Efficacy and safety of fesoterodine 8 mg in subjects with overactive bladder after a suboptimal response to tolterodine ER

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SUMMARY

Aims: To assess fesoterodine 8 mg efficacy over time and vs. placebo in subjects with overactive bladder (OAB) who responded suboptimally to tolterodine extended release (ER) 4 mg. **Methods:** In a 12-week, double-blind trial, subjects with self-reported OAB symptoms for $\geq$ 6 months, mean of $\geq$ 8 micturitions and $\geq$ 2 to < 15 urgency urinary incontinence (UUI) episodes/24 h, and suboptimal response to tolterodine ER 4 mg (defined as $\leq$ 50% reduction in UUI episodes during 2-week run-in) were randomised to fesoterodine (4 mg for 1 week, 8 mg for 11 weeks) or placebo once daily. Change from baseline to week 12 in UUI episodes (primary end-point) was analysed in step-wise fashion: first, baseline vs. week 12 for fesoterodine; if significant, then change from baseline to week 12 for fesoterodine vs. placebo. **Results:** By week 12, subjects receiving fesoterodine 8 mg had significantly greater improvement from baseline vs. placebo in UUI episodes, urgency episodes and scores on the Patient Perception of Bladder Control, Urgency Perception Scale and OAB Questionnaire Symptom Bother and Health-Related Quality of Life scales and domains (all p < 0.05). 50% and 70% UUI responder rates were also significantly higher with fesoterodine 8 mg vs. placebo at week 12 (p < 0.05). Dry mouth (placebo, 4%, 12/301; fesoterodine, 16.6%, 51/308) and constipation (placebo, 1.3%, 4/301; fesoterodine, 3.9%, 12/308) were the most frequent adverse events. **Conclusions:** Subjects who responded suboptimally to tolterodine ER 4 mg showed significant improvements in UUI and other OAB symptoms and patient-reported outcomes, with good tolerability, during treatment with fesoterodine 8 mg vs. placebo.

What's known

Some patients with overactive bladder who experience suboptimal treatment outcomes with one antimuscarinic may benefit from treatment with a different agent. Two prospectively-designed, placebo-controlled, head-to-head studies demonstrated that fesoterodine 8 mg is significantly more efficacious than tolterodine extended release 4 mg for improving UUI episodes and other bladder diary endpoints as well as patient-reported measures of symptom bother and health-related quality of life.

What's new

Subjects who responded suboptimally to tolterodine extended release 4 mg showed significantly greater improvements in urgency urinary incontinence episodes and other overactive bladder symptoms and patient-reported outcomes after treatment with fesoterodine 8 mg versus placebo. These data provide further evidence suggesting that some patients with overactive bladder including urgency urinary incontinence may experience additional treatment benefit with fesoterodine 8 mg versus tolterodine extended release 4 mg.

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Introduction

Urgency urinary incontinence (UUI) is highly bothersome and negatively impacts health-related quality of life (HRQL) (1). UUI is associated with numerous comorbidities, such as falls and fractures, infections and depression (2), and a large proportion of the cost associated with overactive bladder (OAB) is attributable to UUI (3).

Antimuscarinics are the first-line pharmacologic treatment for UUI and OAB. Some antimuscarinics, such as fesoterodine, are available in two doses, allowing the physician to individually titrate dosage for optimal efficacy and manageable side effects (4). Alternatively, some patients with OAB not achieving

optimal treatment outcomes with one agent may benefit from treatment with a different antimuscarinic (5–7). Two prospectively designed, placebo-controlled, head-to-head studies that compared the highest approved doses of fesoterodine (8 mg) and tolterodine extended release (ER) (4 mg) demonstrated that fesoterodine 8 mg was significantly more efficacious than tolterodine ER 4 mg in reducing UUI episodes and produced significantly higher diary-dry rates (8,9). Patient-reported outcomes measuring symptom bother and HRQL were also significantly improved following treatment with fesoterodine 8 mg vs. tolterodine ER 4 mg (8,9). These findings are consistent with a *post hoc* analysis of an earlier trial, which showed that fesoterodine 8 mg

produced significantly greater improvements in UUI episodes, number of continent days/week, and other diary variables than tolterodine ER 4 mg (10).

The objectives of this study were to assess the efficacy and safety of fesoterodine 8 mg in OAB patients who responded suboptimally to tolterodine ER 4 mg in a prospective, randomised, controlled trial.

Materials and Methods

Subjects

This was a 12-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted at 156 sites in 15 countries in Europe, North America, Asia, and Africa between May 2011 and May 2012 (ClinicalTrials.Gov ID: NCT01302054). Before subjects were randomised to the treatment study period, they entered a 2-week, open-label, run-in period to identify subjects who responded suboptimally to tolterodine ER 4 mg once daily (11). Subjects reporting a $\leq 50\%$ reduction in mean UUI episodes/24 h from the eligibility diary (week $- 2$) to the baseline diary (week 0) were randomised 1:1 via a centralised system to 12 weeks of treatment with fesoterodine or placebo. Subjects randomised to fesoterodine received fesoterodine 4 mg once daily for the first week, followed by fesoterodine 8 mg for 11 weeks. Study drug was to be taken once daily in the morning. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines, and all local regulatory requirements. The appropriate Institutional Review Boards and Ethics Committees approved the protocol.

Inclusion criteria were: men or women aged ≥ 18 years, self-reported OAB symptoms for ≥ 6 months, and at least 'some moderate problems' reported on the Patient Perception of Bladder Condition (PPBC) (12) at screening visit; a mean of ≥ 2 to < 15 mean UUI episodes (Urinary Sensation Scale rating of 5) and ≥ 8 micturitions per 24 h on a 3-day bladder diary at the eligibility visit (week $- 2$; beginning of the tolterodine ER run-in); and $\leq 50\%$ change in mean UUI episodes/24 h between eligibility and randomisation (baseline) visits (week 0; end of the tolterodine ER run-in).

Exclusion criteria included any condition contraindicating use of tolterodine or fesoterodine or conditions that may affect assessment of bladder function, such as neurological conditions suspected of influencing bladder function, predominant stress urinary incontinence, lower urinary tract/pelvic surgery with ongoing effect on bladder function, pelvic organ prolapse, clinically significant bladder outflow obstruction evidenced by previous history of acute urinary retention requiring catheterisation, or postvoid residual volume > 200 ml. Subjects with clinically significant or recurrent urinary tract infection; treatment with ≥ 3 antimuscarinic OAB medications within 12 months before screening; new or unstable use of diuretics, α-blockers, 5–alpha reductase inhibitors, estrogens, or tricyclic antidepressants; treatment with drugs capable of influencing hepatic metabolism with potential for drug-drug interaction; and initiation of electrostimulation or behavioural intervention programme within 4 weeks of screening.

Efficacy outcomes

The primary efficacy end-point was the change from baseline (after the tolterodine ER 4 mg run-in) to week 12 in the number of UUI episodes/24 h. The reduction from baseline to week 12 in UUI episodes for fesoterodine 8 mg was assessed. If significant, the change from baseline in number of UUI episodes/24 h at week 12 for fesoterodine 8 mg was then compared with placebo.

Secondary efficacy end-points included treatment differences in changes from baseline to week 4 in number of UUI episodes/24 h; changes from baseline to weeks 4 and 12 in number of micturitions and urgency episodes/24 h; responder rates ($\geq 50\%$ or $\geq 70\%$ reductions in UUI episode frequency) from eligibility (prior to the run-in) and from baseline at weeks 4 and 12; diary-dry rate at weeks 4 and 12 (percentage of subjects with > 1 UUI episode on baseline diary and 0 UUI episodes on postbaseline diary); and changes from baseline to week 12 in PPBC (12), Urgency Perception Scale (UPS) (13), and Overactive Bladder Questionnaire (OAB-q) (14) scores.

Statistical analysis

The run-in period duration was based on previous data showing an approximately 70% reduction in UUI episodes during the first 2 weeks of antimuscarinic treatment (15,16). The threshold of $\leq 50\%$ reduction in UUI episodes to define suboptimal response was based on comparison of cumulative distribution functions between active treatment and placebo groups from previous trials across all levels of percentage changes in UUI (17,18); maximal separation was observed at approximately 50% change in UUI episodes. This is consistent with previous evidence-based recommendations for measuring treatment response in OAB subjects with UUI (11).

Efficacy analyses were based on the full analysis set (all randomised subjects who took ≥ 1 dose of study drug and had a baseline or postbaseline efficacy assessment). The safety analysis set included all subjects who were randomised and received ≥ 1 dose of

double-blind study medication and/or took tolterodine ER in the run-in period. Missing data were imputed with the last observation carried forward method.

For the primary efficacy end-point, multiple hypothesis testing was conducted in a hierarchical sequentially rejective manner. The reduction from baseline to week 12 in UUI episodes for fesoterodine 8 mg (within-group mean change) was assessed using a 1-sided t test based on an α-level of 2.5%. If significant, a 1-sided test of the superiority of fesoterodine 8 mg vs. placebo in reducing the mean number of UUI episodes/24 h was conducted using an analysis of covariance model with treatment and country as factors and centred baseline value as a covariate, based on an α-level of 2.5%.

Changes in secondary bladder diary variables and OAB-q scores were analysed using the same analysis of covariance model. Responder rates, 3-day diary-dry rates, and categorical changes in PPBC and UPS scores were analysed using the Cochran–Mantel–Haenszel tests with modified ridit scoring stratified by country. All tests of secondary outcomes were 2-sided based on an α-level of 5%. All analyses were performed using Statistical Analysis Software versions 8 and 9 (SAS Institute Inc., Cary, NC).

Safety data, from both the tolterodine ER run-in phase and the double-blind phase, were summarised by treatment group.

Results

Subject disposition is presented in Figure 1. Demographical and clinical characteristics were similar for the placebo and fesoterodine groups (Table 1). Subjects in both treatment groups had approximately 4 UUI episodes/24 h at baseline.

For the primary end-point, UUI episodes were significantly reduced from baseline to week 12 within each treatment group (p < 0.0001), and the mean reduction from baseline to week 12 in UUI episodes/24 h was significantly greater with fesoterodine 8 mg vs.
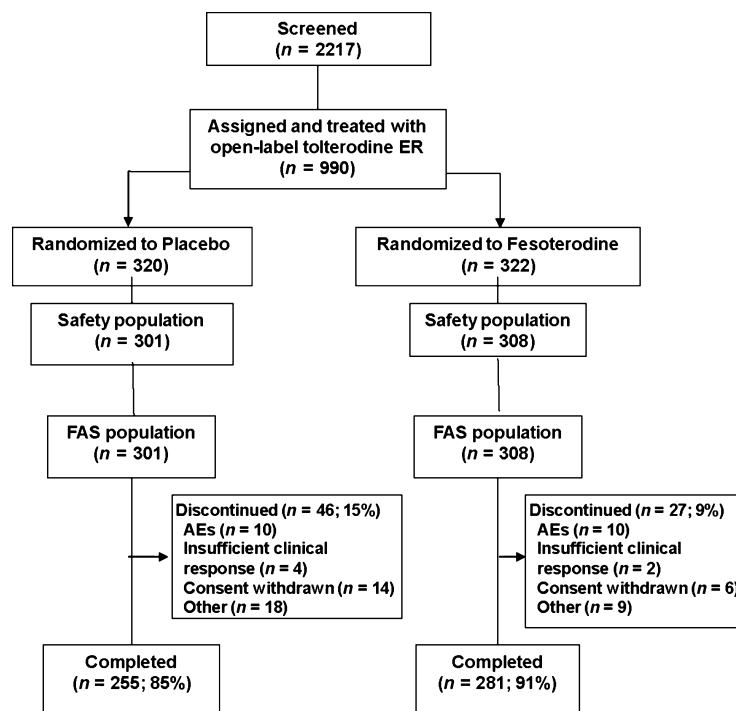

Figure 1 Subject disposition. Full analysis set (FAS) = all randomised subjects who received ≥ 1 dose of study drug and had ≥ 1 efficacy assessment. Safety population = all randomised subjects who received ≥ 1 dose of double-blind study medication and/or took tolterodine ER in the run-in period. Sample size was determined from a subset of data from two of the fesoterodine Phase 3 studies that included subjects previously on tolterodine ER 4 mg with a change in UUI from baseline week 0 to week 2 ≤ 50% (non-responders) and a week 0 UUI value ≥ 2. Sample size was calculated using a two-sample t test to compare fesoterodine 8 mg and placebo (0.05 2-sided significance level). A sample size of 226 in each arm would have > 90% power to detect a difference in mean change from baseline in UUI episodes of −0.98 if the common standard deviation was 3.0, as observed previously. The within-group mean change from baseline to week 12 for fesoterodine 8 mg arm was expected to be no less than that of 8 mg vs. placebo, and thus this sample size had ≥ 90% power to detect a difference in frequency of UUI episodes.

Table 1 Baseline demographical and clinical characteristics

	Placebo (*n* = 301)	Fesoterodine (*n* = 308)
Sex, *n* (%)		
Male	57 (19)	55 (18)
Female	244 (81)	253 (82)
Mean (SD) age, y	58.2 (13.2)	57.3 (13.4)
Race, *n* (%)		
White	246 (81.7)	251 (81.5)
Black	37 (12.3)	38 (12.3)
Asian	8 (2.7)	8 (2.6)
Other	10 (3.3)	11 (3.6)
Mean weight, kg (range)	81.5 (45.8–156.0)	81.3 (45.0–194.1)
Mean (SD) body-mass index, kg/m^2	30.0 (6.9)	29.8 (6.7)
Mean duration since OAB diagnosis, y (range)	6.6 (0.5–50.1)	7.0 (0.5–46.5)
Median duration since diagnosis, y*	4.6	4.7
OAB symptoms at baseline, mean (SD)[†]		
UUI episodes/24 h	3.83 (2.5)	3.93 (2.5)
Micturitions/24 h	12.48 (3.8)	12.44 (3.6)
Urgency episodes/24 h	11.26 (4.0)	11.38 (4.0)

Data for subjects who were randomised and received double-blind treatment, except where noted. *Data for randomised subjects (placebo, *n* = 320; fesoterodine, *n* = 322). [†]Data for the full analysis set of subjects with symptom and change from baseline to week 12 (LOCF) data (placebo, *n* = 279; fesoterodine, *n* = 292). OAB, overactive bladder.

placebo (p = 0.0079; Figure 2). The reduction in UUI episodes from baseline to week 4 was also significantly greater with fesoterodine vs. placebo (p = 0.0031; Figure 2).

The mean reduction from baseline in urgency episodes/24 h was significantly greater with fesoterodine 8 mg vs. placebo at week 12 (p = 0.0438), but not at week 4 (p = 0.2172; Figure 2). The mean reduction from baseline in micturitions/24 h was significantly greater with fesoterodine vs. placebo at week 4 (p = 0.0463), and the difference was not statistically significant at week 12 (p = 0.0931; Figure 2). The diary-dry rate was significantly higher in the fesoterodine group vs. the placebo group at week 4 (p = 0.0427), but not at week 12 (p = 0.1461; Figure 2).

The percentages of subjects with a > 50% (p = 0.0027) or > 70% (p = 0.0010) reduction in UUI episodes from baseline (after the tolterodine ER run-in) to week 12 were significantly higher in the fesoterodine group vs. the placebo group (Figure 2). At week 4, 50% (p = 0.0537) and 70% (p = 0.1648) responder rates were not different between the treatment groups (Figure 2). Similarly, percentages of subjects with a > 50% (60% vs. 73%, p = 0.0023) or > 70% (47% vs. 61%, p = 0.0020) reduction in UUI episodes from eligibility (before the tolterodine ER run-in) to week 12 were significantly higher in the fesoterodine group vs. the placebo group, but 50% (54% vs. 63%, p = 0.089) and 70% (40% vs. 46%,

p = 0.2229) responder rates from eligibility to week 4 were not significantly different.

Categorical changes from baseline in PPBC (p < 0.0001) and UPS (p = 0.0095) scores at week 12 were significantly better in the fesoterodine 8 mg group vs. the placebo group (Figure 3). Changes from baseline in OAB-q Symptom Bother (p = 0.0001) and total HRQL (p < 0.0001) scores, as well as in the Concern (p < 0.0001), Coping (p < 0.0001), Sleep (p = 0.0012) and Social Interaction (*P* = 0.0123) domains, were also significantly better for fesoterodine vs. placebo at week 12 (Figure 3).

Dry mouth and constipation were the only treatment-emergent adverse event (AEs) occurring in ≥ 2% of subjects in any treatment arm; most cases were moderate to moderate in severity (Table 2). Urinary retention was reported by two subjects during the tolterodine run-in phase; neither case was considered severe. Two deaths were reported during the study. A 72-year-old woman who was a screen failure and did not take any study medication died of respiratory failure with urosepsis. A 73-year-old woman in the placebo group discontinued treatment after being diagnosed with gastric cancer and subsequently died because of disease progression 104 days after starting the study. Serious treatment-emergent AEs and discontinuations because of treatment-related AEs were generally similar with all treatments (Table 2).
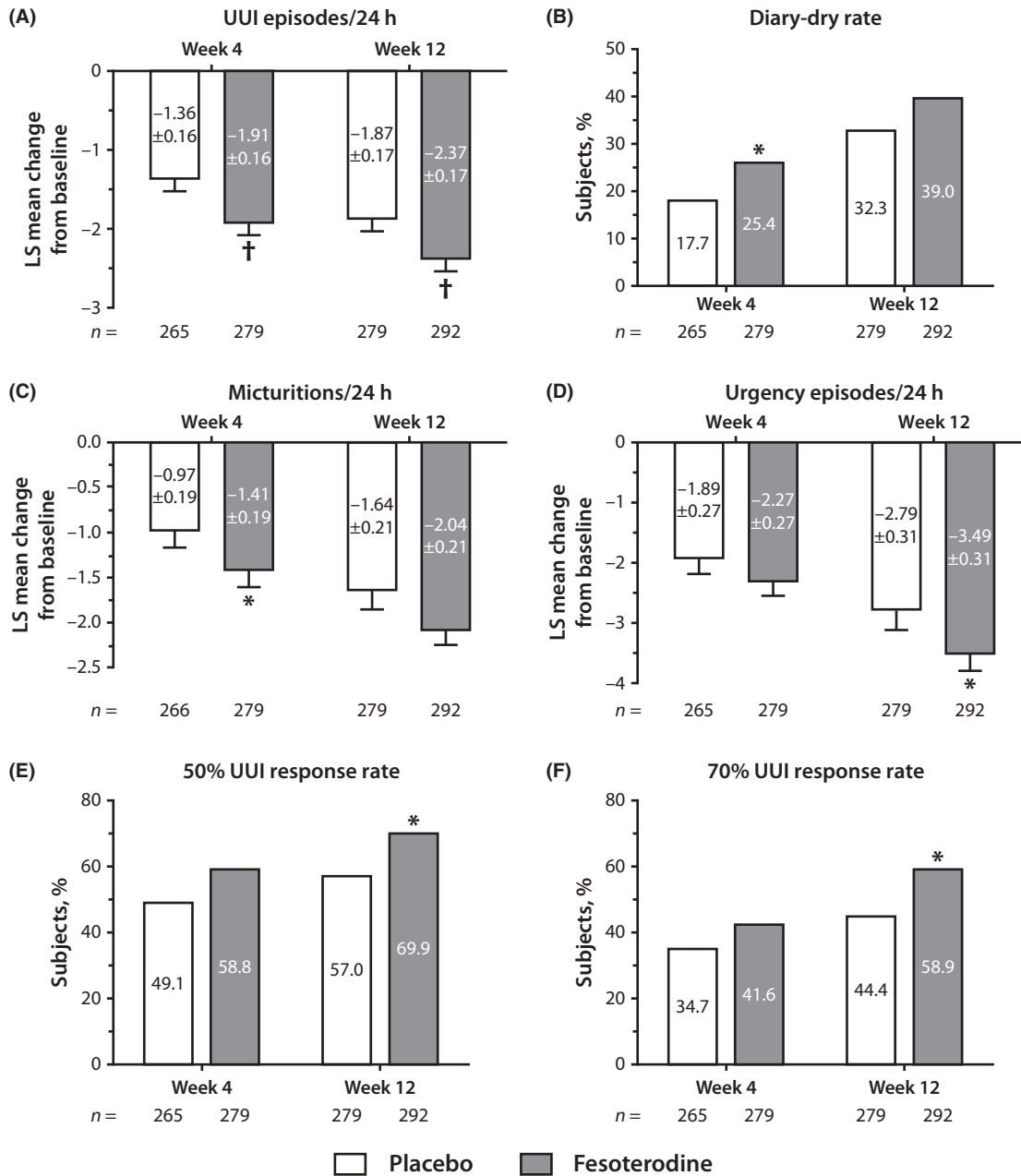
Figure 2 Changes from baseline to weeks 4 and 12 in diary variables. (A) UUI episodes/24 h; (B) diary-dry rate; (C) micturitions/24 h; (D) urgency episodes/24 h; (E) 50% responder rates; (F) 70% responder rates. *p < 0.05; †p < 0.01.

Discussion

Fesoterodine 8 mg treatment was effective and well tolerated in subjects who had a suboptimal response to tolterodine ER 4 mg. The data support the hypothesis that significant UUI reduction can be achieved with fesoterodine 8 mg in patients who respond suboptimally to tolterodine ER 4 mg, as approximately 70% of fesoterodine-treated subjects had a reduction in UUI episodes of 50% or greater

from the eligibility (203/279) or baseline (204/292) visits to week 12 and approximately 60% had a reduction in 70% or greater (eligibility, 170/279; baseline, 172/292). Further, *post hoc* analysis revealed a significant reduction in UUI episodes/24 h (LS mean ±SE) from eligibility to week 12 for fesoterodine- (−2.84 ± 0.17, n = 279) vs. placebo-treated (−2.40 ± 0.17, n = 275) subjects (p = 0.0252). Patient-reported outcomes measuring bladder-related problems, urgency, symptom bother, and HRQL
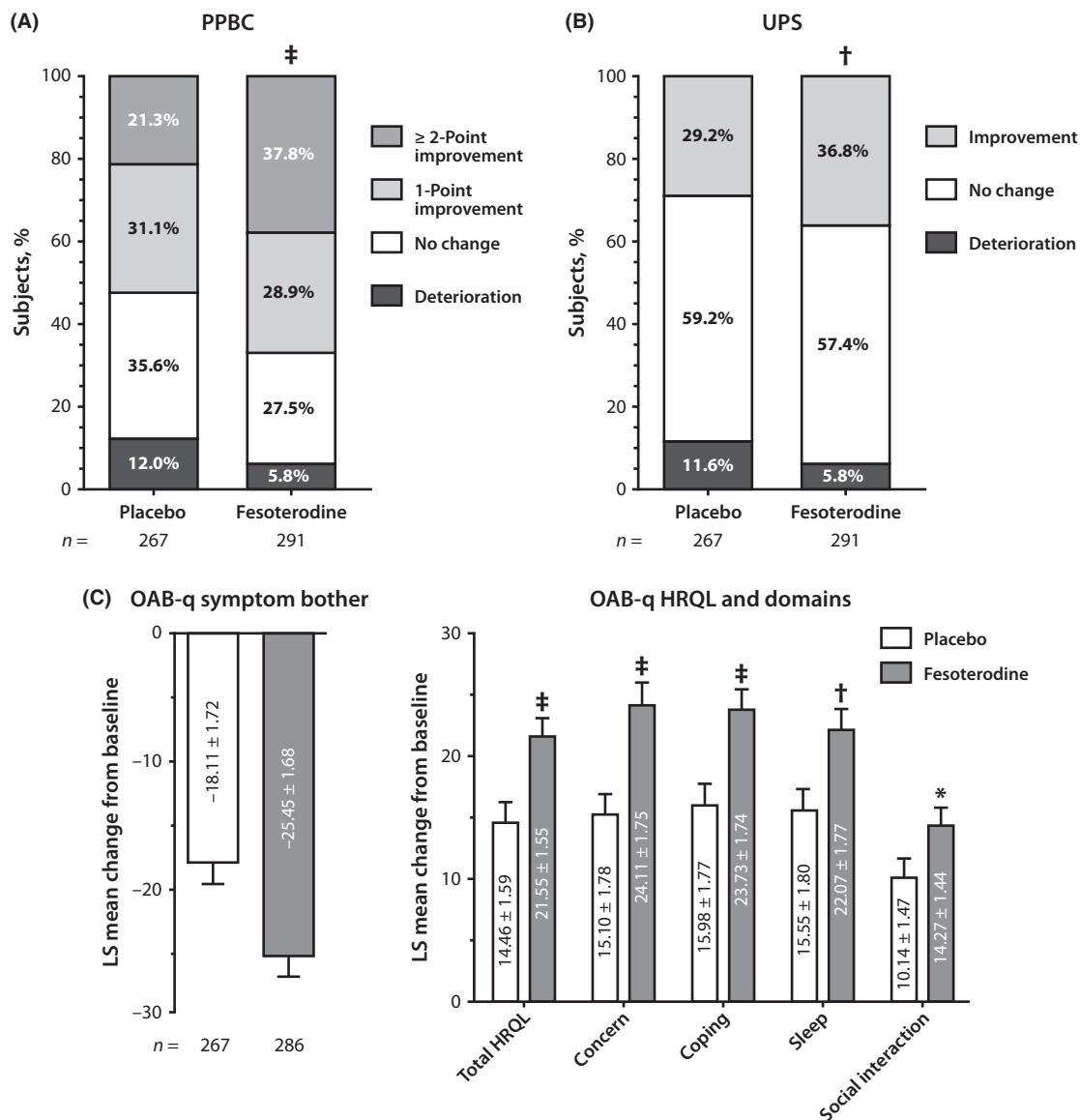
Figure 3 Patient-reported outcomes at week 12. (A) PPBC; (B) UPS; (C) OAB-q. *p < 0.05; †p < 0.01; ‡p < 0.001.

were significantly improved in these subjects, suggesting that the improvements with fesoterodine 8 mg were clinically meaningful.

The present results are consistent with two head-to-head prospective studies comparing fesoterodine 8 mg with tolterodine ER 4 mg (8,9). Significantly greater improvements with fesoterodine 8 mg vs. tolterodine ER 4 mg were observed for UUI episodes and other diary variables and patient-reported outcomes, as well as significantly higher diary-dry rates (8,9). However, the incidence of dry mouth for fesoterodine-treated subjects (28%) (8,9) was higher than in the present study (16.6%).These data are also consistent with an open-label, flexible-dose study of

fesoterodine in subjects with OAB who reported dissatisfaction with tolterodine treatment (ER or immediate-release) within the previous 2 years (5). Significant improvements from baseline to week 12 were observed in UUI episodes, micturitions, urgency episodes, and scores on the PPBC and OAB-q with fesoterodine. Approximately, 80% of subjects who were dissatisfied with previous tolterodine treatment reported being 'satisfied' or 'very satisfied' with flexible-dose fesoterodine treatment.

Studies with other antimuscarinic agents have also shown that subjects with OAB may be successfully treated with one antimuscarinic after unsuccessful treatment with another (6,7). These results, together

Table 2 Treatment-emergent adverse events*

Number of subjects (%)	Open-label	Double-blind	
	Tolterodine ER (*n* = 990)	Placebo (*n* = 301)	Fesoterodine (*n* = 308)
Subjects with AEs			
All-causality	134 (13.5)	75 (24.9)	110 (35.7)
Treatment-related	84 (8.5)	30 (10.0)	68 (22.1)
Discontinued because of AEs			
All-causality	12 (1.2)	12 (4.0)	11 (3.6)
Treatment-related	7 (0.7)	6 (2.0)	7 (2.3)
Subjects with serious AEs	3 (0.3)	7 (2.3)	5 (1.6)
AE rates[†]			
Dry mouth[†]	61 (6.2)	12 (4.0)	51 (16.6)
Constipation[†]	11 (1.1)	4 (1.3)	12 (3.9)

*Includes data up to 7 days after last dose of study drug. [†]AEs occurring in ≥ 2% of subjects in any treatment group.

with results from the present study, suggest that switching medication is a valid approach for patients who fail to achieve OAB symptom resolution with antimuscarinic pharmacotherapy.

As noted above, several studies provide evidence that the highest approved dose of fesoterodine (8 mg) is significantly more effective than the highest approved dose of tolterodine ER (4 mg, which is the only approved dose of tolterodine ER for most OAB populations) (8–10). In addition, the results of a *post hoc* analysis demonstrate that fesoterodine 8 mg is significantly more effective in improving UUI episodes and other diary variables than fesoterodine 4 mg (19). This is important, as a dose-response effect for UUI has not been demonstrated for most antimuscarinic agents with multiple approved doses (20,21).

Many patients stop taking their OAB medication because the drug 'didn't work as expected' or because of side effects (22). The availability of flexible dosing with newer antimuscarinic medications affords additional treatment options when current antimuscarinic treatment fails, because clinicians can adjust patients' dosage in an attempt to achieve favourable efficacy and tolerability before considering more invasive treatment options (4). Data for three flexible-dose fesoterodine studies, in which subjects were initiated on the 4-mg dose and had the opportunity to escalate to the 8-mg dose based on efficacy and tolerability, have been analysed after stratification by subjects' dose escalation status (23–25). In each study, subjects who escalated had more severe symptoms at baseline and a smaller reduction in diary variables and fewer AEs before the dose escalation choice point (23–25). By the end of each study, efficacy and tolerability outcomes were

similar among subjects who escalated and those who did not (23–25). These findings underscore the importance of having an alternative antimuscarinic option or dose escalation when there is a suboptimal response to the first antimuscarinic medication.

Strengths of this study include that it was a prospectively designed, randomised, double-blind, placebo-controlled trial to assess the efficacy and tolerability of fesoterodine 8 mg in a population with a predefined suboptimal response to tolterodine ER 4 mg. In contrast to previous 'switching' studies, this study was unique in identifying a suboptimal response by analysing UUI data before randomisation. In addition, the evaluation of efficacy at early time points and the incorporation of patient-reported outcomes provided measures of the onset and achievement of OAB symptom relief, which are important to patients and critical factors in their decision on whether to continue treatment. The use of a 2-week run-in period and a threshold of a ≤ 50% reduction in UUI episodes to identify suboptimal responders to tolterodine ER are supported by previous evidence (11,17,18). Tolterodine ER was not included as an active comparator because the greater efficacy of fesoterodine 8 mg vs. tolterodine ER 4 mg has been demonstrated previously (8,9).

This study was limited by the measurement of tolterodine treatment response based only on UUI episodes/24 h; other symptoms may also have demonstrated a suboptimal response to treatment with tolterodine ER 4 mg. It is possible that a longer run-in period may have captured additional responders to tolterodine ER 4 mg, although the majority of response is known to occur within the

first 2 weeks of treatment. In a 12-week, prospective, open-label study of tolterodine ER 4 mg in 1138 adult subjects with OAB who were either OAB treatment naïve or had previously received OAB treatment other than tolterodine, the median percentage change from baseline in UUI episodes was assessed at weeks 1, 4 and 12 (26). After week 1 of tolterodine ER 4 mg treatment, 72% of the maximum reduction in UUI episodes was demonstrated in both treatment-naïve and previously treated patients. In a subsequent *post hoc* analysis of the data from this study, the onset of treatment efficacy was assessed based on changes in UUI episodes for treatment days 5, 6 and 7 (27). For subjects with ≥ 1 UUI episodes at baseline, the median percentage decrease from baseline in UUI episodes was 50% at day 5, 67% at day 6, and 75% at day 7 of tolterodine ER treatment (all p < 0.0001 vs. baseline). Using a 50% reduction in UUI episodes to define responders, the responder rate was 58% on day 5, 69% on day 6, and 71% on day 7 of tolterodine ER treatment. These results indicating that subjects with OAB experience significant improvements in UUI episodes and high responder rates, based on a 50% reduction threshold, as early as week 1 of treatment with tolterodine ER 4 mg supported the 2-week duration of the open-label run-in period in the present study. On balance, the 2-week run-in period allowed a pragmatic approach to patient enrolment while maintaining a meaningful period for assessment.

Conclusions

Subjects with OAB who responded suboptimally to tolterodine ER 4 mg achieved significant improvements in UUI episodes after 12 weeks of treatment with fesoterodine 8 mg vs. placebo. Significant improvements in the number of urgency episodes, UUI responder rates, and scores on the PPBC, UPS and all OAB-q scales and domains at week 12 also were observed with fesoterodine vs. placebo treatment. Fesoterodine 8 mg was well tolerated in suboptimal responders to tolterodine ER.

Acknowledgments

Author contributions

All authors participated in the concept/design, data interpretation, drafting and critically revising the article and approval of submission. Statistical analysis was conducted by MC.

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