Efficacy and Tolerability of Fesoterodine in Older People With Overactive Bladder: Results of the Open-Label Phase of the SOFIA Trial

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1 Introduction

- Overactive bladder (OAB) is a widespread condition,[1] with prevalence rates that increase with advancing age, and it has a negative impact on health-related quality of life (HRQL).[2]
- Treatment with fesoterodine (FESO), an oral antimuscarinic agent, resulted in significant improvements in OAB symptoms and HRQL and was well tolerated in fixed- and flexible-dose studies.[3-5]
- Few placebo (PBO)-controlled studies have prospectively evaluated the efficacy and safety of antimuscarinics in subjects aged ≥65 years.
- The Study Of Fesoterodine In an Aging population (SOFIA) trial, a 12-week, randomised, double-blind (DB), PBO-controlled, parallel-group study that was followed by a 12-week open-label (OL) phase, assessed the efficacy and tolerability of flexible-dose FESO (4 and 8 mg) in 794 elderly (aged ≥65 years) subjects (47% men) with OAB.
  - During DB treatment, flexible-dose FESO was associated with significant improvements compared with PBO in most bladder diary variables and patient-reported outcomes (PROs) at week 12.
  - Treatment with flexible-dose FESO was generally well tolerated.

2 Objectives

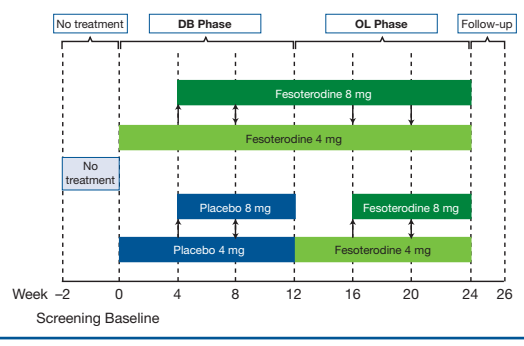
- To assess the efficacy, safety, and tolerability of flexible-dose FESO during the 12-week OL phase of the SOFIA trial, which followed a 12-week DB phase

3 Methods

Study Design

- 12-week, randomised, DB, PBO-controlled, parallel-group study, followed by a 12-week OL phase **(Figure 1)**.

Figure 1. Study Design



- Randomisation was stratified by age (>75 y, ≤75 y) with a 1:1 ratio of FESO:PBO per age stratum.

Subjects

- Key inclusion criteria
  - Men or women aged ≥65 years, with OAB symptoms for ≥3 months
  - Mean of ≥8 micturitions and ≥3 urgency episodes per 24 hours on 3-day baseline bladder diary
  - At least some moderate problems reported on the Patient Perception of Bladder Condition (PPBC) questionnaire
  - Folstein Mini-Mental State Examination (MMSE) score of ≥20/30
- Key exclusion criteria
  - Predominant stress urinary incontinence
  - Clinically significant bladder outlet obstruction, recent surgery, or other urinary tract conditions that could interfere with the assessment of OAB symptoms
  - Multiple sclerosis or spinal cord injury
  - Unwillingness to stop treatment with anticholinergic drugs

Assessments

- Bladder diaries completed on 3 consecutive days during the week preceding each visit
- Overactive Bladder Questionnaire (OAB-q)
- PPBC
- Urgency Perception Scale (UPS)
- Treatment Benefit Scale (TBS)
- Overactive Bladder Satisfaction Questionnaire (OAB-S)
- Adverse events (AEs)

Statistical Analyses

- Efficacy assessments were performed on the OL full-analysis set (FAS), which included all subjects who took ≥1 dose of study medication and provided ≥1 post–DB phase efficacy measurement during the OL phase.
- Efficacy was assessed descriptively for bladder diary variables and PROs
  - Change from week 12 to week 24 and from baseline to week 24 in bladder diary variables
  - Change from week 12 to week 24 in OAB-q scores
  - Proportion of subjects with an improvement (responders) on the PPBC and UPS at week 24
  - Proportion of subjects who were responders on the TBS at week 24 ("improved" or "greatly improved" during treatment)
  - Proportion of subjects who were responders on OAB-S question 5 (OAB medication "met" or "somewhat" or "greatly exceeded" my expectations) at week 24
  - Proportion of subjects who were responders on OAB-S questions 9, 10a-d, and 11a-b ("very satisfied" or "somewhat satisfied" on all 7 questions on OAB control) at week 24

4 Results

- The baseline demographic characteristics of the 654 subjects who were treated with FESO in the OL phase are listed in **Table 1**.

Table 1. Demographics and Clinical Characteristics at DB Baseline

Characteristic	PBO/FESO n=341	FESO/FESO n=313
Gender, n (%)		
Men	167 (49)	144 (46)
Women	174 (51)	169 (54)
Age, y		
Mean (SD)	72.7 (5.6)	72.3 (5.7)
Range	65–88	65–90
Urgency episodes/24 h, mean (SD)	8.8 (4.0)	8.4 (3.5)
Severe urgency episodes/24 h, mean (SD)	4.2 (4.3)	3.6 (3.3)
Micturitions/24 h, mean (SD)	12.0 (3.0)	11.8 (2.8)
Nighttime micturitions/24 h, mean (SD)	2.9 (1.4)	2.7 (1.5)

Demographic characteristics based on the safety analysis set; clinical characteristics based on the OL FAS.

- Of the 654 subjects (PBO, n=341; FESO, n=313) who completed the DB phase and were treated in the OL phase, 299 (88%) and 282 (90%) completed the OL phase, respectively.
- At the beginning of the OL phase (week 12), 60% of subjects from the DB FESO (FESO/FESO) group were receiving a dose of 8 mg once daily.
  - After 4 weeks of OL treatment (week 16), 51% of the subjects in the DB PBO/OL FESO (PBO/FESO) group escalated to 8-mg once-daily FESO.
  - By week 20, 52% of the subjects in each OL group still participating in the study were receiving the 8-mg dose of FESO.

Efficacy

- During OL treatment, the FESO/FESO group maintained the improvements in diary variables and PROs achieved during the DB phase. Clinically significant improvements in diary variables and PROs were seen in the PBO/FESO group.
  - The FESO/FESO group maintained the week 12 (end of DB phase) improvement in the number of urgency episodes per 24 hours (primary endpoint) to week 24 (end of OL phase), whereas the PBO/FESO group had noticeable improvements during OL treatment with FESO **(Figures 2 and 3A)**. By week 24, both the FESO/FESO and PBO/FESO groups had similar improvements in urgency episodes per 24 hours.
  - The PBO/FESO group also demonstrated improvements in severe urgency episodes, micturitions, and nighttime micturitions per 24 hours **(Figure 3B–D)**. Treatment responses for these bladder variables were maintained from week 12 to week 24 for the FESO/FESO group.

Figure 2. Time Course of Mean (95% CI) Change From Baseline in Urgency Episodes per 24 h

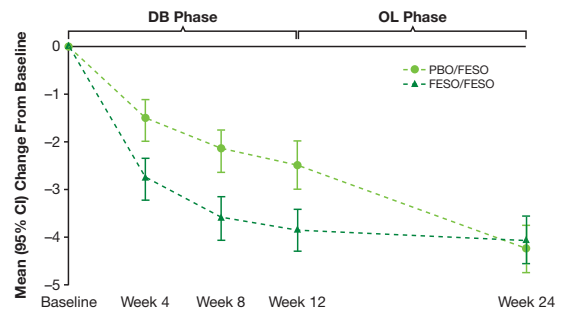
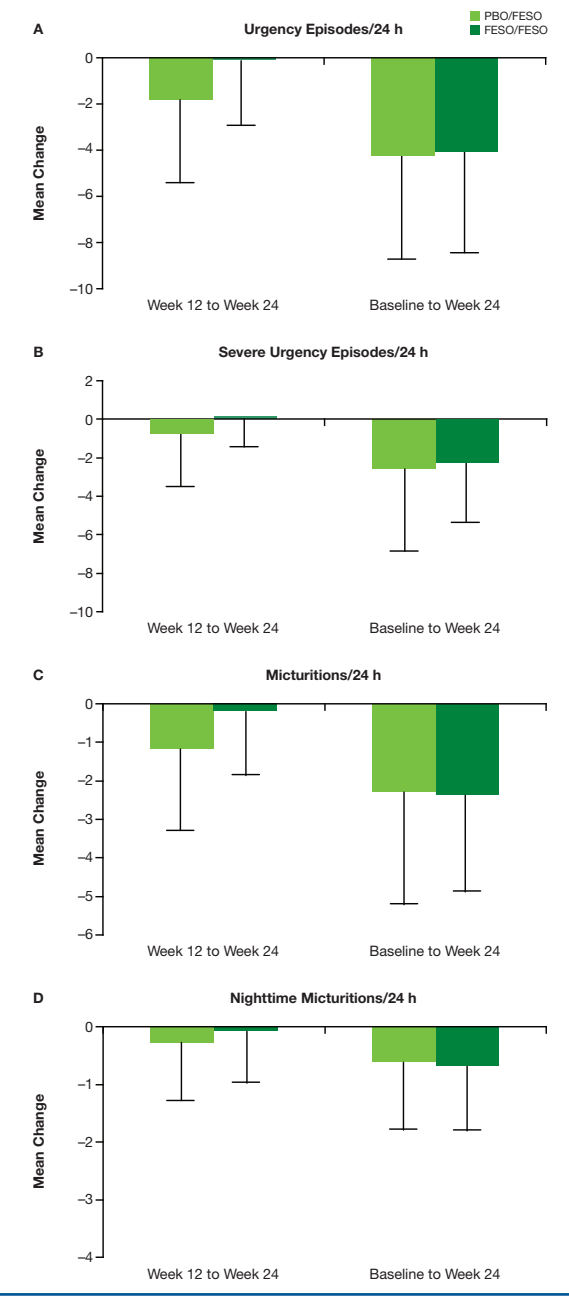


Figure 3. Mean (SD) Change in Bladder Diary Variables



- At week 24, scores on the OAB-q demonstrated that the improvements in HRQL and Symptom Bother after 12 weeks of DB FESO were maintained during OL FESO treatment and improved in subjects who had previously received PBO **(Figure 4)**.
- Responder rates on the PPBC and UPS **(Figure 5A)** from week 12 to week 24 were greater in subjects who had previously received DB PBO.
- By week 24, the proportion of subjects who were responders on the TBS and OAB-S were comparable in the FESO/FESO and PBO/FESO groups **(Figure 5B)**.
- Overall improvements in diary variables and PROs at week 24 were similar among subjects who received PBO/FESO and those who received FESO/FESO.

Figure 4. Change From Week 12 to Week 24 in OAB-q Scores

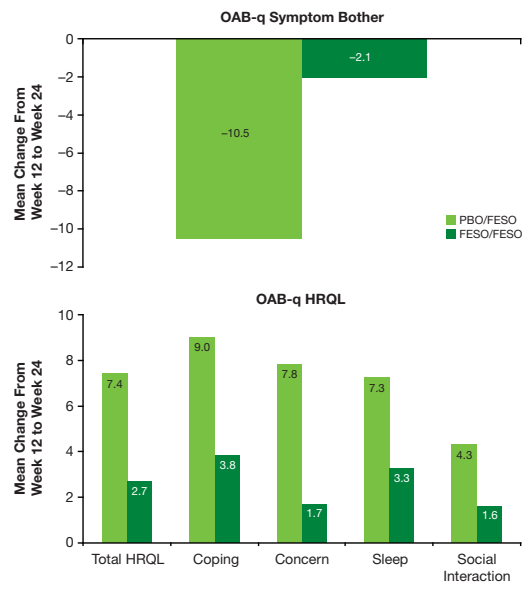
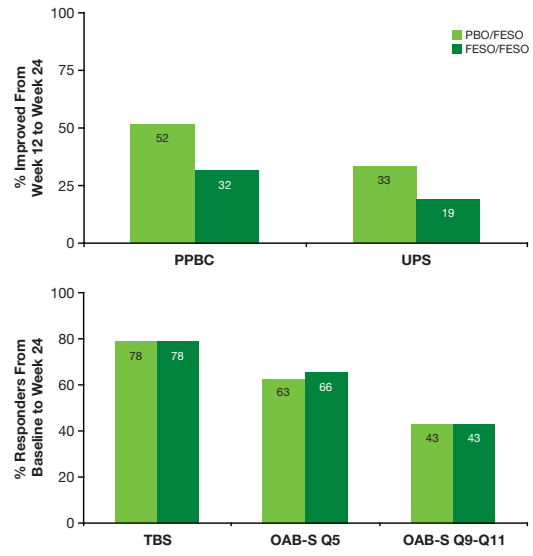


Figure 5. Proportion of Subjects with Improvement (Responders) on PPBC and UPS and TBS and OAB-S Responder Rates at Week 24



Safety

- During the OL phase, treatment-emergent AEs were reported by 164 (48%) subjects in the PBO/FESO group and 96 (31%) subjects in the FESO/FESO group. These AEs were predominantly (96%) of mild or moderate intensity.
- The most common AEs reported during the OL phase among all subjects were dry mouth and constipation **(Table 2)**. Discontinuations due to AEs occurred in 32 (9%) subjects in the PBO/FESO group and 6 (2%) subjects in the FESO/FESO group, with dry mouth the most common AE leading to discontinuation (PBO/FESO group, n=7; FESO/FESO group, n=3).

Table 2. Treatment-Emergent AEs Occurring in ≥3% of Patients in Any Group, Serious AEs, and Discontinuations Due to AEs

	Double-Blind Phase		Open-Label Phase	
AE, n (%)	PBO n=393	FESO n=392	PBO/FESO n=341	FESO/FESO n=313
Dry mouth	21 (5.3)	133 (33.9)	95 (27.9)	21 (6.7)
Constipation	10 (2.5)	35 (8.9)	21 (6.2)	5 (1.6)
Dizziness	4 (1.0)	14 (3.6)	6 (1.8)	2 (0.6)
Nasopharyngitis	9 (2.3)	12 (3.1)	2 (0.6)	6 (1.9)
Urinary tract infection	7 (1.8)	10 (2.6)	4 (1.2)	14 (4.5)
Serious AEs	9 (2.3)	14 (3.6)	7 (2.1)	11 (3.5)
Discontinuations due to AEs	20 (5.1)	53 (13.5)	32 (9.4)	6 (1.9)

- 5 men reported urinary retention during the OL phase (PBO/FESO group, n=4; FESO/FESO group, n=1); 3 subjects in the PBO/FESO group were withdrawn because of this AE, including 1 who required catheterisation.
- 3 serious AEs in the PBO/FESO group were considered treatment related (urinary retention, transient ischaemic attack, and rash).

5 Conclusions

- **Improvements during 12 weeks of OL treatment with FESO allowed elderly men and women who received PBO during the DB phase to achieve similar improvements to those who initially received DB FESO.**
- **Elderly men and women who received FESO during the DB phase maintained their improvement over the 12-week OL phase with few additional AEs.**
- **FESO treatment was generally well tolerated in this elderly population.**

6 References

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