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SUPERIOR EFFICACY OF FESOTERODINE OVER TOLTERODINE WITH RAPID ONSET: A PROSPECTIVE, HEAD-TO-HEAD, PLACEBO-CONTROLLED TRIAL

Hypothesis / aims of study
Few randomized, double-blind, placebo (PBO)-controlled trials have been designed to demonstrate superior efficacy of one antimuscarinic over another in treating overactive bladder (OAB) symptoms; none have reported predefined comparisons in both diary-based and patient-reported outcomes (PROs) measures or the time course of treatment superiority. This study, the largest randomized study to compare antimuscarinic efficacy on OAB to date, used such a design to compare the efficacy of fesoterodine (FESO) 8 mg vs tolterodine extended release (TER) 4 mg at both weeks 12 and 4.

Study design, materials and methods
In this 12-week double-blind, double-dummy trial, eligible subjects reported OAB symptoms for ≥3 months and recorded ≥8 micturitions and ≥1 urgency urinary incontinence (UUI) episode per 24 h in 3-day baseline diaries. Sample size was calculated based on 90% power for comparisons at the 5% significance level. Patients were randomized to FESO (4 mg for 1 week, 8 mg for 11 week); TER 4 mg; or PBO. Subjects completed 3-day diaries, Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) at baseline and weeks 4 and 12 and Overactive Bladder Questionnaire (OAB-q) at baseline and week 12. Subjects rated the sensation associated with each micturition using the 5-point Urinary Sensation Scale; frequency-urgency sum was defined as the sum over the course of 24 hours averaged over the diary period. 3-day diary dry rates were defined as the proportion of subjects with ≥1 UUI episode on baseline diary and 0 UUI episodes on diary at week 4 or 12. The primary endpoint was change from baseline to week 12 in UUI episodes. UUI, MVV, and severe urgency episodes violated normality assumptions and were analyzed with Van Elteren test with baseline quantiles as strata; decreases in these variables were estimated with 5% Winsorized means. Analysis of covariance (ANCOVA) was used for secondary diary and OAB-q data, with covariates of country and baseline, and Cochran-Mantel-Haenszel test for diary dry rate, PPBC, and UPS. Safety and tolerability were assessed throughout the trial.

Results
2417 subjects were randomized (PBO, n=480; TER, n=974, FESO, n=963). At week 12, improvements in UUI episodes (primary endpoint), micturitions, urgency and other diary endpoints except mean voided volume per micturition (MVV) and nocturnal micturitions were significantly greater with FESO vs TER 4 mg and PBO, as were improvements on the PPBC, UPS, and all OAB-q domains (P<0.05). At week 4, 3 weeks after FESO dose escalation to 8 mg, FESO was superior over TER 4 mg on UUI and most diary endpoints, as well as on PPBC and UPS (P<0.05; Table 1). Dry mouth and constipation rates were 28% and 4% with FESO, 13% and 3% with TER 4 mg, and 5% and 2% with PBO. Discontinuation rates due to AEs were 5%, 3%, and 2%, for FESO, TER 4 mg, and PBO.

Interpretation of results
Compared with TER 4 mg, FESO has the advantage of being available in an 8 mg dose. In this study, FESO 8 mg was superior over TER 4 mg for UUI episodes, micturitions, and urgency episodes, as well as for PROs. Superiority was seen as early as 3 weeks after FESO dose titration. Both active treatments were generally well tolerated. The results support those of a previous head-to-head trial demonstrating FESO 8 mg superiority over TER 4 mg (1).

Concluding message
In subjects with OAB symptoms including UUI, FESO 8 mg displayed superior efficacy over TER 4 mg in improving most diary endpoints, as well as in improving subjects' assessments of bladder-related problems, urgency, symptom bother, and HRQL. This study also demonstrates early onset of superiority of FESO 8 mg over TER 4 mg and PBO on almost all endpoints. These results together with those of a previous head-to-head trial of FESO 8 mg versus TER 4 mg (1) provide substantial evidence that FESO 8 mg provides additional clinical benefit compared with TER 4 mg.

Table 1. Changes from Baseline at Weeks 4 and 12.[1]

	Placebo (n=462)	**Tolterodine ER (n=942)**	**Fesoterodine (n=930)**
UUI episodes/24 h[2]			
Baseline	2.4	2.6	2.6
Wk 4	–1.3	–1.5*	–1.7*†
Wk 12	–1.6	–1.7*	–2.0*†
MVV, mL			
Baseline	147.6	141.8	146.6
Wk 4	14.3	26.4*	32.3*†
Wk 12	17.3	28.4*	34.5*
Micturitions/24 h			
Baseline	11.7	11.9	11.7
Wk 4	–1.5	–1.8*	–2.1*†
Wk 12	–2.0	–2.3*	–2.6*†
Nocturnal micturitions/24 h[2]			

Baseline	2.1	2.3	2.2
Wk 4	–0.4	–0.5	–0.5*
Wk 12	–0.5	–0.6	–0.7*
Urgency episodes/24 h[2]			
Baseline	9.5	9.7	9.7
Wk 4	–1.9	–2.5*	–3.1*†
Wk 12	–3.2	–3.5	–4.2*†
Severe urgency episodes/24 h[2]			
Baseline	6.0	6.2	6.4
Wk 4	–2.1	–2.7*	–3.2*†
Wk 12	–3.0	–3.4	–4.1*†
Frequency-urgency sum/24 h			
Baseline	40.7	41.7	41.6
Wk 4	–8.1	–10.1*	–12.0*†
Wk 12	–12.0	–13.2	–15.6*†
3-day Diary-dry rates. %			
Wk 4	39.5	46.7*	51.1*†
Wk 12	53.8	58.1	63.2*†
PPBC, %[3]			
Wk 4	51.6	62.8*	66.9*†
Wk 12	59.8	67.1*	73.6*†
UPS, %[3]			
Wk 4	35.4	40.1	45.9*†
Wk 12	40.2	46.9*	53.9*†

[1]Diary data represent means for full analysis set (using last-observation-carried forward); ANCOVA and Van Elteren test were used to analyze treatment effects in normally (eg, micturition, urgency and OAB-q) and non-normally (eg, UUI) distributed data, respectively; Cochran-Mantel-Haenszel test was used for diary-dry rates, PPBC, and UPS.
[2]Includes only subjects with baseline value >0. [3]Percentage of subjects reporting improvement from baseline; *P* value based on categorical distribution.
**P*<0.05 vs PBO; †*P*<0.05 vs TER.

References
1. Herschorn, et al. BJU Int 2010; 105: 58.

Specify source of funding or grant	**Pfizer Inc**
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 NCT00611026**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**The study was conducted at 210 centers in North America, South America, Europe, Asia, and Africa, and was approved by the appropriate IRB/IEC for each center, including: Comite de Etica em Pesquisa Humana e Animal, Ethics Committee at the Federal Service on Surveillance in Healthcare and Social Development, Ethic Committee for Multicenter Trials, IRB Services, HOSPITAL CIMA, Schulman Associates IRB, Inc, Ethik-Kommission der Aerztekammer Nordrhein, Pharma-Ethics (Pty) Ltd**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**