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# DOSE RESPONSE RELATIONSHIP OF FESOTERODINE 4 MG VS 8 MG AND ONSET OF ACTION IN SUBJECTS WITH OVERACTIVE BLADDER: RESULTS FROM A POOLED ANALYSIS OF 2 RANDOMIZED TRIALS

Hypothesis / aims of study
Although clinical studies suggest that many patients with overactive bladder (OAB) who are successfully managed with antimuscarinic agents could achieve further therapeutic benefit with higher doses, dose escalation has not become routine in clinical practice (1).One reason may be the anticipation of increased adverse effects, that may lead to patient discontinuation. Newer antimuscarinic agents appear to have a better therapeutic index, either through improved efficacy or reduced tolerability concerns. Fesoterodine (FESO), a new antimuscarinic in development for the treatment of OAB, is unique in that it is rapidly and extensively de-esterified to its active metabolite, 5-hydroxymethyl tolterodine (5HMT), resulting in reduced pharmacokinetic variability compared with other antimuscarinics that require hepatic metabolism. In previous reports FESO has been shown to significantly improve OAB symptoms vs placebo (PBO) (2). This pooled analysis of data from 2 phase III trials compared the efficacy of FESO 4 mg vs 8 mg as well as the onset of action in subjects with OAB.
Study design, materials and methods
This is a pooled analysis of 2 multicenter, randomized, double-blind, PBO-controlled phase III trials. Eligible subjects (≥18 y) with frequency (≥8 micturitions per 24 h) and urgency (≥2 episodes per 24 h) or urgency urinary incontinence (UUI; ≥1 episode per 24 h) were randomized to PBO, FESO 4 mg, or FESO 8 mg for 12 weeks. Efficacy was assessed using 3-day bladder diaries, which were completed before randomization and 2, 8, and 12 weeks after initiating treatment. Patients recorded the time of each void, urgency, and incontinence episodes. Volumes for each void were measured for 1 day of the diary. Analysis of endpoints included changes from baseline in micturitions per 24 hours, UUI episodes per 24 hours, Treatment Response (based on a 4-point Treatment Benefit scale), mean volume voided (MVV) per micturition, urgency episodes per 24 hours, and continent days per week. Parametric analysis was performed using analysis of covariance with treatment and region as factors and baseline value as a covariate; nonparametric analysis was conducted using Wilcoxon rank sum test.
Results
By the end of the study, all active-treatment groups showed statistically significant improvements in all efficacy endpoints, including changes from baseline in micturition frequency, UUI episodes, Treatment Response, MVV, urgency episodes, and continent days vs PBO ($P$<0.01) **(Table)**. These effects were seen at the first clinical evaluation, 2 weeks after initiation of treatment, and were sustained throughout the study. FESO 8 mg performed significantly better than FESO 4 mg in improving all diary variables ($P$<0.05), with the exception of micturition frequency, demonstrating a dose response relationship.
Interpretation of results
FESO significantly improved all efficacy endpoints as early as 2 weeks after initiation of treatment, compared with PBO. FESO 8 mg was better than the 4-mg dose in improving UUI episodes, urgency episodes, bladder capacity (assessed as MVV per micturition), continent days, and Treatment Response.
Concluding message
FESO offers 2 efficacious doses, 4 and 8 mg, thus providing flexibility and allowing individualization of treatment paradigms for subjects with OAB. The higher 8-mg dose provides additional benefit compared with the lower dose in improving most bladder diary variables.
References
1. Curr Urol Reports (2003) 4;446
2. J Urol (2006) 175; 57

**Table. Summary of Primary and Secondary Efficacy Endpoints at 2 Weeks and End of Treatment (EOT)**

| | | PBO | FESO 4 mg | FESO 8 mg |
|---|---|---|---|---|
| Number of UUI episodes per 24 h | n | 416 | 427 | 441 |
| | Baseline mean | 3.7 | 3.9 | 3.8 |
| | LS mean change (2 wk) | –0.61 | –1.45* | –1.7*‡ |
| | LS mean change (EOT) | –1.12 | –1.85* | –2.3*† |
| | Median % change (2 wk) | –23.0 | –43.2* | –58.3*† |
| | Median % change (EOT) | –42.9 | –75.0* | –83.3*† |
| Number of micturitions per 24 h | n | 545 | 532 | 543 |
| | Baseline mean | 12.1 | 12.2 | 12.0 |
| | LS mean change (2 wk) | –0.73 | –1.0* | –1.4* |
| | LS mean change (EOT) | –1.01 | –1.7* | –2.0* |
| | Median % change (2 wk) | –4.5 | –8.3* | –10.7* |
| | Median % change (EOT) | –10.0 | –15.5* | –17.1* |

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|---|---|---|---|---|
| Treatment Response | n | 545 | 532 | 543 |
| | % yes (2 wk) | 45 | 61* | 67*† |
| | % yes (EOT) | 49 | 69* | 77*† |
| MVV, mL | n | 543 | 531 | 542 |
| | Baseline mean | 154.7 | 156.0 | 154.8 |
| | LS mean change (2 wk) | 7.2 | 18.4* | 33.3*† |
| | LS mean change (EOT) | 9.0 | 22.2* | 33.6*† |
| Urgency episodes per 24 h | n | 545 | 532 | 543 |
| | Baseline mean | 11.4 | 11.8 | 11.5 |
| | LS mean change (2 wk) | –0.7 | –1.2* | –1.6*† |
| | LS mean change (EOT) | –0.9 | –2.0* | –2.3* |
| | Median % change (2 wk) | –4.1 | –8.8 | –12.1*† |
| | Median % change (EOT) | –7.7 | –16.7* | –18.6* |
| Continent d per wk‡ | n | 416 | 427 | 441 |
| | Baseline mean | 0.7 | 0.8 | 0.7 |
| | LS mean change (2 wk) | 0.83 | 1.5* | 2.0*† |
| | LS Mean change (EOT) | 1.77 | 2.6* | 3.1*† |

FESO=fesoterodine; LS=least squares; MVV=mean volume voided; PBO=placebo; UUI=urgency urinary incontinence

*$P$<0.01 vs PBO.

†$P$<0.05 vs FESO 4 mg.

‡Normalized from the 3-day bladder diary.

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**CLINICAL TRIAL REGISTRATION:** **Schwarz Pharma, NCT00220376; Schwarz Pharma, NCT00220363**

**HUMAN SUBJECTS:** **This study was approved by the Patience B. Stevens, MD, MPH, CIP, Copernicus Group IRB, 118 Mackenan Drive, Suite 400, Cary, NC, 27511; Dr. Rodney Rivers, LREC, 1st Floor, Mint Wing, St Mary's Hospital, Praed Street, London W2 1NY, UK and followed the Declaration of Helsinki Informed consent was obtained from the patients.**