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A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF FLEXIBLE-DOSE FESOTERODINE FOR OVERACTIVE BLADDER

Hypothesis / aims of study Fesoterodine 4 mg or 8 mg once daily has been shown to significantly improve overactive bladder (OAB) symptoms [1,2] and patient-reported outcomes, including health-related quality of life (HRQL) measures [3], in fixed-dose studies. The aim of this study was to assess the efficacy of a flexible-dose regimen of fesoterodine versus placebo in subjects with OAB.

Study design, materials and methods Subjects were eligible for this 12-week double-blind, placebo-controlled trial if they were aged ≥18 years; had OAB symptoms for ≥3 months, including ≥8 micturitions and ≥3 urgency episodes per 24 hours as documented in 3-day bladder diaries; and reported at least some moderate bladder-related problems on the Patient Perception of Bladder Condition (PPBC) at baseline. Subjects were randomly assigned to treatment with fesoterodine 4 mg once daily or placebo. 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). Subjects completed 3-day bladder diaries, PPBC, and Urgency Perception Scale (UPS) at baseline and weeks 2, 6, and 12 and Overactive Bladder Questionnaire (OAB-q) at baseline and week 12. Subjects rated urgency using the 5-point Urinary Sensation Scale; frequency-urgency sum was the sum of urgency ratings recorded for all micturitions. All efficacy endpoints were based on the full analysis set, except for urgency urinary incontinence (UUI) episodes, nocturnal micturitions, and nocturnal urgency episodes, which were based only on subjects who reported these symptoms at baseline.

Results Of 883 subjects, 63% and 73% of the fesoterodine (n=438) and placebo (n=445) groups, respectively, opted for dose escalation. At baseline, 517 subjects reported UUI (placebo, n=260; fesoterodine, n=257), 860 reported nocturnal micturitions (placebo, n=433, fesoterodine, n=427), and 842 reported nocturnal urgency episodes (placebo, n=424, fesoterodine, n=418) at baseline. In each group, 87% of subjects completed the study; 8% and 5% of subjects in the fesoterodine and placebo groups, respectively, discontinued because of an adverse event. At week 12, subjects receiving flexible-dose fesoterodine had significantly greater improvements versus placebo in 24-hour micturitions, UUI episodes, urgency episodes, frequency-urgency sum, and OAB-q Symptom Bother and HRQL total and domain scores, but not nocturnal micturitions or nocturnal urgency episodes **(Table 1)**. Among subjects who reported >0 UUI episodes on bladder diary at baseline, a post hoc analysis revealed that 63% in the fesoterodine group and 51% in the placebo group recorded no UUI episodes in their 3-day bladder diaries at week 12 ($P<0.01$). The categorical distributions of changes on the PPBC ($P<0.01$) and UPS ($P<0.01$) were significantly better among subjects taking fesoterodine compared with placebo **(Table 2)**. The most common adverse events were dry mouth (fesoterodine, 26%; placebo, 8%) and constipation (fesoterodine, 11%; placebo, 6%); most cases were of mild or moderate severity.

Interpretation of results Fesoterodine 4 mg or 8 mg, administered in a flexible-dose regimen, is efficacious in the treatment of OAB symptoms. The availability of two well-tolerated doses of fesoterodine allows clinicians and patients to adjust the dosing regimen based on efficacy and tolerability.

Concluding message In this randomized, double-blind, flexible-dose clinical trial, fesoterodine 4 mg or 8 mg produced significantly greater improvements in key OAB efficacy endpoints and OAB-specific patient-reported outcomes than did placebo.

Table 1. Least Squares (LS) Mean Change from Baseline to Week 12[1]

	Placebo		Fesoterodine	
	Baseline	**LS Mean Change**	**Baseline**	**LS Mean Change**
Bladder diary variables per 24 h				
Micturitions (primary endpoint)	13.0	–2.1	12.8	–2.9†
UUI episodes	2.2	–1.2	2.0	–1.5*
Urgency episodes	9.2	–3.0	9.2	–4.0†
Nocturnal micturitions	2.7	–0.7	2.6	–0.8
Nocturnal urgency episodes	2.2	–0.9	2.2	–1.0
Frequency-urgency sum	39.9	–10.3	39.4	–13.6‡
OAB-q[2]				
Symptom bother	58.5	–20.0	58.9	–27.8‡
Total HRQL	54.7	18.9	53.3	25.1‡
Concern	49.0	20.9	46.9	29.3‡
Coping	50.3	20.2	48.7	27.2‡
Sleep	47.0	21.2	47.6	25.9†
Social interaction	76.9	11.6	75.4	15.3†

[1]For micturitions, urgency episodes, and frequency-urgency sum, results are based on the full analysis set with non-missing numerical change from baseline to week 12 (placebo n=434, fesoterodine n=428). For all other variables, results are based on number of subjects with non-missing numerical change who reported >0 episodes at baseline (UUI episodes: placebo n=257, fesoterodine n=251; nocturnal micturitions: placebo n=423, fesoterodine n=418; nocturnal urgency episodes: placebo n=414, fesoterodine n=409).
[2]On the OAB-q, higher symptom bother scores represent greater symptom bother and higher HRQL scores represent better HRQL.
*P<0.05 vs placebo; †P<0.01 vs placebo; ‡P<0.0001 vs placebo.

Table 2. Percentage of Subjects Reporting Change on PPBC and UPS from Baseline to Week 12

	Placebo	Fesoterodine
PPBC		
≥2-point improvement	29.2	36.8*
1-point improvement	31.0	34.5
No change	33.0	25.5
Deterioration	6.8	3.2
UPS		
Improvement	30.9	41.8*
No change	62.3	52.4
Deterioration	6.8	5.7

*P<0.01 vs placebo for categorical distribution of changes.

References

1. Nitti VW, Dmochowski R, Sand PK, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J Urol 2007;178(6):2488-94
2. 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(4):1204-12
3. 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

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Specify Name of Public Registry, Registration Number	**ClinicalTrials.gov**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Human Investigation Committee** **3811 West 13 Mile Road** **Royal Oak, MI 48073** **United States**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**