder function; current or recurrent UTI; treatment with other anticholinergic medications within 2–3 weeks of screening; new or unstable use of certain medications, including diuretics, α-blockers, tricyclic antidepressants, and oestrogens; treatment with potent CYP3A4 inhibitors within 2 weeks of screening, CYP3A4 inducers within 30 days of screening, or botulinum toxin within 6 months of screening; or initiation of

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electrostimulation, bladder training, or pelvic floor exercises within 4 weeks of screening (patients on stable therapy were permitted).

Outcome Measures

Patients completed 3-day diaries at baseline and after 4 and 12 weeks. The primary endpoint was change from baseline to week 12 in UUI episodes/24 h (USS rating of 5) for fesoterodine 8 mg vs fesoterodine 4 mg and placebo. Secondary endpoints, including changes in micturitions and urgency episodes/24 h, were also assessed.

Patients also completed the PPBC [15], Urgency Perception Scale (UPS) [16], and Overactive Bladder Questionnaire (OAB-q) [17] at baseline and week 12. The PPBC is a validated single-item instrument used by patients to rate the severity of their bladder-related problems on a scale from 1 to 6 (1, no problems at all; 2, some very minor problems; 3, some minor problems; 4, some moderate problems; 5, severe problems; 6, many severe problems) [15]. The UPS is a validated single-item instrument with a 3-point scale used by patients to rate their typical sensation of urgency (1, I am usually not able to hold urine; 2, I am usually able to hold urine [without leaking] until I reach a toilet if I go to the toilet immediately; 3, I am usually able to finish what I am doing before going to the toilet [without leaking]) [16]. The validated OAB-q contains an eight-item Symptom Bother Scale and a 25-item HRQL Scale with four domains (Concern, Coping, Sleep, and Social Interaction); scores on each scale and domain are normalised to a scale of 0–100. Higher scores on the Symptom Bother Scale reflect greater bother, and higher scores on the HRQL scale and domains reflect better HRQL [17].

Adverse events (AEs) were monitored throughout the study, with severity and causal relationship to study drug assessed by the study investigator. A physical examination was conducted at the screening visit; blood pressure and heart rate measurements and laboratory testing were assessed at all clinic visits.

Statistical Analysis

Sample size was calculated based on an 85% power to detect a mean (SD) difference of −0.43 (2.71) in UUI episodes/24 h at 5% significance level (two-sided). The Safety Analysis Set (SAS) included all patients who took at least one dose of the study drug. The Full Analysis Set (FAS) included all patients who took at least one dose of the assigned study drug and had at least one baseline or post-baseline efficacy assessment. Efficacy analyses were based on the FAS. For the primary efficacy endpoint, an analysis of covariance (ANCOVA) model was used to compare the fesoterodine 8 mg, 4 mg, and placebo arms for the change in the mean number of UUI episodes/24 h at week 12 relative to baseline in patients with >0 UUI episodes at baseline (i.e. protocol violators with UUI = 0 were excluded). The ANCOVA model included terms for treatment, country, and baseline UUI as a covariate. The secondary interaction terms, treatment by baseline and treatment by country, were assessed at the 10% level of significance. Treatment comparisons were performed with a two-sided test at a 5% significance level and conducted using a step-down procedure in order to preserve the Type I error at 5%. For each outcome, fesoterodine 8 mg was compared with placebo; the primary comparison of fesoterodine 8 mg vs 4 mg was performed only if there was a statistically significant treatment effect of 8 mg vs placebo. The comparison of fesoterodine 4 mg vs placebo also was performed. Treatment differences in change from baseline were estimated by least squares (LS) means and 95% CIs. The interaction terms (treatment × baseline and treatment × country) were assessed at the 10% level of significance. Similar to the analysis of the primary endpoint, ANCOVA models were performed for changes in secondary bladder diary endpoints and OAB-q scores. Diary-dry rate was analysed using a Cochran-Mantel-Haenszel general association test and controlling for country. Changes in PPBC and UPS scores were analysed using a Cochran-Mantel-Haenszel test with modified ridit scoring controlling for country. Missing data were imputed with last-observation-carried-forward (LOCF) method.

Results

Of 2012 randomised patients (placebo, 402; fesoterodine 4 mg, 806; fesoterodine 8 mg, 804), 1955 received ≥1 dose of double-blind study drug (placebo, 386; fesoterodine 4 mg, 790; fesoterodine 8 mg, 779) (Fig. 1). Baseline demographic and clinical characteristics were similar in patients randomised to fesoterodine 8 mg, fesoterodine 4 mg, and placebo (Table 1).

Fesoterodine 8 mg treatment resulted in significantly greater improvements in the change from baseline in UUI episodes/24 h (primary outcome) at week 12 compared with placebo ($P < 0.001$) and compared with fesoterodine 4 mg ($P = 0.011$; Fig. 2). There was a significant baseline by treatment interaction ($P < 0.1$) that was quantitative, indicating a larger treatment difference for patients with larger baseline values. The diary-dry rate was significantly higher with fesoterodine 8 mg vs placebo ($P < 0.001$) and fesoterodine 4 mg ($P < 0.001$) at week 12. Patients receiving fesoterodine 8 mg also had significantly greater improvements in micturition frequency and urgency episodes/24 h than patients receiving placebo (both $P < 0.001$) or fesoterodine 4 mg (both $P < 0.001$) (Fig. 2). Improvements in scores on the PPBC, UPS, and all OAB-q scales and domains at week 12 were significantly greater with fesoterodine 8 mg compared with placebo (all $P < 0.001$) and fesoterodine 4 mg (all $P < 0.01$) (Figs 3,4).

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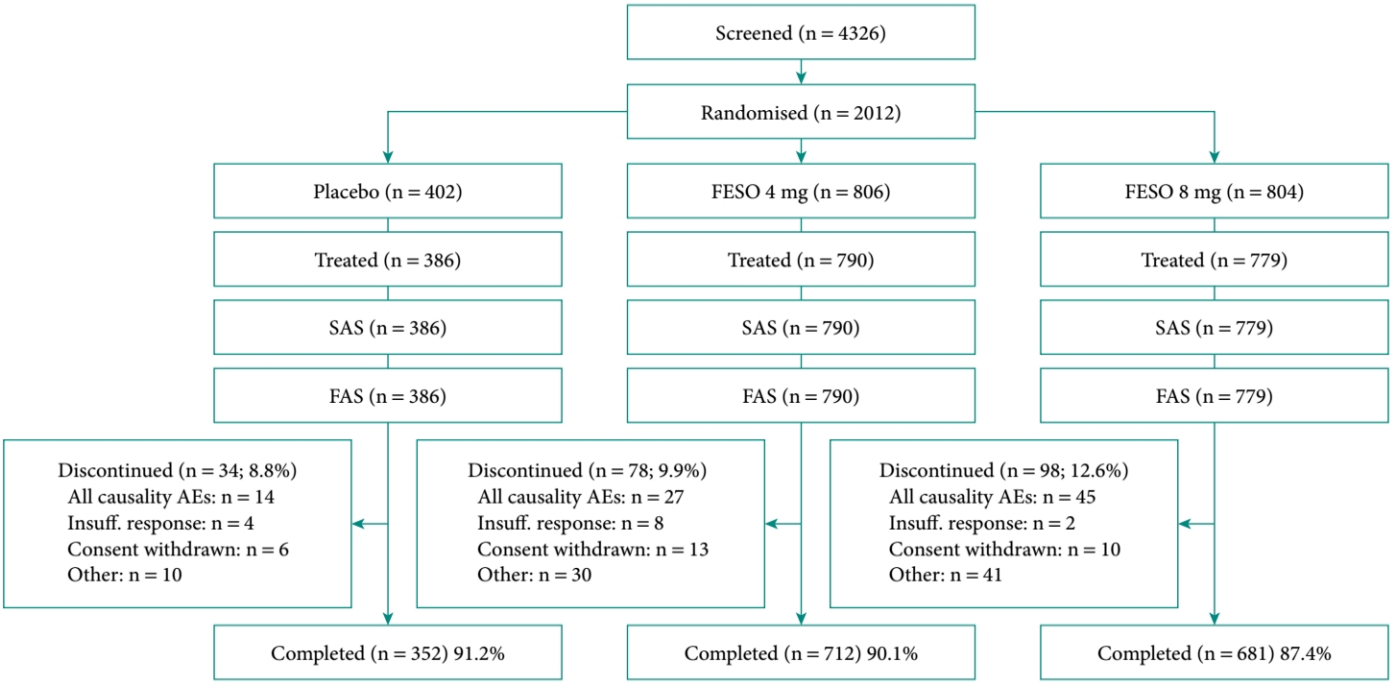
Fig. 1 Patient disposition. FESO, fesoterodine; FAS, Full Analysis Set; SAS, Safety Analysis Set.



Changes in micturitions ($P = 0.008$) and urgency episodes ($P = 0.012$) were significantly greater in patients receiving fesoterodine 8 mg than in patients receiving fesoterodine 4 mg at week 4; the difference in the change in UUI episodes ($P = 0.066$) and difference in diary-dry rate ($P = 0.812$) were not statistically significant at week 4 (Fig. 2). UUI episodes, micturitions, and urgency episodes were significantly improved and diary-dry rate was significantly higher with fesoterodine 8 mg vs placebo at week 4 (all $P < 0.01$).

Fesoterodine 4 mg also significantly improved all outcomes and produced a higher diary-dry rate vs placebo (all $P < 0.05$), with the exception of UPS scores ($P = 0.39$) at week 12. Fesoterodine 4 mg significantly improved all diary variables and produced a higher diary-dry rate (all $P < 0.05$) vs placebo at week 4 (Figs 2–4).

Dry mouth was the most commonly reported treatment-emergent AE (TEAE; Table 2). Most TEAEs were of mild or moderate intensity in all treatment groups. The rate of discontinuations due to TEAEs was 3.4% (13 patients) in the placebo group, 3.4% (27) in the fesoterodine 4-mg group, and 5.4% (42) in the fesoterodine 8-mg group. The rate of serious TEAEs was 2.8% (11 patients) in the placebo group, 1.3% (10) in the fesoterodine 4-mg group, and 1.3% (10) in the fesoterodine 8-mg group. Two patients receiving fesoterodine 8 mg died during the study (one due to hypertensive heart disease and pulmonary embolism; one due to bladder cancer); both deaths were considered unrelated to study treatment. Urinary retention was reported in two patients receiving fesoterodine 8 mg and two receiving fesoterodine 4 mg; one patient in the fesoterodine 4-mg group was catheterised.

Discussion

The present study shows that fesoterodine 8 mg is significantly more effective than fesoterodine 4 mg in reducing UUI episodes and increasing diary-dry rate in patients with OAB symptoms including UUI. Fesoterodine 8 mg also produced significantly greater reductions in micturitions and urgency episodes than fesoterodine 4 mg. Significantly greater reductions in symptom bother and significantly greater improvements in HRQL, PPBC, and UPS scores show that the difference in symptom reduction between 8 and 4 mg fesoterodine is meaningful to patients. The changes in OAB-q Symptom Bother and HRQL scores exceeded the minimally important difference in all groups [18]. Both 8 and 4 mg fesoterodine were significantly more effective than placebo, with the exception of UPS scores for fesoterodine 4 mg vs placebo. The incidence of TEAEs appeared higher in the fesoterodine 8-mg group than in the 4-mg group, particularly for dry mouth and constipation, although there was no increase in the incidence of serious TEAEs and the rate of discontinuations due to TEAEs was low in all groups. The results of the present prospective, fixed-dose trial comparing fesoterodine 8 mg vs fesoterodine 4 mg and placebo are consistent with a *post hoc* analysis of data pooled from two fixed-dose trials [12] and models using data from phase II and phase III trials [13].

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Table 1 Baseline demographic and clinical characteristics*.

Variable	Placebo (*n* = 386)	Fesoterodine 4 mg (*n* = 790)	Fesoterodine 8 mg (*n* = 779)
Mean (range) age, years	59.6 (19–85)	58.8 (18–89)	59.8 (21–94)
Gender, *n* (%)			
Men	70 (18)	143 (18)	152 (20)
Women	316 (82)	647 (82)	627 (80)
Race, *n* (%)			
White	308 (80)	650 (82)	635 (82)
Black	52 (14)	92 (12)	88 (11)
Asian	18 (5)	34 (4)	47 (6)
Other	8 (2)	14 (2)	9 (1)
Mean (range) weight, kg	83.3 (36.0–172.4)	82.6 (42.2–197.0)	82.4 (43.1–163.6)
Mean (range) BMI, kg/m^2	30.7 (17.9–61.3)	30.5 (16.9–65.8)	30.3 (17.1–60.8)
Mean (range) duration since OAB diagnosis, years	8.4 (0.0–61.8)	7.1 (0.1–48.5)	7.3 (0.5–69.3)
Mean (SD) diary variables:			
UUI episodes/24 h	4.1 (2.4)	3.9 (2.1)	3.9 (2.3)
Micturitions/24 h	12.8 (3.9)	12.6 (3.7)	12.7 (3.5)
Urgency episodes/24 h	11.2 (4.2)	11.1 (3.9)	11.0 (3.9)
Mean (SD) OAB-q scores:			
Symptom Bother	70.1 (18.3)	68.6 (18.7)	68.8 (18.6)
HRQL	44.4 (22.8)	46.6 (23.3)	45.2 (22.8)
Coping	37.2 (26.3)	39.7 (26.7)	37.8 (26.0)
Concern	40.0 (25.4)	42.3 (26.3)	40.9 (24.9)
Sleep	41.6 (26.5)	43.6 (26.3)	43.9 (27.5)
Social Interaction	64.8 (27.2)	66.8 (27.4)	64.5 (27.7)
PPBC, *n* (%)			
Not many problems at all (1)	0 (0)	1 (0.1)	3 (0.4)
Some very minor problems (2)	3 (0.9)	0 (0)	3 (0.4)
Some minor problems (3)	3 (0.9)	10 (1.4)	9 (1.3)
Some moderate problems (4)	85 (24.4)	178 (25.4)	164 (24.2)
Severe problems (5)	175 (50.3)	340 (48.6)	337 (49.8)
Many severe problems (6)	82 (23.6)	171 (24.4)	161 (23.8)
UPS, *n* (%)			
1	180 (51.7)	333 (47.6)	329 (48.6)
2	164 (47.1)	349 (49.9)	332 (49.0)
3	4 (1.1)	18 (2.6)	16 (2.4)

*BMI, body mass index; UPS: 1, Not able to hold urine; 2, Able to hold urine [without leaking] until I reach a toilet immediately; 3, Able to finish the ongoing work before going to the toilet [without leaking]. *Demographic data represent the safety set; baseline diary variable and PRO data represent full analysis set.*

Table 2 Most commonly reported TEAEs*.

Event, *n* (%)	Placebo (*n* = 386)	Fesoterodine 4 mg (*n* = 790)	Fesoterodine 4 or 8 mg† (*n* = 779)
Dry mouth:	13 (3.4)	102 (12.9)	203 (26.1)
Mild	12 (3.1)	77 (9.7)	144 (18.5)
Moderate	1 (0.2)	23 (2.9)	50 (6.4)
Severe	0	2 (0.2)	9 (1.2)
Constipation:	7 (1.8)	12 (1.5)	31 (4.0)
Mild	7 (1.8)	8 (1.0)	19 (2.4)
Moderate	0	3 (0.4)	11 (1.4)
Severe	0	1 (0.1)	1 (0.1)
UTI:	5 (1.3)	16 (2.0)	17 (2.2)
Mild	2 (0.5)	12 (1.5)	9 (1.2)
Moderate	3 (0.8)	4 (0.5)	8 (1.0)
Severe	0	0	0

**All-causality adverse events reported by >2% subjects in the safety set in either active treatment group with higher incidence than placebo. The severity of adverse events was assessed by the investigator, with adverse events that did 'not interfere with subject's usual function' rated as mild, adverse events that interfered "to some extent with subject's usual function" rated as moderate, and adverse events that interfered 'significantly with subject's usual function' rated as severe; †Subjects in the fesoterodine 8-mg group received fesoterodine 4 mg for the first week and then fesoterodine 8 mg for the remaining 11 weeks.*

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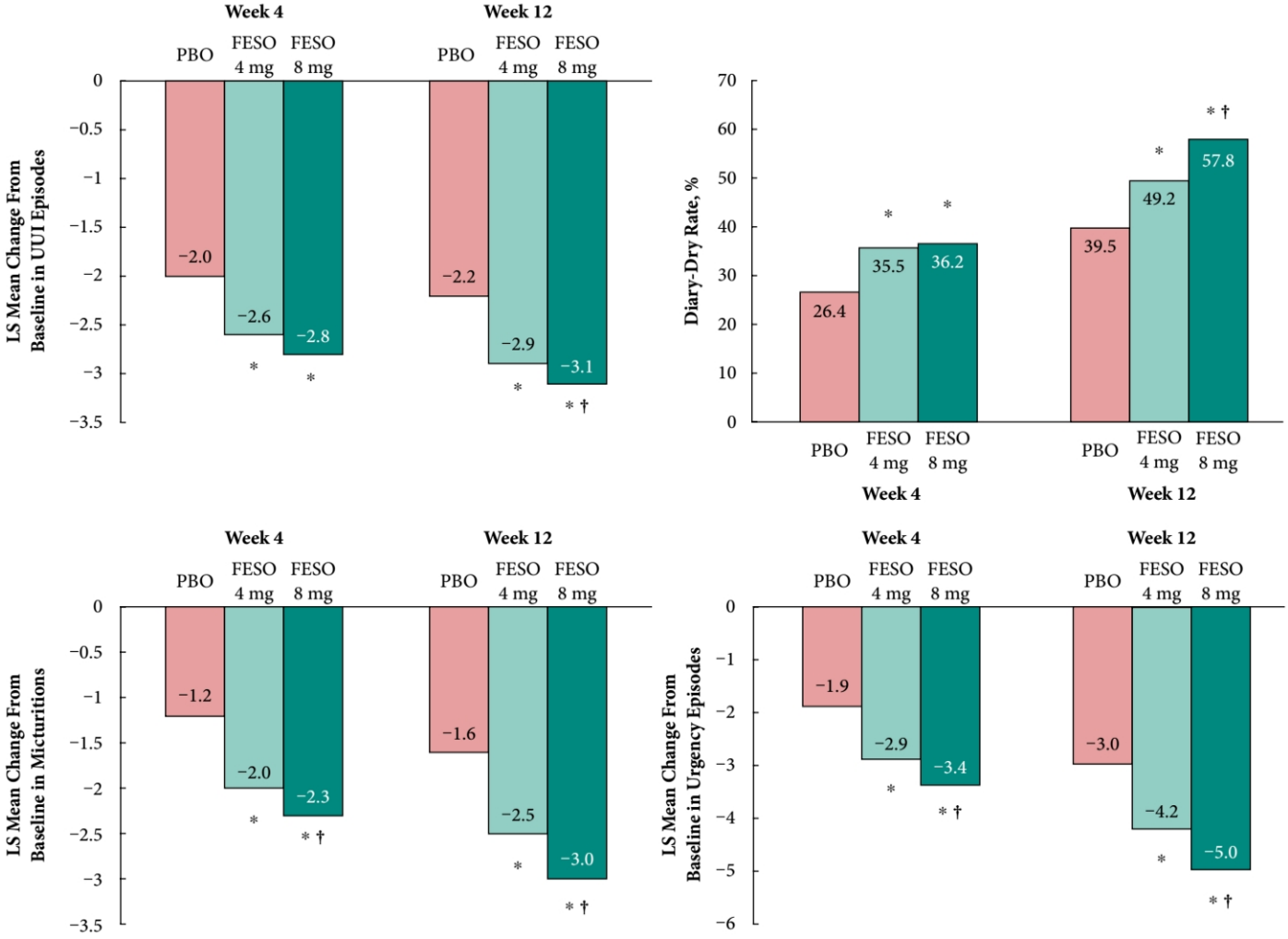
Fig. 2 Change from baseline to weeks 4 and 12 in UUI episodes, micturitions, and urgency episodes/24 h. *$P < 0.01$ vs placebo; †$P < 0.05$ vs fesoterodine 4 mg. FESO, fesoterodine; PBO, placebo.



The findings of the present study have important clinical implications. Availability of multiple doses is an important therapeutic consideration for many conditions, including OAB [5,19]. The utility of multiple doses is predicated on the concept that the dose-response curve differs between individual patients [5]. That is, patients with high drug sensitivity may have sufficient efficacy on a lower dose of drug but experience unacceptable tolerability on a higher dose, whereas patients with low drug sensitivity may have insufficient efficacy on a lower dose but achieve increased benefit with acceptable tolerability on a higher dose [5]. These differences in drug response may be due to a combination of pharmacodynamic and pharmacokinetic differences resulting from variations in genotype, age, comorbidity, concomitant medications, or other factors. The utility of multiple doses is based on the assumption of a dose-response effect.

In flexible-dose trials of fesoterodine, approximately 50–63% of patients opted for dose escalation from fesoterodine 4 to 8 mg [20–25]. In a long-term, open-label extension trial, patients who completed a phase III trial were treated with open-label fesoterodine 8 mg but could reduce their dose to 4 mg and increase back to the 8-mg dose once per year; 71% of patients remained on the 8-mg dose throughout treatment [26]. Fesoterodine treatment was continued for ≥24 months by 61% of 417 patients, and statistically significant improvements in diary variables and PROs were achieved and maintained across this period. Collectively, these findings suggest that about half of the patients treated with fesoterodine derive adequate efficacy and/or achieve a favourable balance of efficacy and tolerability with the 4-mg dose, but at least half of the patients treated with fesoterodine may opt for the higher dose, suggesting a desire for greater efficacy with acceptable tolerability after treatment with fesoterodine 4 mg. The

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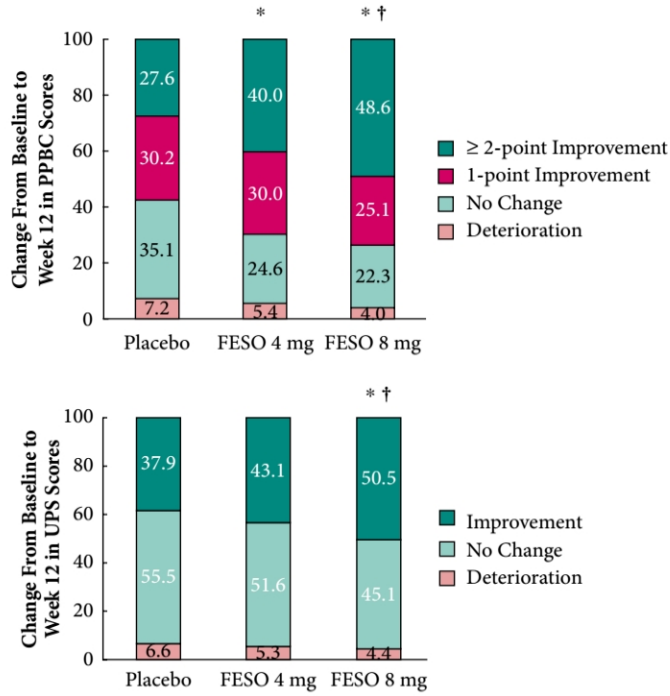
present study, which prospectively compared the efficacy of fesoterodine 4 and 8 mg, confirm that the 8-mg dose produces superior improvements in diary variables, as well as a higher diary-dry rate in patients with OAB symptoms including UUI. The differences in improving bladder diary variables appear to be clinically meaningful, as evidenced by significantly greater improvements in measures of symptom bother, HRQL, and other PROs in patients treated with fesoterodine 8 mg vs those who received fesoterodine 4 mg or placebo. These data suggest that dose escalation should be attempted in patients who do not achieve optimal efficacy with the initial 4-mg dose, rather than switching to another agent. Notably, solid evidence of increased efficacy with higher approved doses has not been shown with other agents used in the treatment of OAB [6–8] or have only been demonstrated over a short (4-week) period [9].

The results of the present study should be interpreted within the context of its limitations. The present study used a fixed-dose design. However, in clinical practice patients have the option of choosing the dose of fesoterodine that provides them with the best balance between efficacy and tolerability. For example, the rate of AEs among the fesoterodine 8-mg group in the present study may be higher than would be seen in clinical practice, as some patients randomised to the 8-mg group may have opted for the 4-mg dose as their best treatment option if given the choice. The use of a fixed-dose design was necessary to demonstrate the superiority of the higher dose, which suggests that patients in clinical practice who show good tolerability and need additional efficacy should be tried at the higher dose before considering other treatment options for OAB symptoms.

In conclusion, in this OAB study population, both fesoterodine 4 and 8 mg were effective in improving OAB symptoms compared with placebo, including UUI. Fesoterodine 8 mg showed statistically significantly superior efficacy vs fesoterodine 4 mg in reducing the mean number of UUI episodes/24 h from baseline to week 12. Patients treated with fesoterodine 8 mg also had significantly superior improvements vs those treated with fesoterodine 4 mg in the mean number of micturitions and urgency episodes/24 h, and in PPBC, UPS, and OAB-q scores at week 12, as well as a higher diary-dry rate. Fesoterodine 4 and 8 mg were generally well tolerated and showed a comparable safety profile to that reported in other studies. The data from the EIGHT study, together with data from phase III studies, provide confirmation that fesoterodine 8 mg demonstrates superior efficacy for improving OAB symptoms, including UUI, and

Fig. 3 Change from baseline to weeks 4 and 12 in PPBC scores and UPS scores. *$P < 0.001$ vs placebo; †$P < 0.01$ vs fesoterodine 4 mg. FESO, fesoterodine.



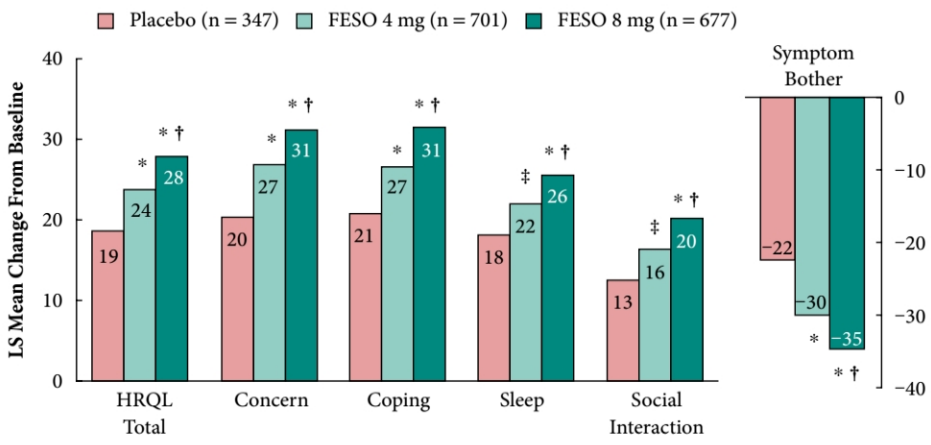


Fig. 4 Change from baseline to week 12 in OAB-q scores. *$P < 0.001$ vs placebo; †$P < 0.01$ vs fesoterodine 4 mg; ‡$P < 0.05$ vs placebo.

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PROs compared with fesoterodine 4 mg. The demonstrations of statistically significant dose-dependent efficacy effects for fesoterodine are unique among antimuscarinics and other oral agents for the treatment of OAB. The greater efficacy of fesoterodine 8 mg supports the benefit of having two doses of fesoterodine and the recommended starting dose of 4 mg with dose escalation for patients in clinical practice who require a higher dose to achieve optimal symptom relief. The variability in treatment response supports the clinical utility of having two approved doses of fesoterodine to optimise symptom control for patients who desire greater efficacy and can tolerate the higher dose.

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Conflict of Interest

C.C.: Pfizer – Consultant, Researcher, Speaker and Trial Participation.
Allergan – Consultant, Researcher, Speaker and Trial Participation.
American Medical Systems – Consultant.
Astellas – Consultant, Researcher, Speaker and Trial Participation.
Lilly – Consultant.
ONO – Consultant.
Ranbaxy – Speaker.
Recordati – Consultant, Researcher, Speaker and Trial Participation.
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F.H.: Astellas – Consultant and Lecturer.
Allergan – Consultant and Lecturer.
Pfizer – Consultant and Lecturer.
F.S., L.W., D.S., E.D., and E.M. are all employees of Pfizer.

References

1 **Irwin DE, Mungapen L, Milsom I, Kopp Z, Reeves P, Kelleher C.** The economic impact of overactive bladder syndrome in six Western countries. *BJU Int* 2009; 103: 202–9
2 **Reeves P, Irwin D, Kelleher C et al.** The current and future burden and cost of overactive bladder in five European countries. *Eur Urol* 2006; 50: 1050–7
3 **Michel MC.** Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. *Expert Opin Pharmacother* 2008; 9: 1787–96
4 **Malhotra B, Gandelman K, Sachse R, Wood N, Michel MC.** The design and development of fesoterodine as a prodrug of 5- hydroxymethyl tolterodine (5-HMT), the active metabolite of tolterodine. *Curr Med Chem* 2009; 16: 4481–9
5 **Michel MC, Staskin D.** Understanding dose titration: overactive bladder treatment with fesoterodine as an example. *Eur Urol Suppl* 2011; 10: 8–13
6 **Hill S, Khullar V, Wyndaele JJ, Lheritier K.** Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for thetreatment of overactive bladder: results of a fixed dose study. *Int Urogynecol J Pelvic Floor Dysfunct* 2006; 17: 239–47
7 **Cardozo L, Lisec M, Millard R et al.** Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol* 2004; 172: 1919–24
8 **Nitti VW, Khullar V, van Kerrebroeck P et al.** Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract* 2013; 67: 619–32
9 **Corcos J, Casey R, Patrick A et al.** A double-blind randomized dose-response study comparing daily doses of 5, 10 and 15 mg controlled-release oxybutynin: balancing efficacy with severity of dry mouth. *BJU Int* 2006; 97: 520–7
10 **Chapple C, Van Kerrebroeck P, Tubaro A et al.** Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol* 2007; 52: 1204–12
11 **Nitti VW, Dmochowski R, Sand PK et al.** Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007; 178: 2488–94
12 **Khullar V, Rovner ES, Dmochowski R, Nitti V, Wang J, Guan Z.** Fesoterodine dose response in subjects with overactive bladder syndrome. *Urology* 2008; 71: 839–43
13 **Cardozo L, Khullar V, El-Tahtawy A, Guan Z, Malhotra B, Staskin D.** Modeling dose-response relationships of the effects of fesoterodine in patients with overactive bladder. *BMC Urol* 2010; 10: 14
14 **Coyne KS, Margolis MK, Hsieh R, Vats V, Chapple CR.** Validation of the urinary sensation scale (USS). *Neurourol Urodyn* 2011; 30: 360–5
15 **Coyne KS, Matza LS, Kopp Z, Abrams P.** The validation of the Patient Perception of Bladder Condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur Urol* 2006; 49: 1079–86
16 **Cardozo L, Coyne KS, Versi E.** Validation of the Urgency Perception Scale. *BJU Int* 2005; 95: 591–6
17 **Coyne K, Revicki D, Hunt T et al.** Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res* 2002; 11: 563–74
18 **Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V.** Determining the importance of change in the overactive bladder questionnaire. *J Urol* 2006; 176: 627–32
19 **Chapple CR, Rosenberg MT, Brenes FJ.** Listening to the patient: a flexible approach to the use of antimuscarinic agents in overactive bladder syndrome. *BJU Int* 2009; 104: 960–7
20 **Wyndaele JJ, Goldfischer ER, Morrow JD et al.** Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. *Int J Clin Pract* 2009; 63: 560–7
21 **Dmochowski RR, Peters KM, Morrow JD et al.** Randomized, double-blind, placebo-controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. *Urology* 2010; 75: 62–8
22 **Cardozo L, Hall T, Ryan J et al.** Safety and efficacy of flexible-dose fesoterodine in British subjects with overactive bladder: insights into factors associated with dose escalation. *Int Urogynecol J* 2012; 23: 1581–90
23 **Wagg A, Khullar V, Marschall-Kehrel D et al.** Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. *J Am Geriatr Soc* 2013; 61: 185–93
24 **Weiss JP, Jumadilova Z, Johnson TM 2nd et al.** Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency. *J Urol* 2013; 189: 1396–401

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25 **DuBeau CE, Kraus SR, Griebling TL et al.** Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo-controlled trial. *J Urol* 2014; 191: 395–404

26 **Van Kerrebroeck PE, Heesakkers J, Berriman S, Padmanabhan Aiyer L, Carlsson M, Guan Z.** Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. *Int J Clin Pract* 2010; 64: 584–93

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Abbreviations: ANCOVA, analysis of covariance; (TE)AE, (treatment-emergent) adverse event; EIGHT, Evaluation of urinary urge Incontinence patients Given fesoterodine 8 mg vs fesoterodine 4 mg in a Head-to-head efficacy Trial; HRQL, health-related quality of life; LS, least squares (means); OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; PPBC, Patient Perception of Bladder Condition; PRO, patient-reported outcome; UPS, Urgency Perception Scale; USS, Urinary Sensation Scale; UUI, urgency urinary incontinence.

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