**Evaluation of Cognitive Function in Healthy Older Adults Treated With Fesoterodine**

### 1 Introduction

- Muscarinic agonists are first-line pharmacologic treatment for overactive bladder (OAB).[^1]
- Safety and tolerability are important considerations in older individuals with OAB due to increased permeability of the blood-brain barrier, changes in hepatic and renal function, the presence of comorbidities, and polypharmacy that may lead to additive antimuscarinic effects or competition for metabolic resources.[^2]
- The propensity for an antimuscarinic agent to cause central nervous system (CNS) effects depends upon its physicochemical properties, which determine its potential to cross the blood-brain barrier and its muscarinic receptor subtype selectivity.[^3]
- Data from in vivo studies and clinical trials suggest that 5-hydroxy methyltolterodine (5-HMT), the active metabolite of fesoterodine (FESO), has a low potential for CNS penetration.[^4]
- However, the potential of FESO to impair cognitive functioning in older individuals has not been assessed.

### 2 Objective

- To evaluate the cognitive effects of FESO 4 and 8 mg compared with placebo (PBO) in healthy older adults.

### 3 Methods

**Study Design**

- This was a single-center, randomized, active- and PBO-controlled, double-blind, double-dummy, 4-way crossover study.[^5]
- Subjects were randomized to 1 of 4 crossover sequences, and the study comprised 4 treatment periods, each lasting for 6 days, with a 3- to 6-day washout period.[^6]
  - FESO 4 mg/day for 6 days with alprazolam-matching PBO on day 6
  - FESO 4 mg for 3 days followed by FESO 8 mg for 3 days, with alprazolam-matching PBO on day 6
  - FESO-matching PBO for 6 days, with single-dose alprazolam 1 mg on day 6
  - Cognitive assessments on day 6 coincided with maximum drug concentration for FESO and alprazolam

**Subjects**

- Key inclusion criteria:
  - Healthy male or female subjects aged 65–85 years
  - Score of at least 26 on the Mini-Mental State Examination (MMSE)
- Key exclusion criteria:
  - Cognitive impairment due to any concurrent conditions
  - Any condition that could possibly affect drug absorption
  - Current or previous bladder outlet obstruction
  - Recent use of psychotropic medications or medications that could have affected cognitive function

**Assessments**

- Subjects completed validated computer-based cognitive assessments (Cogstate subtests) and the Rey Auditory Verbal Learning Test (RAVLT) on day 1 (before dosing) and day 6 (after dosing) of each treatment period (Table 1).

### 4 Results

**20 subjects were randomized and treated (Table 2).**

- 1 subject discontinued for personal reasons and 1 was excluded from the PPAS for a violation of the study protocol (receiving a prohibited medication).

### 5 Conclusions

- All steady state, FESO 4 and 8 mg resulted in no statistically significant effects vs PBO on any cognitive function measures, including psychomotor speed, memory, attention, and executive function, in healthy older adults.
- In contrast, the same subjects showed a large, generalized, and statistically significant deterioration on all cognitive function measures with alprazolam.
- The study treatments were well tolerated, and the treatment-emergent AEs reported were consistent with the respective pharmacologic properties of FESO and alprazolam.
- Results from this trial support previous findings demonstrating the CNS safety of FESO.

### References

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**3** Curr Med Chem. 2009;16(33):4481-4489.

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**6** Curr Med Chem. 2009;16(33):4481-4489.

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This study was sponsored by Pfizer Inc. Medical writing assistance was provided by Colin Mitchell at Complete Healthcare Communications, Inc., and was funded by Pfizer Inc.