118

Goldman H[1], Oelke M[2], Kaplan S A[3], Kitta T[4], Russell D[5], Carlsson M[5], Arumi D[6], Mangan E[5], Ntanios F[5]
1. *The Cleveland Clinic,* ***2.*** *Hannover Medical School,* ***3.*** *Weill Cornell Medical College,* ***4.*** *Hokkaido University,* ***5.*** *Pfizer Inc,* ***6.*** *Pfizer Europe*

CHARACTERISTICS OF PATIENTS WITH OVERACTIVE BLADDER WHO ESCALATE TO A HIGHER DOSE OF ANTIMUSCARINIC: EFFICACY AND SAFETY OUTCOMES

Hypothesis / aims of study
Patients with OAB who start on low-dose fesoterodine (FESO) but are dissatisfied with the symptomatic outcome, when given the option to escalate to higher-dose FESO (52–63%), have significant improvement in efficacy endpoints and a tolerability profile close to that observed in the pivotal trials. Does the population with the phenotype of the escalator group respond differently to FESO with fixed-dose treatment? Post-hoc analyses were conducted to define the dose-escalator phenotype from flexible-dose trials. We matched the defined phenotype to patients in fixed-dose pivotal trials. We compared the efficacy of FESO 8 mg and FESO 4 mg vs placebo (PBO) in these matched patients and evaluated safety profiles.

Study design, materials and methods
Based on four 12-week, double-blind, PBO-controlled, flexible-dose trials of FESO, we characterized the phenotype of FESO-treated OAB patients with ≥1 urgency urinary incontinence (UUI) episodes/24 h at baseline (BL) who opted to escalate their FESO dose from 4 mg to 8 mg (at week 2 or 4) and completed the trial. Possible predictors of dose escalation [age; sex; previous antimuscarinic (AM) use; UUI, micturitions, and urgency episodes/24 h at BL; race (white vs other); body mass index (BMI); time to dose escalation; OAB duration; study; and treatment] were assessed by comparing escalators vs non-escalators in univariate and multivariate logistic regression analyses. Using this dose-escalator phenotype, we identified a matched escalator phenotype sample of treated patients from two pivotal double-blind, PBO-controlled, fixed-dose, FESO trials using propensity score analysis. Efficacy [change from BL to week 12 in UUI, micturitions, and urgency episodes/24 h for FESO 4 mg and FESO 8 mg vs PBO with analysis of covariance (ANCOVA) model] and safety (adverse events; AEs) outcomes were assessed in the matched escalator phenotype sample (N=630) from the two pivotal trials. All trials had ethical committee approval and all enrolled patients provided informed consent.

Results
In four flexible-dose trials, significant (univariate *P* <0.001) predictors of dose escalation in 333 OAB patients with ≥1 UUI episodes/24 h who escalated to the FESO 8-mg dose vs 242 non-escalators (remained on 4-mg dose) were: age (65.8 vs 71.0 y), micturitions/24 h at BL (13.1 vs 11.0), urgency episodes/24 h at BL (10.9 vs 9.2), OAB duration (9.1 vs 7.1 y), and previous AM use (58.3% vs 22.3%); micturitions/24 h at BL (*P*=0.016) and previous AM use (*P*=0.008) were independent predictors in multivariate analyses. Based on significant predictors of dose escalation in flexible-dose trials, a matched sample of 630 patients (FESO 4 mg: n=215; FESO 8 mg: n=198; PBO: n=217) with the dose-escalator phenotype was identified from two fixed-dose pivotal trials (**Table 1**). For patients in this matched escalator phenotype sample, the change from BL to week 12 in UUI episodes was statistically significantly improved with FESO 8 mg and FESO 4 mg vs PBO (each *P* <0.001; **Table 2**); the comparison between FESO 8 mg vs FESO 4 mg also was significant (*P*=0.043). The improvements from BL to week 12 in micturitions/24 h and urgency episodes/24 h with FESO 4 mg and 8 mg vs PBO were not statistically significant. The most frequent AEs (all causes) in the matched escalator phenotype sample were dry mouth and constipation (**Table 3**).

Interpretation of results
Patients who matched the escalator phenotype had a significant UUI response vs PBO with both doses of FESO and a safety profile that was comparable to the pivotal trials, with a proportional change in their AEs with the increase in dose. The significant UUI response with FESO 8 mg vs FESO 4 mg in the matched phenotype sample suggests that these patients gain an additional UUI response with the higher FESO dose.

Concluding message
The dose escalator phenotype was able to identify patients who would have a robust UUI response to FESO 8 mg without compromising the safety profile, which remained similar to that in the larger population in the pivotal trials.

Table 1. Patient Characteristics After Matching Patients in Pivotal Trials to Escalator Phenotype Sample From Flexible-Dose Trials			
Characteristic	**Pivotal Trials: Matched Escalator Phenotype Sample (N=630)**	**Escalator Phenotype From 4 Flexible-Dose Trials (N=333)**	***P* Value***
Mean age, y	63.1	65.8	0.889
Mean BMI, kg/m^2	30.4	31.1	0.632
Mean UUI episodes/24 h at BL	3.4	3.1	0.162
Mean micturitions/24 h at BL	12.6	13.1	0.807
Mean urgency episodes/24 h at BL	11.3	10.9	0.995
Duration of OAB, y	9.6	9.1	0.163
Race, White, %	89.5	90.1	0.524
Female, %	81.7	85.6	0.658
Previous AM use, %	55.9	58.3	>0.9

P values from paired *t*-test for continuous variables or McNemar test for proportions at the 5% level of significance, with a non-significant value indicating a comparable mean or proportion between the 2 patient samples.

Table 2. Efficacy Outcomes in Matched Escalator Phenotype Sample (N=630)			
Pivotal Trials: Matched Sample Phenotype – ANCOVA*	**FESO 4 mg (n=215)**	**FESO 8 mg (n=198)**	**PBO (n=217)**
Mean UUI episodes/24 h at BL	3.3	3.5	3.3
Change from BL to wk 12, LS mean	–1.6	–2.1	–0.7
P value: FESO vs PBO	<0.001	<0.001	
P value: FESO 8 mg vs FESO 4 mg		**0.043**	
Mean micturitions/24 h at BL	12.8	12.4	12.7
Change from BL to wk 12, LS mean	–2.0	–2.5	–1.0
P value: FESO vs PBO	<0.001	<0.001	
P value: FESO 8 mg vs FESO 4 mg		0.159	
Mean urgency episodes/24 h at BL	11.5	11.2	11.4
Change from BL to wk 12, LS mean	–1.9	–2.4	–0.3
P value: FESO vs PBO	<0.001	<0.001	
P value: FESO 8 mg vs FESO 4 mg		0.170	

**P* values based on ANCOVA, with terms for study, treatment, baseline value, and treatment-by-baseline value interaction, at the 5% level o significance. LS=least squares.

Table 3. Treatment-Emergent Adverse Events (All-Causalities) in Matched Escalator Phenotype Sample (N=630)			
Adverse Event, n (%)*	**FESO 4 mg (n=215)**	**FESO 8 mg (n=198)**	**PBO (n=217)**
Dry mouth	42 (19.5)	75 (37.9)	15 (6.9)
Constipation	7 (3.3)	15 (7.6)	5 (2.3)
Urinary tract infection	9 (4.2)	9 (4.5)	8 (3.7)
Dry eye	3 (1.4)	7 (3.5)	0
Headache	13 (6.0)	3 (1.5)	11 (5.1)

*Adverse events occurring in ≥3% of patients in any treatment group.

Disclosures
Funding: The study was sponsored by Pfizer Inc. **Clinical Trial:** Yes **Registration Number:** NCT IDs for 6 trials: NCT00220363; NCT00138723; NCT00911937; NCT00928070; NCT00536484; NCT00798434 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** Independent Ethics Committees or Institutional Review Boards **Helsinki:** Yes **Informed Consent:** Yes