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Kaplan S A[1], Herschorn S[2], Carlsson M[3], Ntanios F[3]
1. *Weill Cornell Medical College,* ***2.*** *Sunnybrook Health Science Centre - University of Toronto,* ***3.*** *Pfizer Inc*

URGENCY URINARY INCONTINENCE RESPONSE RATES IN SUBJECTS WITH OVERACTIVE BLADDER TREATED WITH FESOTERODINE 8 MG AFTER SUBOPTIMAL RESPONSE TO TOLTERODINE EXTENDED RELEASE 4 MG: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Hypothesis / aims of study

Two head-to-head randomized studies demonstrated that fesoterodine (FESO) 8 mg is significantly more effective than tolterodine extended release (TOL ER) 4 mg in reducing urgency urinary incontinence (UUI) episodes and other bladder diary variables in subjects with overactive bladder (OAB) [1, 2]. In the Assessment of Fesoterodine after Tolterodine ER (AFTER) study, the efficacy and safety of FESO 8 mg over time and versus placebo (PBO) were assessed in subjects with OAB who showed a suboptimal response to TOL ER 4 mg.

Study design, materials and methods

This double-blind (subjects and investigators), PBO-controlled, parallel-group, multicenter study (ClinicalTrials.gov ID: NCT01302054) evaluated subjects aged ≥18 years who self-reported OAB symptoms for ≥6 months and had ≥8 micturitions and ≥2 and <15 UUI episodes per 24 hours in a 3-day diary. Subjects entered a 2-week, open-label run-in with TOL ER 4 mg, followed by randomization of suboptimal responders (≤50% decrease in UUI episodes during run-in phase) by a centralized internet/telephone registration/randomization system (Impala) to PBO or FESO (4 mg for 1 week; 8 mg for weeks 2–12) once daily, with each dose taken orally in the morning. Sample size was calculated based on >90% power to detect a mean treatment difference of −0.98 in UUI episodes per 24 hours at 5% significance level (2-sided). Subjects completed 3-day diaries before the TOL ER run-in and at baseline (after the run-in), week 4, and week 12. Change from baseline in UUI episodes per 24 hours at week 12 (primary outcome) was analyzed in a hierarchical sequentially rejective manner using a step-down procedure, first comparing baseline versus week 12 for FESO 8 mg using paired *t* test, then comparing the change from baseline to week 12 for FESO 8 mg versus PBO using analysis of covariance (ANCOVA). Responder rates (>50% and >70% decrease from baseline in UUI episodes) to weeks 4 and 12 were analyzed with a Cochran-Mental-Haenszel (CMH) test with modified ridit scoring. Post hoc analyses comparing subject characteristics of TOL ER sub-optimal responders versus responders were conducted using a *t* test.

Results

Of 990 subjects who received open-label TOL ER 4 mg in the run-in phase, 642 subjects met the sub-optimal response criteria (65% patients) and were randomized to double-blind treatment with PBO (n=320) and FESO (n=322). Treatment with FESO 8 mg significantly reduced UUI episodes from baseline to week 12 (within-group $P<0.0001$). The difference in change from baseline in UUI episodes between FESO 8 mg and PBO also was significant at week 12 (primary outcome; $P=0.0079$) and at week 4 ($P=0.0031$; **Table**). Responder rates for UUI episode frequency (>50% and >70% decrease from baseline) were higher with FESO 8 mg vs PBO at week 4, although the differences were not statistically significant. There was a significant treatment difference for FESO 8 mg versus PBO at week 12 with both the >50% ($P=0.0027$) and >70% ($P=0.0010$) reduction cut-off (**Figure**). Dry mouth (PBO, 4.0%; FESO 8 mg, 16.6%) and constipation (PBO, 1.3%; FESO 8 mg, 3.9%) were the most frequently reported adverse events, with most mild in severity. Discontinuation rates due to adverse events were 4.0% for PBO and 3.6% for FESO 8 mg. Post hoc analyses indicated the duration since OAB symptoms were diagnosed was significantly shorter for subjects who showed a suboptimal response to TOL ER during the run-in period (6.8 years) compared with subjects who responded to TOL ER during the run-in period (8.1 years; $P=0.0164$). A higher percentage of TOL ER suboptimal responders (31.5%) reported previous antimuscarinic use versus 23.6% of TOL ER responders. Demographic characteristics, including age, gender, race, weight, and BMI, were similar in TOL ER suboptimal responders and responders. Additionally, clinical characteristics (number of micturitions, UUI episodes, and urgency episodes) prior to the TOL ER run-in period were similar in TOL ER suboptimal responders and responders.

Interpretation of results

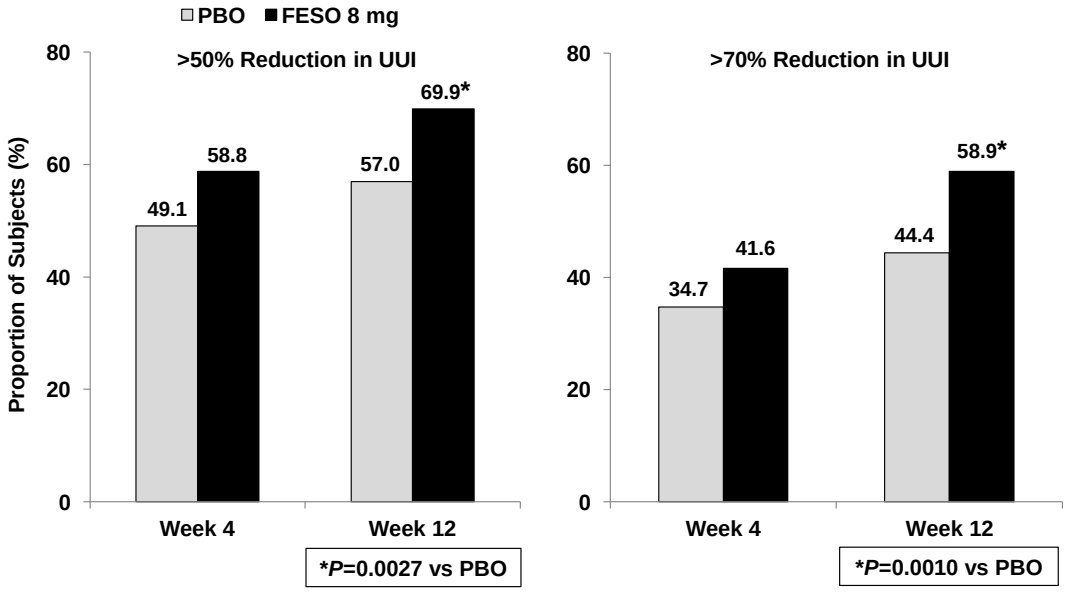
FESO 8 mg showed significantly greater efficacy versus PBO in reducing UUI episodes from baseline to week 12 and week 4 in subjects who responded suboptimally to TOL ER 4 mg. A significant treatment difference in responder rates for UUI episode frequency (>50% reduction and >70% reduction) between FESO 8 mg and PBO was demonstrated at week 12. FESO 8 mg was generally well tolerated. TOL ER suboptimal responders had a shorter duration of OAB symptoms and a greater proportion reported previous antimuscarinic use compared with TOL ER responders. Other demographic characteristics and baseline symptom severity were not associated with a suboptimal TOL ER response.

Concluding message

The results of the AFTER study demonstrate the efficacy of FESO 8 mg in reducing UUI episode frequency in OAB subjects with a suboptimal response to TOL ER 4 mg. The present results, together with those from 2 head-to-head comparison trials showing the superior efficacy of FESO 8 mg [1, 2], indicate that FESO 8 mg can provide additional clinical benefit versus TOL ER 4 mg to many subjects with OAB and UUI.

Table. Change from Baseline to Weeks 4 and 12 in UUI Episodes for Subjects with Suboptimal Response to TOL ER 4 mg		
	PBO	**FESO 8 mg**
UUI episodes/24 h[a]		
Baseline	3.8	3.9
Week 4	−1.4	−1.9*
Week 12	−1.9	−2.4*
[a]Baseline data represent means; week 4 and 12 data represent least squares mean change for subjects with baseline UUI >0 and with non-missing change from baseline. **P*<0.001 versus PBO from ANCOVA model.		

Figure. Responder Rates for Change from Baseline in UUI Episodes



References
1. Herschorn et al. BJU Int 2010;105:58-66.
2. Kaplan et al. BJU Int 2011;107:1432-40.

Disclosures
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