Randomized, Double-blind, Placebo-controlled Trial of Flexible-dose Fesoterodine in Subjects With Overactive Bladder

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OBJECTIVES To evaluate the efficacy and tolerability of flexible-dose fesoterodine vs placebo in subjects with overactive bladder (OAB).

METHODS In a 12-week double-blind trial, subjects were randomized to fesoterodine 4 mg or placebo once daily, taken within 4 hours of bedtime. At week 2, subjects could increase the fesoterodine dose to 8 mg (sham escalation for placebo). Subjects completed 3-day bladder diaries, Patient Perception of Bladder Condition, and Urgency Perception Scale at baseline and weeks 2, 6, and 12 as well as OAB Questionnaire at baseline and week 12.

RESULTS Of 883 subjects, 63% and 73% of the fesoterodine (n = 438) and placebo (n = 445) groups, respectively, opted for dose escalation. Week 12 improvements from baseline in total micturitions, urgency episodes, urgency urinary incontinence episodes, frequency-urgency sum, and all OAB Questionnaire scales and domains, but not nocturnal micturitions or nocturnal urgency episodes, were significantly greater with fesoterodine than placebo (all $P < .05$). Treatment differences in micturitions and frequency-urgency sum were significant by week 2 and in urgency urinary incontinence and urgency episodes by week 6. Significantly greater percentages of subjects taking fesoterodine had improved Patient Perception of Bladder Condition and Urgency Perception Scale scores at weeks 2, 6, and 12 ($P < .05$). Dry mouth (fesoterodine, 26%; placebo, 8%) and constipation (fesoterodine, 11%; placebo, 6%) were the most common adverse events. In both groups, 87% of the subjects completed the trial; 8% and 5% of the fesoterodine and placebo groups, respectively, discontinued because of an adverse event.

CONCLUSIONS Flexible-dose fesoterodine was efficacious and generally well tolerated for treatment of OAB symptoms. UROLOGY 75: 62–68, 2010. © 2010 Elsevier Inc.

Overactive bladder (OAB) is defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.[1] Approximately 13%-17% of adults have OAB, with prevalence increasing with age.[2-4] OAB can considerably impair health-related quality of life (HRQL).[5]

Antimuscarinics are the principal pharmacologic treatment for OAB, but patient response and ability to tolerate these drugs can vary.[6] Fesoterodine is an antimuscarinic developed for treating OAB symptoms and is available as 4- or 8-mg tablets given once daily. Fesoterodine is rapidly and extensively converted by ubiquitous esterases to its primary metabolite, 5-hydroxymethyl tolterodine (5-HMT); 5-HMT alone is responsible for the antimuscarinic effects of fesoterodine. Tolterodine is also converted to 5-HMT, albeit by cytochrome P450 (CYP) 2D6, primarily in the liver.[7] In patients taking tolterodine, both tolterodine and 5-HMT produce antimuscarinic effects.

The efficacy and safety of fesoterodine 4 and 8 mg were demonstrated in 2 fixed-dose 12-week phase III trials.[8,9] Pooled data from these studies indicate that treatment of OAB symptoms with fesoterodine improves HRQL outcomes.[10] However, flexible dosing reflects clinical practice better than fixed dosing. The recommended starting dose of fesoterodine is 4 mg once daily, which can be increased to 8 mg based on patient response and tolerability.[11] This phase IIIb study assessed the efficacy, safety, and tolerability of a flexible-dose regimen of fesoterodine in subjects with OAB.

MATERIAL AND METHODS

This randomized, double-blind, placebo-controlled, flexible-dose trial of fesoterodine was conducted from August 2007 to

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April 2008 at 88 sites in the United States. The study protocol was approved by the appropriate institutional review boards, and all subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines on Good Clinical Practice.

Men and women aged ≥18 years were eligible if they reported OAB symptoms for ≥3 months before screening, recorded a mean of ≥8 micturitions per 24 hours and ≥3 urgency episodes per 24 hours in a 3-day bladder diary at baseline, and rated their bladder condition at baseline as causing at least some moderate problems using the Patient Perception of Bladder Condition (PPBC).[12] Key exclusion criteria were a history of acute urinary retention requiring catheterization, severe voiding difficulties in the judgment of the investigator, urinary incontinence symptoms attributed by the investigator primarily to stress urinary incontinence, significant pelvic organ prolapse or lower urinary tract surgery within the preceding 6 months, clinically significant hepatic or renal diseases, neurologic disease that significantly affected bladder function, treatment with an antimuscarinic OAB medication or potent CYP3A4 inhibitor within 2 weeks of screening, and any contraindication to fesoterodine. Also excluded were men with intermittent or unstable use of alpha blockers or 5-alpha reductase inhibitors (consistent use was permitted) or who started such treatment within 4 weeks of screening.

On the basis of previous studies,[8,9] it was calculated that a sample size of 350 subjects per arm would provide ≥85% power to detect a difference between fesoterodine and placebo in 24-hour micturitions using a 2-sided *t* test with a .05 significance level.

Subjects completed a 2-week screening period during which no treatment was given, followed by 12 weeks of treatment. Subjects meeting eligibility criteria were randomized in a 1:1 ratio, with no blocking, to fesoterodine 4 mg or placebo taken once daily within 4 hours of bedtime. Randomization was implemented using a centralized system accessed by phone or Internet that generated single subject identification and randomization numbers, both of which were to be entered on the electronic case report form. The randomization schedule was generated, secured, distributed, and stored by Pfizer Global Clinical Data Services; neither the investigator nor subject was aware of the treatment administered.

At the end of week 2, after subjective consultation with the investigator regarding efficacy and tolerability, subjects could choose to increase the fesoterodine dose to 8 mg once daily for the remaining 10 weeks (for placebo, sham dose escalation). No dose adjustments were permitted after week 2.

Efficacy Assessments

Subjects completed bladder diaries for 3 consecutive days immediately before the baseline visit and each subsequent visit (weeks 2, 6, and 12). Subjects recorded all micturitions, including incontinence episodes, and rated the sensation associated with each micturition using the Urinary Sensation Scale, with ratings ranging from 1 (no feeling of urgency) to 5 (unable to hold; leaked urine).[13] Urgency episodes were those rated ≥3; severe urgency episodes were those rated ≥4. Frequency-urgency sum (a composite measurement of urgency and frequency) was defined as the total of Urinary Sensation Scale ratings for all micturitions.

Subjects completed the validated PPBC[12] and urgency perception scale (UPS)[14] at baseline and weeks 2, 6, and 12. On the PPBC, subjects rate their bladder-related problems on a scale from 1 (does not cause me any problems at all) to 6 (causes me many severe problems). On the UPS, subjects rate the urgency associated with their typical urination experience as 1 (usually not able to hold urine), 2 (usually able to hold urine until reaching a toilet if I go immediately), or 3 (usually able to finish what I am doing before going to the toilet). Subjects completed the validated Overactive Bladder Questionnaire (OAB-q)[15] at baseline and week 12. Increases in OAB-q total HRQL and domain scores indicate improved HRQL; increases in Symptom Bother scores indicate increased bother. The minimally important difference (the least change considered clinically meaningful) is 10 points for all OAB-q scales and domains.[16]

Safety Assessments

All adverse events (AEs), either reported by the subject or observed by the investigator, were recorded, as was the investigator's opinion of whether the event was treatment related. Blood pressure and heart rate were recorded at each visit.

Statistical Analysis

Efficacy analyses were performed using data from the full analysis set (subjects who took ≥1 dose of study drug and had ≥1 baseline or postbaseline efficacy assessment). Safety analyses were performed using data from the safety analysis set (all subjects who took ≥1 dose of study drug). Data from all subjects given fesoterodine were compared as a group with data from all subjects given placebo; the statistical analysis plan did not provide for stratification of subjects by final dose.

The primary endpoint was the change from baseline to week 12 in mean number of micturitions per 24 hours; analysis of covariance (ANCOVA) was used to assess treatment differences. The ANCOVA model included treatment, center, and baseline value as a covariate. Changes from baseline in between-treatment differences were estimated using least squares means, and treatments were compared using a 2-sided *F* test at the 5% significance level. Missing data at weeks 6 and 12 were inputed using last observation carried forward.

Secondary endpoints included changes in other bladder diary variables and the OAB-q as well as the proportion of subjects reporting improvement on the PPBC and UPS. Bladder diary variables, with the exception of nocturnal micturitions and nocturnal urgency episodes, and OAB-q data were analyzed using an ANCOVA model similar to that used for the primary endpoint. Treatment differences for nocturnal micturitions and nocturnal urgency episodes were analyzed using analysis of variance because there was a significant qualitative baseline by treatment interaction (ie, the treatment effect reversed direction at a given baseline value); the ANCOVA model is not valid in this situation. Percentage change for bladder diary variables was analyzed using ranked ANCOVA, with ranked percentage change as the response and terms for treatment, center, and ranked baseline value in the model. Categorical analyses for PPBC and UPS data were conducted using the Cochran–Mantel–Haenszel test adjusting for center. The PPBC data were categorized as a ≥2-point improvement, 1-point improvement, no change, or deterioration from baseline. The UPS data were categorized as improvement, no change, or deterioration from baseline.

RESULTS

Of the 1338 subjects screened, 896 were enrolled and randomly assigned to treatment (n = 448 each for fesoterodine and placebo). Of the 438 and 445 subjects who took ≥1 dose of fesoterodine and placebo, respectively, 382 and 385 subjects (87% for both groups), respectively, completed the trial. Demographic and clinical characteristics were similar between groups, with a slightly higher proportion of postmenopausal women in the placebo group (Table 1). During the 3-day bladder diary period at baseline, 59% and 58% of subjects in the fesoterodine and placebo groups, respectively, reported urgency urinary incontinence (UUI). Approximately 40% of subjects in both groups had been previously treated with an antimuscarinic for OAB. After 2 weeks of treatment, 274 of 438 subjects (63%) treated with fesoterodine and 325 of 445 subjects (73%) given placebo opted to increase study drug dose.

Efficacy

Improvement in mean number of micturitions per 24 hours at week 12 (primary endpoint) was significantly greater with fesoterodine than placebo (Fig. 1). At week 12, the least squares mean (standard error) change from baseline was −2.9 (0.1) for fesoterodine and −2.1 (0.1) for placebo ($P = .0002$); median percentage change was −22.2% and −14.4%, respectively ($P = .002$).

At week 12, improvements in urgency episodes ($P = .0003$), UUI episodes ($P = .022$), and frequency-urgency sum ($P < .0001$) were also significantly greater with fesoterodine vs placebo (Fig. 1). Between-group differences at week 12 in nocturnal micturitions ($P = .32$) and nocturnal urgency episodes ($P = .08$) were not statistically significant. Improvements in number of micturitions ($P = .014$) and frequency-urgency sum ($P = .020$) were significantly greater in the fesoterodine group compared with the placebo group by week 2; improvements in urgency ($P = .034$) and UUI episodes ($P = .023$) were significantly greater with fesoterodine vs placebo by week 6 (Fig. 1).

The median percentage change at week 12 for urgency episodes was −49.4% for fesoterodine and −32.1% for placebo ($P = .0001$). The median percentage change in number of UUI episodes at week 12 was −100% in both groups in subjects with UUI at baseline, indicating that more than half of such subjects reported no UUI at the end of treatment. To illuminate this finding, a post hoc analysis of the UUI data was conducted; among subjects reporting >0 UUI episodes at baseline, 63% of the fesoterodine group and 51% of the placebo group recorded no UUI episodes in their 3-day bladder diaries at week 12 ($P < .01$).

The categorical distribution of changes in PPBC scores at week 2 ($P = .011$), week 6 ($P = .0008$), and week 12 ($P = .0006$) and UPS scores at week 2 ($P = .013$), week 6 ($P = .010$), and week 12 ($P = .0009$) was significantly better with fesoterodine than placebo (Fig. 2). In addition, mean change in scores from baseline to week 12 was significantly better with fesoterodine than placebo for the OAB-q Symptom Bother scale (treatment difference = −7.8; $P < .0001$); total HRQL score (treatment difference = 6.2; $P < .0001$); and Concern (treatment difference =

Table 1. Baseline demographic and clinical characteristics*

	Placebo (n = 445)	Fesoterodine (n = 438)
Sex, n (%)		
Female	368 (83)	364 (83)
Male	77 (17)	74 (17)
Age, y		
Mean (SD)	60.1 (12.9)	59.7 (13.7)
Range	22-88	22-100
Race, n (%)		
White	389 (87)	388 (89)
Black	40 (9)	38 (9)
Asian	4 (1)	3 (1)
Other	12 (3)	9 (2)
Postmenopausal, n (%)†	312 (85)	281 (77)
UUI episodes >0, n (%)	260 (58)	257 (59)
Female	234 (64)	231 (64)
Male	26 (34)	26 (35)
Bladder diary variables, mean (SD)/24 h		
Micturitions	13.0 (3.8)	12.8 (3.8)
Urgency episodes	9.2 (4.3)	9.2 (3.8)
UUI episodes	2.2 (2.7)	2.0 (1.9)
Frequency-urgency sum	39.9 (15.0)	39.4 (13.4)
Nocturnal micturitions	2.7 (1.5)	2.6 (1.5)
Nocturnal urgency episodes	2.2 (1.4)	2.2 (1.4)
PPBC, n (%)		
1 (No problems at all)	0	0
2 (Some very minor problems)	0	0
3 (Some minor problems)	1 (<1)	1 (<1)
4 (Some moderate problems)	207 (47)	211 (49)
5 (Severe problems)	170 (39)	164 (38)
6 (Many severe problems)	64 (15)	59 (14)
UPS, n (%)		
1 (Not able to hold urine)	128 (29)	126 (29)
2 (Able to hold urine)	298 (67)	286 (66)
3 (Able to finish what I am doing)	17 (4)	23 (5)
OAB-q, mean (SD)		
Symptom bother	58.5 (18.2)	58.9 (18.3)
Total HRQL	54.7 (22.0)	53.3 (21.6)
Concern	49.0 (25.2)	46.9 (24.8)
Coping	50.3 (26.0)	48.7 (25.5)
Sleep	47.0 (27.4)	47.6 (26.7)
Social interaction	76.9 (23.9)	75.4 (24.1)

HRQL = health-related quality of life; OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition; SD = standard deviation; UPS = Urgency Perception Scale; UUI = urgency urinary incontinence.

* Demographic characteristics and percentage of subjects with UUI at baseline are based on the safety set (placebo, n = 445; fesoterodine, n = 438). Baseline mean number of UUI episodes are based on the full analysis set and include only subjects with UUI at baseline (placebo, n = 257; fesoterodine, n = 251). Other baseline bladder diary variables are based on the full analysis set (placebo, n = 434; fesoterodine, n = 428).

† Percentage of female subjects.

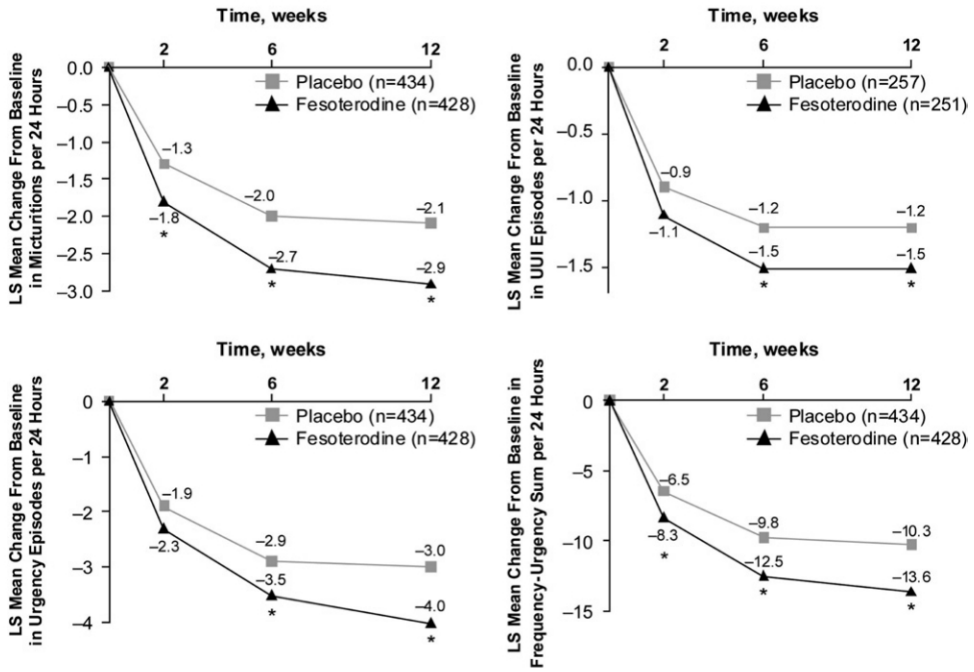

Figure 1. Least squares (LS) mean change from baseline in number of micturitions, urgency episodes, urgency urinary incontinence (UUI) episodes, and frequency-urgency sum per 24 hours. * $P < .05$ vs placebo.

8.4; $P < .0001$), Coping (treatment difference = 7.1; $P < .0001$), Sleep (treatment difference = 4.7; $P = .0044$), and Social Interaction (treatment difference = 3.7; $P < .0007$) domains (Fig. 2). All mean improvements on all OAB-q scales and domains in both the fesoterodine and placebo groups exceeded the 10-point minimally important difference.[14]

Tolerability and Safety

Dry mouth and constipation were the most common treatment-emergent AEs (Table 2). Most AEs were mild or moderate. No serious treatment-related AEs or deaths occurred in either group. Subjective urinary retention occurred in 3 subjects (all women) taking fesoterodine, 1 of whom discontinued; none of the cases of urinary retention were classified as a serious AE by the investigators, and none of these subjects required catheterization. No clinically significant changes in blood pressure or heart rate occurred in either group.

Thirteen percent of subjects in the fesoterodine and placebo groups discontinued the study, with 8% from the fesoterodine group and 5% from the placebo group withdrawing because of an AE (Table 2).

COMMENT

This study is the first to report on the use of a flexible-dose regimen of fesoterodine in a double-blind, placebo-controlled design. It is also the first to evaluate the efficacy and safety of night-time dosing of fesoterodine in subjects with OAB. In this population, fesoterodine 4 or 8 mg given once daily within 4 hours of bedtime significantly decreased the number of micturitions by week 2 (first evaluation) and urgency and UUI episodes by week 6, with all improvements maintained through week 12. Subjects treated with fesoterodine also had significantly greater improvement in OAB-q Symptom Bother and HRQL scores compared with placebo, and subjects in the fesoterodine group reported better improvement than the placebo group on the PPBC and UPS. These data, in conjunction with previous reports, suggest that fesoterodine is effective when taken either in the morning or evening.

To approximate clinical practice, the flexible-dosing design of the study allowed subjects to decide whether to increase the drug dose at week 2. In the fesoterodine group, 63% of subjects increased the drug dose, suggesting that the 4 mg dose was sufficiently well tolerated to allow subjects to seek greater improvement in symptoms. Discussions between subjects and investigators regarding efficacy and tolerability at week 2 were unstructured and not recorded; thus, the reasons why subjects did or did not choose to increase the dose are not known. However, as in real-world clinical practice, subjects may have chosen to optimize the balance between efficacy and tolerability.

Our results are similar to those of the 2 fixed-dose phase III trials,[17] with expected variations based on study design and variations in the definition of specific metrics. The median percentage change at week 12 in micturitions per 24 hours was −22% in the fesoterodine group in the current study vs −16% for the fesoterodine 4-mg group and −17% for the fesoterodine 8-mg group in the fixed-dose phase III trials.[17] For urgency episodes, median percentage change was −49% with fesoterodine in our study and −17% and −19% for the fesoterodine 4- and

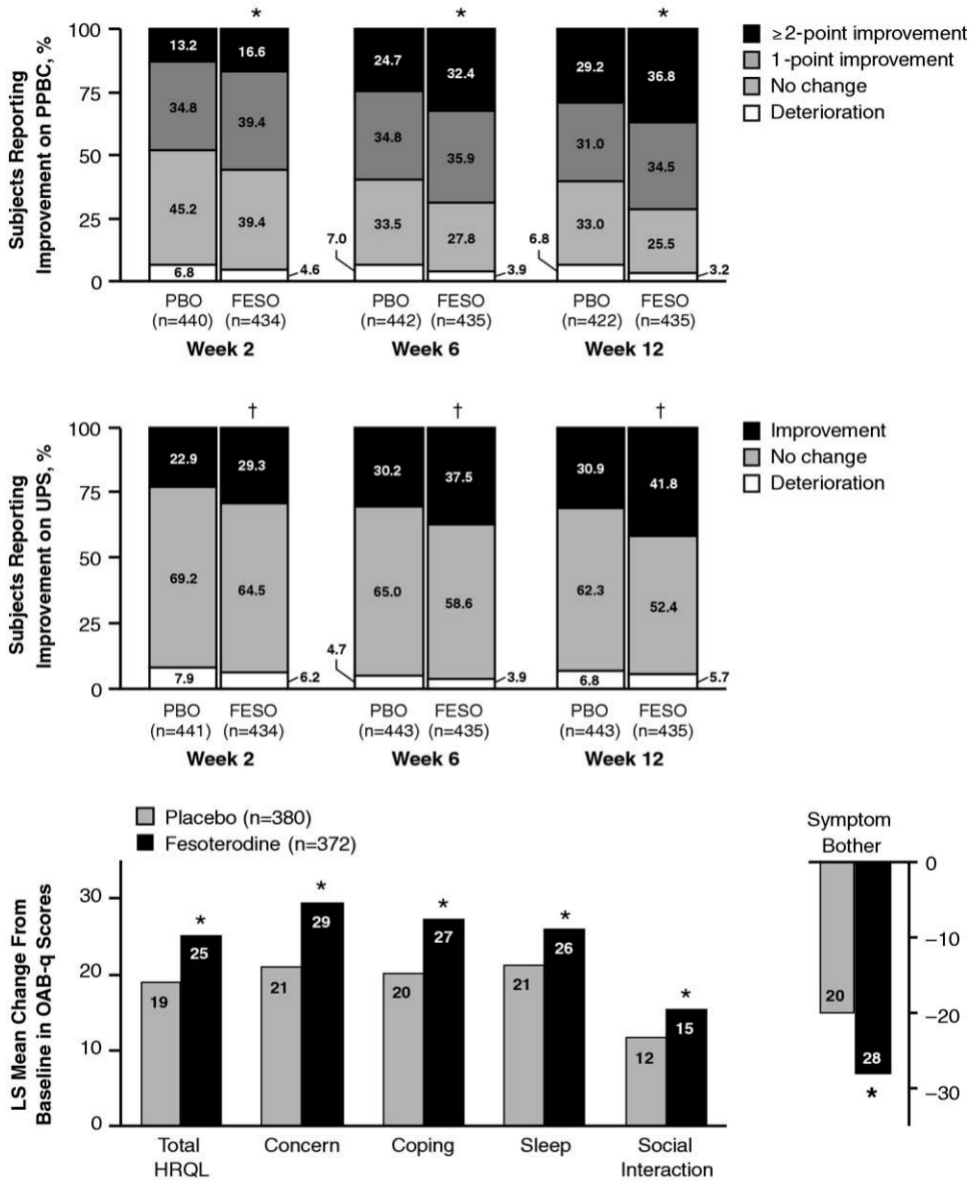

Figure 2. Percentage of subjects with improvement on the Patient Perception of Bladder Condition (PPBC) and Urgency Perception Scale (UPS) and least squares (LS) mean change from baseline to week 12 in Overactive Bladder Questionnaire (OAB-q) scales and domains. FESO = fesoterodine; PBO = placebo. * $P < .01$ vs placebo; † $P < .05$ vs placebo.

8-mg groups, respectively, in the fixed-dose trials,[17] although the definition of urgency and the scale used to measure it in the current study differed from that in the fixed-dose trials. The median percentage change in UUI episodes at week 12 was −100% with fesoterodine in the current study and −75% and −83% in the fesoterodine 4- and 8-mg groups, respectively, in the fixed-dose trials.[17] However, a smaller proportion of fesoterodine subjects in the current trial had UUI at baseline (59%) compared with the fesoterodine 4-mg group (80%) and 8-mg group (81%) in the fixed-dose trials, and the mean reduction in UUI episodes per 24 hours was greater in the fesoterodine 4-mg group (−1.9) and 8-mg group (−2.3) in the fixed-dose trials[17] than in the fesoterodine group in the current study (−1.5).

In the current study, significantly greater improvements were noted in subjects' assessment of symptom bother, HRQL, and bladder-related problems with flexible-dose fesoterodine vs placebo. Although different instruments were used in the fixed-dose trials, subjects in those studies treated with fesoterodine 4 and 8 mg showed significantly greater improvements in HRQL and in bladder-related problems, and significantly greater treatment response than subjects who received placebo.[10]

The findings from the current study are also similar to those of an open-label, flexible-dose study of fesoterodine,[18] in which subjects could increase the dose from 4 to 8 mg at week 4. In that study, there were significant improvements compared with baseline values in the number of 24-hour micturitions, urgency episodes and

Table 2. Summary of treatment-emergent adverse events* and discontinuations

	Subjects, n (%)	
	Placebo (n = 445)	Fesoterodine (n = 438)
Adverse event		
Dry mouth	34 (8)	113 (26)
Mild	23 (5)	66 (15)
Moderate	9 (2)	40 (9)
Severe	2 (0.4)	7 (2)
Constipation	25 (6)	48 (11)
Mild	19 (4)	26 (6)
Moderate	5 (1)	18 (4)
Severe	1 (0.2)	4 (1)
Headache	15 (3)	19 (4)
Dry eye	8 (2)	13 (3)
Insomnia	2 (<1)	11 (3)
Fatigue	2 (<1)	11 (3)
Dry throat	1 (<1)	9 (2)
Cough	2 (<1)	9 (2)
Discontinuations	60 (13)	56 (13)
Adverse event†	21 (5)	34 (8)
Voluntary withdrawal	11 (3)	11 (3)
Lost to follow-up	8 (2)	6 (1)
Lack of efficacy	16 (4)	5 (1)
Other	4 (1)	0

* Adverse events, of any causality, occurring in ≥2% of subjects in the fesoterodine group and exceeding placebo incidence are shown.
† Regardless of causality.

severe urgency episodes, UUI episodes, and nocturnal micturitions, as well as in all OAB-q scales and domains. Fifty percent of subjects opted for dose escalation at week 4 in the open-label study, compared with 63% of subjects who opted for dose escalation at week 2 in the current study; the difference may be related to the earlier escalation decision point in our study.

Treatment-emergent AEs reported with fesoterodine in the current study were generally mild or moderate and led to treatment discontinuation in 8% of subjects compared with 5% for placebo. Dry mouth and constipation were the most commonly reported AEs and are typical of the antimuscarinic drug class.[19] The incidence of dry mouth (26%) with fesoterodine in the current flexible-dose study was higher than that for fesoterodine 4 mg (19%) but lower than that for fesoterodine 8 mg (35%) in the pooled results of the 2 fixed-dose trials.[17] In the current study, in which subjects took doses in the evening, the constipation rate in the fesoterodine group (11%) was higher than that in the fixed-doses trials (4% for fesoterodine 4 mg; 6% for fesoterodine 8 mg), in which subjects took doses in the morning.[17] The constipation rate for placebo (6%) in the current study was also higher than in the fixed-dose trials (2%).[17] In the open-label, flexible-dose fesoterodine study,[18] which also used morning dosing, the rates of dry mouth (23%) and constipation (5%) were somewhat lower than in the current study. This may also be due in part to the difference in dose-escalation timing; some subjects who chose to increase the dose to 8 mg at week 2 in the current study might have remained on 4 mg, with fewer AEs, had the decision been made at week 4 as in the open-label study.

Results from the current flexible-dose study are not unexpected, given the findings in the fixed-dose trials.[17] However, subjects in the flexible-dose study were not randomly assigned to a fesoterodine 4- or 8-mg–dose group as in the fixed-dose trials. In the current study, subjects who desired greater efficacy and had acceptable tolerability with fesoterodine 4 mg could increase the dose to 8 mg. Subjects satisfied with efficacy or reluctant to increase dose because of tolerability concerns could remain at the 4-mg dose. This study design reflects how OAB might be managed in clinical practice, with patients and clinicians consulting on appropriate dosing.

Our study was not designed a priori to compare results by dose, so we cannot draw primary conclusions regarding the relative efficacy and tolerability of the individual 4 and 8 mg doses of fesoterodine in the flexible-dose setting. Analyses of data by dose will be performed post hoc and reported separately. An additional study limitation is the absence of data on the reasons for subjects' decisions regarding optional dose escalation.

CONCLUSION

In this study, a flexible-dose regimen of fesoterodine 4 or 8 mg given once daily in the evening was effective for the treatment of OAB symptoms and was generally well tolerated. The availability of 2 doses of fesoterodine allows clinicians to tailor the dosing regimen to meet individual patient needs.

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