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ABSTRACT TITLE:

EFFICACY AND SAFETY OF FESOTERODINE FOR OVERACTIVE BLADDER IN A DOUBLE-BLIND, HEAD-TO-HEAD COMPARISON TRIAL WITH TOLTERODINE ER AND PLACEBO

Hypothesis / aims of study The efficacy and safety of fesoterodine for overactive bladder (OAB) have been demonstrated in 2 placebo-controlled phase III trials,[1,2] one of which included tolterodine extended release (ER) as an active comparator.[2] A post hoc analysis of that study suggested that fesoterodine 8 mg is more effective than tolterodine ER 4 mg (maximum recommended dose for each drug) for several key OAB measures, including urgency urinary incontinence (UUI) episodes.[3] The principal aim of this study was to compare the efficacy and safety of fesoterodine with tolterodine ER and placebo.

Study design, materials and methods In this 12-week double-blind, double-dummy trial, eligible subjects reported OAB symptoms for ≥3 months and reported ≥8 micturitions per 24 hours and ≥1 UUI episode per 24 hours in baseline bladder diaries. Subjects were randomized in a 2:2:1 ratio to treatment with fesoterodine 4 mg for 1 week, then 8 mg for 11 weeks; tolterodine ER 4 mg; or placebo (with sham dose escalation for tolterodine ER and placebo at week 1). All doses were given once daily in the morning. Subjects completed 3-day bladder diaries, Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) at baseline and weeks 1, 4, and 12 and Overactive Bladder questionnaire (OAB-q) at baseline and week 12. The primary endpoint was the change from baseline to week 12 in mean number of UUI episodes per 24 hours. Efficacy analyses were conducted using data from all subjects who took ≥1 dose of study medication and had ≥1 baseline or postbaseline assessment, with last observations carried forward (LOCF). A closed testing procedure was used for the primary endpoint comparing fesoterodine with placebo, then with tolterodine ER if the comparison with placebo was significant. All tests were 2-sided (alpha level, 5%). Because the observed data for the primary endpoint violated normality assumptions, and in accordance with the statistical analysis plan, data for this endpoint were analyzed using the Van-Elteren test (a stratified Wilcoxon-Mann-Whitney test) with baseline quartiles as strata; 5% Winsorized means were used to estimate the mean decrease in UUI episodes per treatment group. Analysis of covariance was used for secondary bladder diary and OAB-q data by treatment, with covariates of country and baseline; Cochran-Mantel-Haenszel test was used for PPBC and UPS data.

Results Of 1712 subjects randomized, 1697 subjects (679 fesoterodine, 684 tolterodine ER, 334 placebo) received ≥1 dose of study medication. Subjects were predominately women (82%) and white (78%), with a mean age of 58 years and mean OAB symptom duration of 7 years; about half had previously used antimuscarinics. Approximately 90% of subjects in each group completed the study. At week 12, both fesoterodine and tolterodine ER significantly decreased the mean number of UUI episodes per 24 hours versus placebo, as reflected by a significant location shift between the treatments (P<0.001). Furthermore, fesoterodine produced significantly greater improvement versus tolterodine ER on this primary endpoint (P=0.0172; **Table 1**). In a post hoc analysis, among subjects with >0 UUI episodes at baseline, a significantly greater percentage of subjects receiving fesoterodine (64%) reported 0 UUI episodes at week 12 versus tolterodine ER (57%) and placebo (45%) (P<0.001 for both); the difference between tolterodine ER and placebo also was significant (P=0.0153). Fesoterodine and tolterodine ER produced significantly greater improvements in 24-hour micturitions, urgency episodes, and mean voided volume (MVV) per micturition versus placebo at week 12 **(Table 1)**. The increase in MVV was significantly greater with fesoterodine compared with tolterodine ER (P=0.0048); the decrease in number of 24-hour micturitions (P=0.3798) and urgency episodes (P=0.0542) with fesoterodine versus tolterodine ER was not significant. Improvements on PPBC and UPS and on all OAB-q scale and domain scores were significantly greater with fesoterodine than placebo at week 12 (P<0.001; **Table 2**). In a post hoc analysis, improvement on these endpoints was significantly greater with fesoterodine than with tolterodine ER (P<0.05; **Table 2**), except for the OAB-q sleep domain (P=0.08 versus tolterodine ER). At week 1, fesoterodine, at the initial 4-mg dose, significantly improved UUI episodes, urgency episodes, micturitions, and MVV versus placebo (P<0.001), as did tolterodine ER. Active treatments were well tolerated, although adverse events were more commonly reported with fesoterodine than tolterodine ER or placebo **(Table 3)**. Discontinuations due to treatment-emergent adverse events were 2%, 4%, and 6% in the placebo, tolterodine ER, and fesoterodine groups, respectively.

Interpretation of results At week 12, fesoterodine was significantly better than placebo on key bladder diary efficacy measures and significantly better than tolterodine ER in decreasing UUI episodes and increasing MVV. Post hoc analysis of subjects with incontinence at baseline who reported no UUI episodes in the end-of-treatment diary clearly supported the results for the primary endpoint. Greater improvement with fesoterodine than tolterodine ER was also demonstrated on PPBC, UPS, and OAB-q in a post hoc comparison. Onset of effect was seen by week 1 with the initial 4-mg dose of fesoterodine and with tolterodine ER.

Concluding message In subjects with OAB, fesoterodine showed good tolerability and superior efficacy over tolterodine ER on the primary endpoint, reduction in UUI episodes, as well as on a number of secondary endpoints, including patient-reported outcome measures. Response to fesoterodine was seen as early as week 1.

Table 1. Change in bladder diary variables from baseline to week 12[1]

	Placebo	Tolterodine ER	Fesoterodine

UUI (episodes/24 h)			
Number of subjects[2]	307	626	619
Baseline mean	2.6	2.5	2.4
Winsorized mean change	–1.5	–1.6*	–1.7*†
Urgency (episodes/24 h)			
Number of subjects[2]	311	631	628
Baseline mean	9.4	9.3	9.3
Least squares mean change	–2.0	–3.1*	–3.5*
Micturitions (episodes/24 h)			
Number of subjects[2]	313	634	628
Baseline mean	11.9	11.7	11.7
Least squares mean change	–1.5	–2.1*	–2.2*
MVV (mL)			
Number of subjects[2]	313	633	626
Baseline mean	147.9	154.1	155.3
Least squares mean change	16.8	23.5	32.9*‡

[1]107 subjects from 2 sites were not included in the efficacy analyses because of data irregularities identified in the site audits. This decision was made before database unblinding and documented in the final statistical analysis plan. Sensitivity analyses conducted with those subjects demonstrated consistent efficacy results.
[2]Number of subjects with baseline >0 and non-missing change from baseline to week 12 (LOCF).
*P<0.001 vs placebo; †P=0.0172 vs tolterodine ER; ‡P=0.0048 vs tolterodine ER.

Table 2. Change in patient-reported outcome measures from baseline to week 12.

	Placebo	Tolterodine ER	Fesoterodine
PPBC, % of subjects			
≥2-point improvement	21.4	33.2*	40.3*†
1-point improvement	32.6	29.9	31.4
No change	35.5	27.1	23.5
Deterioration	10.5	9.8	4.8
UPS, % of subjects			
Improvement	35.8	40.1	46.2*†
No change	57.8	54.3	49.8
Deterioration	6.4	5.5	4.0
OAB-q, least squares mean (SE)			
HRQL total	12.0 (1.3)	16.3 (1.0)*	19.3 (1.0)*†
Symptom bother	–16.3 (1.4)	–22.5 (1.1)*	–27.1 (1.1)*†

*P<0.001 vs placebo; †P<0.05 vs tolterodine ER (for PPBC and UPS, P values represent differences in the categorical distribution).

References

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**ClinicalTrials.gov** **Identifier: NCT00444925**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Schulman Associates IRB, Inc** **4290 Glendale-Milford Road** **Cincinnati, Ohio 45242** **Tel: 513-761-4100** **Fax: 513-761-1460** **www.sairb.com**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**

Table 3. Most commonly reported treatment-emergent adverse events (all causality).*

Event, n (%)	Placebo (n=334)	Tolterodine ER (n=684)	Fesoterodine (n=679)
Dry mouth	20 (6.0)	112 (16.4)	189 (27.8)
Headache	8 (2.4)	23 (3.4)	38 (5.6)
Constipation	10 (3.0)	28 (4.1)	37 (5.4)
Urinary tract infection	2 (0.6)	10 (1.5)	15 (2.2)
Diarrhea	4 (1.2)	15 (2.2)	14 (2.1)

*Reported by ≥2% subjects in either active treatment group with higher incidence than placebo.