

## EFFICACY AND TOLERABILITY OF FESOTERODINE IN SUBJECTS STRATIFIED BY DOSE ESCALATION IN AN OPEN-LABEL FLEXIBLE-DOSE STUDY

**Hypothesis / aims of study** Fesoterodine (FESO) is an antimuscarinic for the treatment of symptoms of overactive bladder (OAB) that is available as 4- or 8-mg once-daily tablets. Fixed-dose studies demonstrated that both doses significantly improve OAB symptoms and measures of health-related quality of life (HRQL); significantly greater improvements in several OAB symptoms and aspects of HRQL were observed with the 8-mg versus the 4-mg dose, and rates of adverse events (AEs) were generally higher with the 8-mg dose [1,2]. An open-label study using flexible dosing of FESO showed significant improvements from baseline in overactive bladder (OAB) symptoms and patient-reported measures of treatment satisfaction, bladder-related problems, urgency, symptom bother, and health-related quality of life (HRQL), with all subjects considered as a single group, regardless of dose escalation [3]. In this post-hoc analysis, data from that study were stratified according to whether patients opted for dose escalation.

**Study design, materials and methods** This 12-week, open-label, single-arm study enrolled adult subjects who reported urinary frequency ( $\geq 8$  micturitions per 24 h) and urgency ( $\geq 3$  episodes per 24 h) in 5-day bladder diaries at baseline and dissatisfaction with tolterodine or tolterodine extended release within 2 y of screening [3]. Subjects received FESO 4 mg once daily for the first 4 weeks of treatment, with an optional dose increase to FESO 8 mg after week 4 based on discussion of efficacy and tolerability between the subject and investigator. Subjects recorded total and nocturnal micturitions, urgency urinary incontinence (UUI) episodes, and the sensation associated with each micturition using the 5-point Urinary Sensation Scale (USS; 1 = no urgency, 5 = UUI) in 5-day diaries at weeks 1, 4, and 12. Urgency and severe urgency episodes were defined as those with a USS rating  $\geq 3$  and  $\geq 4$ , respectively; frequency-urgency sum was defined as the sum of all USS ratings per 24 h. Subjects completed the Patient Perception of Bladder Condition (PPBC) and Urgency Perception Scale (UPS) at baseline and weeks 4 and 12, and the Overactive Bladder Questionnaire (OAB-q) at baseline and week 12. Two-sided paired *t*-tests assessed mean changes from baseline. Subjects assessed treatment satisfaction at 12 weeks using the Treatment Satisfaction Question; response options for "Overall, how satisfied are you with your current OAB treatment?" ranged from 1 (very satisfied) to 5 (very dissatisfied); responses of "very satisfied" or "somewhat satisfied" indicated treatment satisfaction. Reports of adverse events (AEs) were collected throughout the study.

**Results** Dose escalation to 8 mg was chosen by 255 (50%) of 513 subjects. Compared with baseline, all bladder-diary variables significantly improved after 1, 4, and 12 weeks of treatment with FESO (all  $P < 0.0001$ ), regardless of whether subjects opted for dose escalation after week 4 (**Table 1**). On baseline diary, 123 of 256 subjects (47%) who did not escalate at week 4 and 131 of 255 subjects (51%) who chose dose escalation at week 4 reported  $>0$  UUI episodes. On the 5-day diary completed before week 4 (immediately before the dose-escalation decision), 62% of subjects who did not escalate and 42% of subjects who did escalate reported UUI=0; at week 12, 68% and 60% of these subjects, respectively, reported UUI=0. Satisfaction with treatment was reported by 82.1% of subjects who did not escalate and 78.1% of subjects who opted for dose escalation at week 12. Regardless of escalation status, significant improvements from baseline to weeks 4 and 12 occurred in PPBC and UPS scores, and from baseline to week 12 for all scales and domains of the OAB-q (**Table 1**). Mean improvements in all OAB-q scales and domains exceeded the 10-point minimally important difference in both dose groups. AE rates were similar between subjects who did and did not escalate; dry mouth was the most-frequently reported AE and most cases were mild (**Table 2**).

**Interpretation of results** This flexible-dose study demonstrated that FESO improved OAB symptoms and patient-reported outcomes in subjects who chose to remain on the initial 4-mg dose as well as in subjects who escalated to the 8-mg dose after 4 weeks. Improvements seen in both escalators and non-escalators occurred as early as week 1 (when all subjects received FESO 4 mg); improvements also occurred at weeks 4 and 12. These improvements and reports of AEs were generally similar in the two groups throughout the study, unlike the separation observed in fixed-dose studies when subjects were assigned to 1 of 2 doses. These data suggest that flexible dosing of FESO allows patients to optimize overall treatment benefit.

**Concluding message** Fesoterodine 4 and 8 mg significantly improved bladder diary variables and patient-reported measures of bladder-related problems, urgency, symptom bother, and health-related quality of life (HRQL) and produced high rates of treatment satisfaction rates in this flexible-dose study of subjects who were previously dissatisfied with tolterodine treatment.

**Table 1. Baseline Values and Mean Changes From Baseline At Weeks 1, 4 and 12 By Dose Escalation Decision at Week 4\***

Outcome <sup>†</sup>	Baseline		Week 1		Week 4		Week 12	
	No ESC	ESC	No ESC	ESC	No ESC	ESC	No ESC	ESC
n	256	255	253	247	256	255	256	255
Micturitions	12.0	13.4	-1.3 <sup>‡</sup>	-1.4 <sup>‡</sup>	-2.4 <sup>‡</sup>	-2.3 <sup>‡</sup>	-2.8 <sup>‡</sup>	-3.2 <sup>‡</sup>
UUI episodes <sup>§</sup>	2.0	2.5	-0.9 <sup>‡</sup>	-1.0 <sup>‡</sup>	-1.3 <sup>‡</sup>	-1.5 <sup>‡</sup>	-1.6 <sup>‡</sup>	-1.8 <sup>‡</sup>
Urgency episodes	9.3	10.7	-2.1 <sup>‡</sup>	-2.2 <sup>‡</sup>	-4.1 <sup>‡</sup>	-3.3 <sup>‡</sup>	-5.0 <sup>‡</sup>	-5.0 <sup>‡</sup>
Nocturnal micturitions	2.4	2.8	-0.4 <sup>‡</sup>	-0.4 <sup>‡</sup>	-0.7 <sup>‡</sup>	-0.6 <sup>‡</sup>	-0.8 <sup>‡</sup>	-0.9 <sup>‡</sup>
Severe urgency episodes <sup>§</sup>	4.5	5.5	-1.7 <sup>‡</sup>	-1.8 <sup>‡</sup>	-2.8 <sup>‡</sup>	-2.8 <sup>‡</sup>	-3.2 <sup>‡</sup>	-3.8 <sup>‡</sup>
Frequency-urgency sum	37.6	43.3	-6.8 <sup>‡</sup>	-7.1 <sup>‡</sup>	-12.2 <sup>‡</sup>	-11.3 <sup>‡</sup>	-14.4 <sup>‡</sup>	-16.1 <sup>‡</sup>
PPBC Score <sup>  </sup>	4.8	4.9	NA	NA	-1.4 <sup>‡</sup>	-0.9 <sup>‡</sup>	-2.0 <sup>‡</sup>	-1.7 <sup>‡</sup>
UPS Score <sup>  </sup>	1.8	1.8	NA	NA	0.5 <sup>‡</sup>	0.3 <sup>‡</sup>	0.6 <sup>‡</sup>	0.5 <sup>‡</sup>
OAB-q Score <sup>#</sup>								
Symptom Bother	55.1	59.5	NA	NA	NA	NA	-29.0 <sup>‡</sup>	-28.7 <sup>‡</sup>
Total HRQL	56.1	48.6	NA	NA	NA	NA	25.7 <sup>‡</sup>	26.8 <sup>‡</sup>
Concern	55.0	46.5	NA	NA	NA	NA	27.4 <sup>‡</sup>	29.8 <sup>‡</sup>
Coping	48.2	41.4	NA	NA	NA	NA	30.8 <sup>‡</sup>	30.6 <sup>‡</sup>

Sleep	50.5	44.5	NA	NA	NA	NA	25.0 <sup>‡</sup>	25.2 <sup>‡</sup>
Social Interaction	75.6	67.1	NA	NA	NA	NA	15.7 <sup>‡</sup>	18.0 <sup>‡</sup>

ESC=escalation; NA=not assessed.

\*Three subjects started the study on FESO 8 mg; these subjects were excluded from this analysis.

<sup>†</sup>Diary variables presented as mean change per 24 h from baseline.

<sup>‡</sup>P<0.0001 vs baseline.

<sup>§</sup>Includes only subjects reporting symptom at baseline (UUI: No ESC n=123, ESC n=131; Severe urgency: No ESC n=215, ESC n=224). <sup>||</sup>Lower scores represent fewer bladder-related problems on the PPBC. <sup>¶</sup>Higher scores represent less urgency on the UPS. <sup>#</sup>On the OAB-q, lower Symptom Bother scores represent less symptom bother and higher HRQL scores represent better HRQL.

**Table 2. Treatment-Emergent Adverse Events Reported by ≥2% of Subjects (All Causality)**

Adverse Event, n (%)	No (n=258)	escalation	Escalation (n=255)
Dry mouth	59 (22.9)		61 (23.9)
Mild	52 (20.2)		46 (18.0)
Moderate	6 (2.3)		10 (3.9)
Severe	1 (0.4)		5 (2.0)
Constipation	12 (4.7)		13 (5.1)
Mild	9 (3.5)		7 (2.7)
Moderate	2 (0.8)		5 (2.0)
Severe	1 (0.4)		1 (0.4)
Headache	9 (3.5)		10 (3.9)
Diarrhea	6 (2.3)		6 (2.4)
Abdominal pain, upper	5 (1.9)		6 (2.4)

## References

1. Khullar V, Rovner ES, Dmochowski R, et al. Fesoterodine dose response in subjects with overactive bladder syndrome. *Urology* 2008;71(5):839-43
2. Kelleher CJ, Tubaro A, Wang JT, Kopp Z. Impact of fesoterodine on quality of life: pooled data from two randomized trials. *BJU Int* 2008;102(1):56-61
3. Wyndaele J-J, 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;63:560-67

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<b>Is this study registered in a public clinical trials registry?</b>	<b>Yes</b>
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	<b>Identifier: NCT00425100</b>
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<b>Was this study approved by an ethics committee?</b>	<b>Yes</b>
<b>Specify Name of Ethics Committee</b>	<b>Schulman Associates IRB 4290 Glendale- Miford Road Cincinnati, OH 45242 United States</b>
<b>Was the Declaration of Helsinki followed?</b>	<b>Yes</b>
<b>Was informed consent obtained from the patients?</b>	<b>Yes</b>