Efficacy, Safety and Tolerability of Fesoterodine for Overactive Bladder Syndrome

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Purpose: We evaluated the efficacy, tolerability and safety of the new antimuscarinic agent fesoterodine relative to placebo for overactive bladder syndrome.

Materials and Methods: This was a randomized, double-blind, placebo controlled, multicenter trial performed in the United States. Overall 836 subjects with urinary frequency, urinary urgency or urgency urinary incontinence were randomized to placebo (274), 4 mg fesoterodine (283) or 8 mg fesoterodine (279) once daily for 12 weeks. The primary efficacy end point was the change in the number of micturitions per 24 hours. Co-primary end points were the change in the number of urgency urinary incontinence episodes per 24 hours and the treatment response. Secondary efficacy end points were other bladder diary variables, such as the change in mean voided volume per micturition, number of continent days and number of urgency episodes per 24 hours. Tolerability and safety were assessed by evaluating adverse events, electrocardiograms, post-void residual urine volume, laboratory parameters and treatment withdrawals.

Results: Treatment with 4 or 8 mg fesoterodine resulted in statistically significant and clinically relevant improvements from baseline to end of treatment for the primary and co-primary end points compared with placebo ($p < 0.05$). Results for most secondary end points, including mean voided volume per micturition, number of continent days and number of urgency episodes per 24 hours, were also significantly improved vs placebo. The adverse events reported more frequently with fesoterodine than with placebo were dry mouth, constipation and urinary tract infection.

Conclusions: The 2 doses of fesoterodine were well tolerated and they statistically significantly improved overactive bladder symptoms.

Key Words: bladder; bladder, overactive; muscarinic antagonists; urinary incontinence; 5-hydroxymethyl tolterodine

Overactive bladder syndrome is defined by the International Continence Society as urgency with or without UUI, usually with frequency and nocturia.[1] It is a widespread condition affecting men and women, and incidence rates increase with age.[2,3] The prevalence rate in the United States and Europe was reported to be 12% to 17%.[2–4]

The mainstay of OAB pharmacotherapy consists of antimuscarinic agents, such as oxybutynin,[5] darifenacin,[6] trospium chloride,[7] solifenacin[8] and tolterodine,[9] which have shown efficacy for improving OAB symptoms. However, these benefits are offset by dose related increases in AEs, such as dry mouth, constipation and blurred vision. There remains a need for antimuscarinic agents that may provide further improvement of the therapeutic index for OAB treatment.

FESO is a novel antimuscarinic agent that acts functionally as a prodrug. It is rapidly and extensively hydrolyzed by nonspecific esterases to 5-HMT, which is an active metabolite responsible for all antimuscarinic activity of FESO.[10] Also, 5-HMT is the active metabolite of tolterodine, which is formed via CYP 2D6 mediated oxidation. The conversion of FESO to its active metabolite bypasses the hepatic CYP pathway, although CYP3A4 and CYP2D6 isozymes are involved in the further inactivation of 5-HMT.[11]

Data from phase II studies demonstrated that FESO improves OAB symptoms in dose dependent fashion and it is well tolerated.[12,13] The primary goal of this 12-week, PBO controlled, multicenter study was to evaluate the efficacy, safety and tolerability of 4 and 8 mg FESO for OAB.

METHODS

This was a double-blind, randomized, placebo controlled trial performed at 83 sites in the United States between October 30,

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Study received approval from the respective institutional review boards.

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2003 and February 10, 2005. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the respective institutional review boards and all subjects provided written informed consent before the start of the study.

Subject Selection

Eligible subjects included men and women 18 years or older with OAB syndrome for 6 months or greater, including urinary frequency (8 micturitions or greater per 24 hours) and urinary urgency (6 episodes or greater during the 3-day diary period) or UUI (3 episodes or greater during the 3-day diary period). Slow accrual of subjects with UUI led to the introduction of an amendment to ensure enrollment of a sufficient number, which was prespecified in the protocol to be 80% of each treatment group. The amended inclusion criterion required 3 or greater UUI episodes to be recorded in the 3-day diary at the end of the placebo run-in for all remaining subjects. In addition, subjects had to report at least moderate bladder problems on a Likert scale that was almost identical to the patient perception of bladder condition.[14] Women participating in the trial had to have a negative pregnancy test and use adequate contraception throughout the trial.

Key exclusion criteria were lower urinary tract pathology that could in the opinion of the investigator be responsible for urgency or incontinence, such as significant stress incontinence, urolithiasis, interstitial cystitis or urothelial tumors; pelvic organ prolapse grade III or greater; clinically relevant bladder outlet obstruction; PVR volume greater than 100 ml; polyuria (greater than 3 l/24 hours); symptomatic or recurrent urinary tract infections; current treatment with antimuscarinic agents; a neurogenic cause of OAB; clinically relevant arrhythmia, unstable angina or a corrected QT interval (Bazett's formula) of greater than 500 milliseconds; or current treatment or treatment within the last 4 weeks with electrostimulation or bladder training.

Study Design

After a 2-week placebo run-in period eligible subjects were randomized 1:1:1 to PBO, or 4 or 8 mg FESO per day orally once daily for 12 weeks according to a computer generated randomization schedule stratified by site (fig. 1). Treatment began the day following randomization. PBO tablets were identical in appearance to 4 and 8 mg FESO tablets. Treatment compliance was assessed by counting unused trial medication and assessing diaries for completion. Subjects completed a 3-day bladder diary before randomization, and 2, 8 and 12 weeks after initiating treatment, in which the time of each micturition, incontinence episode and urgency episode, including severity, was recorded. Voided volumes were recorded on 1 of the 3 diary days. Treatment response was assessed using a self-administered treatment benefit scale.

Clinical Assessments

The primary end point was the change from baseline in the number of micturitions per 24 hours. Co-primary end points were the change from baseline in the mean number of UUI episodes per 24 hours and the treatment response (a yes/no variable derived from a 4-point treatment benefit scale). Secondary efficacy end points were MVV per micturition, and the number of daytime micturitions, nocturnal micturitions, urgency episodes per 24 hours and continent days per week (data normalized from the 3-day bladder diary). Missing responses were imputed via last observation carried

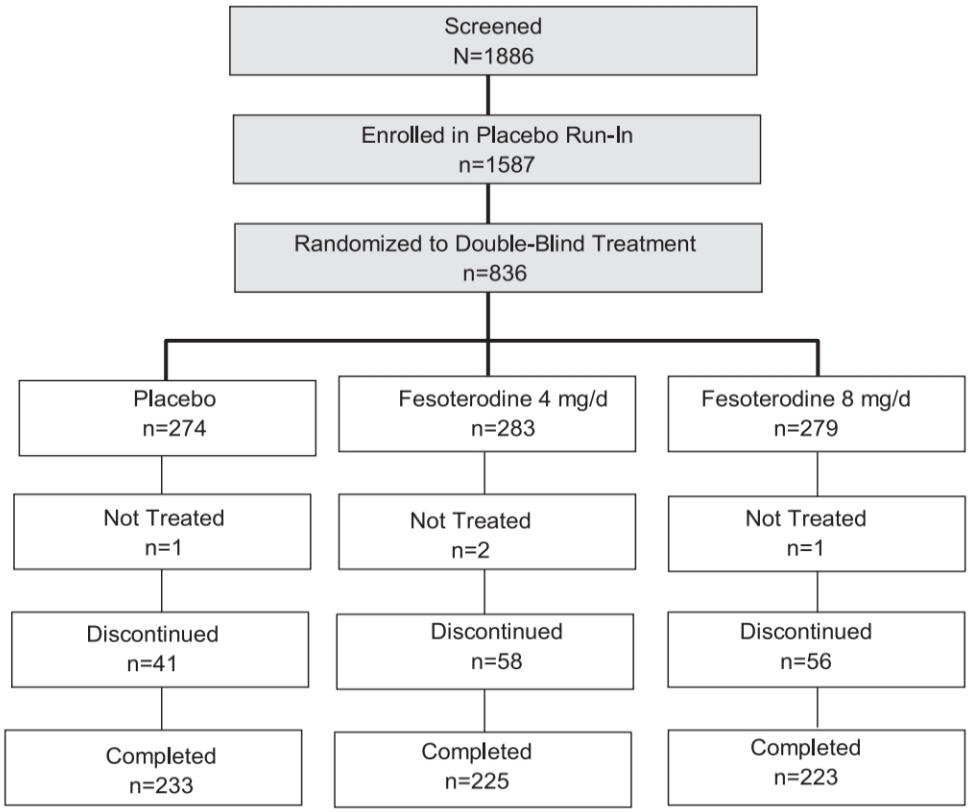

FIG. 1. Study design. *d*, day

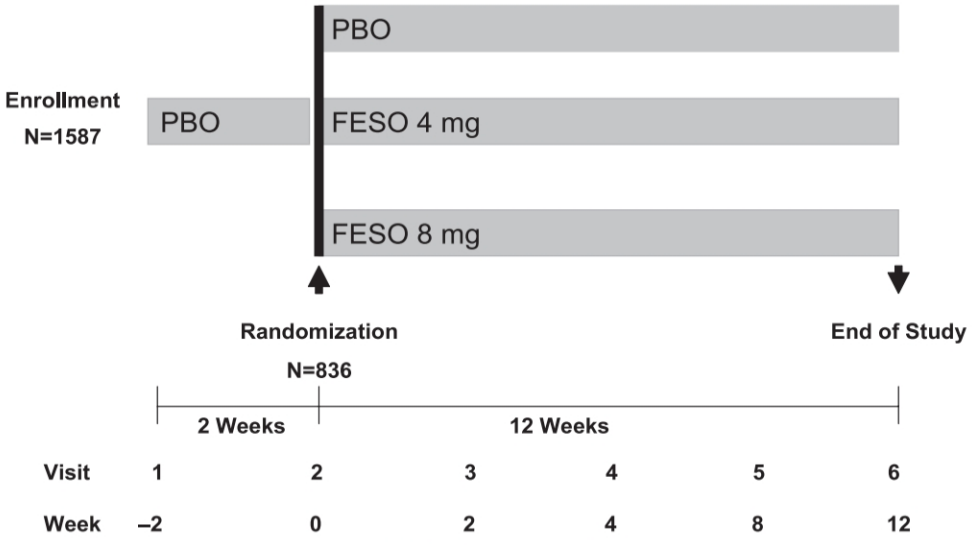

FIG. 2. Subject disposition

forward. The Appendix lists the definitions of all end points. At 12 weeks subjects had the option to continue in a long-term, open label study or complete a 2-week safety followup after the end of treatment.

Statistical Analysis

Parametric analysis for continuous variables (micturition frequency and UUI episodes) was performed in the full analysis set population, ie all randomized subjects receiving trial medication for whom a baseline and double-blind treatment measure was obtained, using an ANCOVA model with treatment and region as factors, and the baseline value as a covariate. Nonparametric sensitivity analysis was performed using the Wilcoxon rank sum test. Treatment response was analyzed using the normal approximation method. In exploratory analyses the median percent change from baseline to week 12 was calculated for bladder diary end points and statistical hypothesis testing was performed for secondary end points.

A sequentially rejective closed test procedure was applied to the primary variables to adequately account for multiplicity. According to requirements of the United States Food and Drug Administration the test procedure started with micturition frequency per 24 hours and performed the test of 8 mg FESO vs PBO for this variable, stepped down to the 4 mg FESO vs PBO test in the event of statistical significance and continuing with the respective tests for the number of UUI episodes per 24 hours. According to the requirements of the European Agency for the Evaluation of Medicinal Products the test procedure considered micturition frequency per 24 hours and treatment response simultaneously, tested 8 mg FESO vs PBO for the 2 variables first and in the event of a statistically significant result continued to test the 4 mg dose vs PBO for the 2 variables.

Tolerability and Safety

Adverse events reported throughout the study duration were categorized and the likelihood of a causal relationship to study medication was determined. Clinical laboratory parameters, vital signs and a centrally read 12 lead electrocardiogram were assessed at each visit. PVR volume was measured at each visit except at week 4 and the safety followup.

RESULTS

Subjects

A total of 836 subjects were randomized and included in the full analysis set population (fig. 2). Table 1 lists subject demographic and clinical characteristics. Of the subjects 76% were women and 82% were white. Mean age was 59 years (range 21 to 91). Mean time since the first OAB diagnosis was 10 years. Approximately half of the subjects had previously received OAB treatment and 81% of randomized subjects were incontinent based on a bladder diary completed during the placebo run-in. Compliance with study medication was noted in 96% or greater of subjects during the double-blind phase.

Efficacy

Treatment with 4 and 8 mg FESO resulted in statistically significant and clinically relevant improvements vs PBO from baseline to end of treatment in the primary and in the 2

TABLE 1. *Baseline demographic and clinical characteristics*

Characteristic	PBO		4 mg FESO		8 mg FESO	
No. subjects	271		282		279	
No. women (%)	200	(74)	213	(76)	218	(78)
Mean age (range)	59 (24–88)		59 (21–85)		59 (23–91)	
No. ethnic origin (%):						
White	218	(80)	230	(82)	233	(84)
Black	28	(10)	26	(9)	21	(8)
Asian	4	(2)	3	(1)	4	(1)
Yrs since OAB diagnosis:						
Mean ± SD	9.8 ± 10.3		9.1 ± 10.3		10.1 ± 11.5	
No. 0–less than 1 (%)	11	(4)	16	(6)	8	(3)
No. 1–less than 5 (%)	97	(36)	118	(42)	111	(40)
No. 5–less than 10 (%)	65	(24)	59	(21)	68	(24)
No. 10–less than 15 (%)	44	(16)	39	(14)	40	(14)
No. 15 or greater (%)	51	(19)	50	(18)	52	(19)
No. previous OAB treatment (%):	145	(54)	139	(49)	149	(53)
Tolterodine	90	(33)	88	(31)	95	(34)
Oxybutynin	101	(37)	94	(33)	97	(35)
Trospium chloride	7	(2.6)	6	(2.1)	3	(1.1)
No. incontinence (%)	205	(77)	228	(85)	218	(82)

Based on safety population, ie all subjects who received 1 or greater medication dose, and incontinence based on full analysis set population of 800.

co-primary end points ($p < 0.05$, table 2 and fig. 3). For most diary variables LS mean changes from baseline with 8 mg FESO were approximately twice those with PBO. The mean change from baseline in the number of micturitions and incontinence episodes per 24 hours was significantly improved by the 2 FESO doses compared with that of PBO. Subject reported treatment response rates with the 2 FESO doses were significantly higher than those with PBO at study end ($p < 0.001$, fig. 4). With respect to secondary end points 4 mg FESO showed significant improvement in the mean change from baseline compared with PBO for the number of nocturnal micturitions ($p < 0.05$), urgency episodes ($p < 0.001$) and continent days per week ($p < 0.001$), whereas 8 mg FESO was significantly better than PBO for MVV per micturition, number of urgency episodes, number of daytime micturitions and continent days per week (each $p < 0.001$, table 2).

Tolerability and Safety

AEs. Treatment emergent AEs occurred in 55% (149 of 271), 61% (171 of 282) and 69% (193 of 279) of subjects receiving PBO, and 4 and 8 mg FESO, respectively. Table 3 lists all treatment emergent AEs irrespective of the relationship to study medication that were reported by 2% or greater of subjects in any treatment group. Dry mouth was the most commonly reported AE. It was usually mild to moderate in severity and it occurred in 7% (19 of 271), 16% (45 of 282) and 36% of subjects (99 of 279) receiving PBO, and 4 and 8 mg FESO, respectively.

Urinary retention was reported in 2 ways, including PVR more than 200 ml in 8 subjects and urinary retention as an AE in 11. Three men had a PVR of more than 200 ml and they reported urinary retention as an AE. One man (less than 1%) in the 4 mg FESO group, 5 female and 2 male subjects (2%) in the 8 mg FESO group and 0 in the PBO

TABLE 2. *Efficacy results (change from baseline to study end)*

	PBO	4 mg FESO	8 mg FESO
	Primary end points		
Micturitions/24 hrs:			
No. subjects	266	267	267
Baseline mean ± SD	12.2 ± 3.7	12.9 ± 3.9	12.0 ± 3.3
LS mean change ± SE	−1.08 ± 0.18	−1.61 ± 0.18	−2.09 ± 0.18
p Value		0.032	<0.001
Median % change	−6.9	−14.9	−16.0
p Value		<0.001	<0.001
UUI episodes/24 hrs:*			
No. subjects	205	228	218
Baseline mean ± SD	3.7 ± 3.3	3.9 ± 3.5	3.9 ± 3.3
LS mean change ± SE	−0.96 ± 0.17	−1.65 ± 0.16	−2.28 ± 0.16
p Value		0.003	<0.001
Median % change	−40.0	−67.4	−81.8
p Value		<0.001	<0.001
No. treatment response (% yes)	266 (45)	267 (64)	267 (74)
p Value		<0.001	<0.001
	Secondary end points		
MVV/micturition:			
No. subjects	261	266	265
Baseline mean ± SD (ml)	159 ± 69	152 ± 60	156 ± 58
LS mean change ± SE (ml)	8.38 ± 4.06	16.5 ± 4.00	33.6 ± 4.04
p Value		0.150	<0.001
Daytime micturitions/24 hrs:			
No. subjects	266	267	267
Baseline mean ± SD	10.2 ± 3.3	10.7 ± 3.4	10.1 ± 2.9
LS mean change ± SE	−0.69 ± 0.16	−1.04 ± 0.16	−1.54 ± 0.16
p Value		0.107	<0.001
Median % change	−5.9	−11.1	−15.6
p Value		0.008	<0.001
Nocturnal micturitions/24 hrs:			
No. subjects LS mean change (median)	266 (251)	267 (246)	267 (244)
Baseline mean ± SD	2.0 ± 1.3	2.2 ± 1.6	1.9 ± 1.4
LS mean change ± SE	−0.39 ± 0.07	−0.58 ± 0.07	−0.55 ± 0.07
p Value		0.042	0.09
Median % change	−25.0	−33.3	−25.0
p Value		0.013	0.267
Urgency episodes/24 hrs:			
No. subjects	266	267	267
Baseline mean ± SD	11.4 ± 3.8	12.5 ± 4.1	11.6 ± 3.7
LS mean change ± SE	−0.79 ± 0.20	−1.91 ± 0.20	−2.30 ± 0.20
p Value		<0.001	<0.001
Median % change	−3.3	−16.3	−18.4
p Value		<0.001	<0.001
Continent days/wk:*,†			
No. subjects	205	228	218
Baseline mean ± SD	0.6 ± 1.3	0.7 ± 1.5	0.7 ± 1.4
LS mean change ± SE	1.31 ± 0.20	2.33 ± 0.19	2.80 ± 0.19
p Value		<0.001	<0.001

Median percent values derived from exploratory analysis and missing end of treatment data imputed using last observation carried forward method.
* Analysis including only subjects with 1 or greater UUI episode at baseline.
† Normalized from 3-day voiding diary.

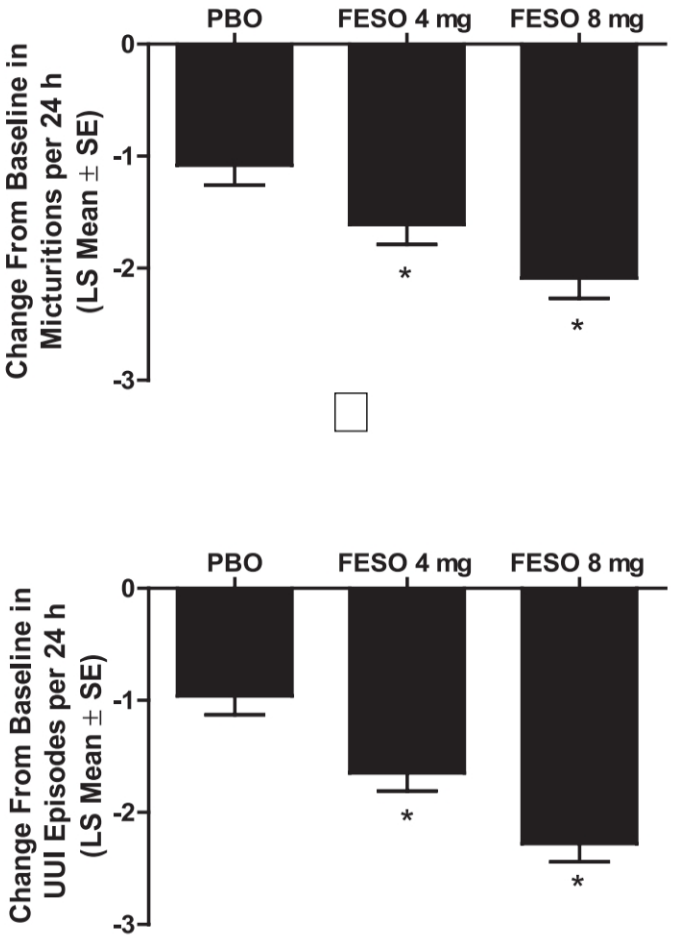

FIG. 3. LS mean change from baseline to trial end in number of micturitions and UUI episodes per 24 hours. Asterisk indicates $p < 0.05$ vs PBO.

group had a PVR of more than 200 ml. None of these cases required catheterization. Of the 11 subjects reporting urinary retention as an AE 1 was in the PBO group, 4 were in the 4 mg FESO group and 6 were in the 8 mg FESO group. All patients showed mild to moderate symptoms except the 1 male subject on PBO. Medication was interrupted, symptoms resolved and he continued in the study. Decreased urinary flow was reported in 1 male subject receiving 4 mg FESO, and hesitancy was reported in 2 male and 1 female subjects on 8 mg FESO, and in 1 female on 4 mg FESO. Urinary retention as an AE and/or increased PVR led to discontinuation in 1% of the subjects in the 4 mg FESO group (2 of 282, including 1 male and 1 female) and in the 8 mg FESO group (3 of 279, including 2 males and 1 female).

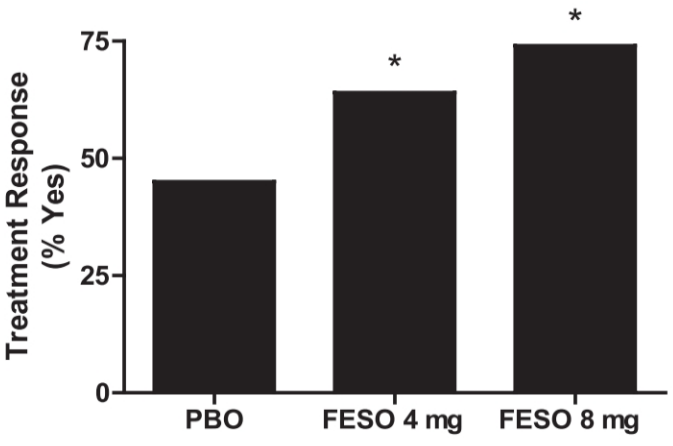

FIG. 4. Proportion of subjects at trial end with positive treatment response. Asterisk indicates $p < 0.001$ vs PBO.

TABLE 3. *Treatment emergent AEs*

AE	No. PBO (%)	No. 4 mg FESO (%)	No. 8 mg FESO (%)
Overall	271	282	279
Any AE	149 (55)	171 (61)	193 (69)
Dry mouth	19 (7)	45 (16)	99 (36)
Constipation	7 (3)	14 (5)	21 (8)
Urinary tract infection	11 (4)	10 (4)	15 (5)
Upper respiratory tract infection	7 (3)	12 (4)	9 (3)
Dry eye	0	2 (less than 1)	9 (3)
Headache	9 (3)	12 (4)	8 (3)
Nausea	6 (2)	3 (1)	7 (3)
Diarrhea	8 (3)	7 (3)	6 (2)
Sinusitis	6 (2)	3 (1)	6 (2)
Urinary retention	1 (less than 1)	4 (1)	6 (2)
Cough	3 (1)	6 (2)	4 (1)
Back pain	1 (less than 1)	7 (3)	2 (1)
Nasopharyngitis	7 (3)	10 (4)	2 (1)
Hypertension	6 (2)	7 (3)	0

Reported by 2% or greater of subjects in 1 or greater treatment group.

Only 1 of the 21 subjects with serious AEs experienced a serious AE (atrial fibrillation) that was deemed possibly related to study medication. This subject was found to have been on PBO. No deaths occurred during this trial.

No clinically relevant changes were noted in the mean change from baseline to end of study in systolic blood pressure, diastolic blood pressure or heart rate. The percent of subjects with a QT or corrected QT interval (Fridericia's formula) of greater than 450 milliseconds, or a change from baseline of 30 milliseconds or greater at the end of treatment was comparable in the active and PBO groups. The mean change in heart rate for PBO, and 4 and 8 mg FESO was 1, 3 and 4 bpm, respectively. There were no clinically relevant changes in laboratory parameters in the active and PBO treatment groups.

Discontinuations. Of 836 randomized subjects 681 (81%) completed the 12-week study. Overall 19% of subjects (155 of 836) discontinued the study prematurely. A total of 53 subjects withdrew because of AEs, including 4% on PBO (11 of 271), 6% on 4 mg FESO (17 of 282) and 9% on 8 mg FESO (25 of 279) (table 4). Of AEs leading to discontinuation dry mouth was given as the reason by 1% of subjects (3 of 282) on 4 mg FESO and by 1.8% (5 of 279) on 8 mg FESO. Constipation led to discontinuation in less than 1% of subjects (2 of 279, both female) on 8 mg FESO.

DISCUSSION

OAB is a widespread and chronic condition that has been shown to decrease subject health related quality of life and require long-term treatment.[15–17] In this study treatment with 4 or 8 mg FESO demonstrated statistically significant and clinically relevant improvements compared with placebo for OAB symptoms and it was also associated with a significantly higher treatment response. Treatment with 8 mg FESO resulted in significant decreases in the number of daytime micturitions, number of urgency episodes and continent days per week, and in significant increases in MVV per micturition.

TABLE 4. *AEs leading to discontinuation*

AE	No. PBO (%)	No. 4 mg FESO (%)	No. 8 mg FESO (%)
Overall	271	282	279
Dry mouth	1 (less than 1)	3 (1)	5 (2)
Urinary retention	0	2 (1)	3 (1)
Increased γ-glutamyl transferase	1 (less than 1)	1 (less than 1)	2 (1)
Constipation	0	0	2 (1)
Increased alanine aminotransferase	2 (1)	0	1 (1)
Headache	0	2 (1)	0
Hypertension	2 (1)	1 (less than 1)	0

In greater than 1 subject in any treatment group.

FESO at doses of 4 and 8 mg increased MVV per micturition by 8 and 25 ml, respectively, compared with PBO.

The magnitude of the improvement in symptoms in subjects treated with 4 mg FESO was generally consistent with that reported for tolterodine extended release.[9] More pronounced effects were apparent with the 8 mg dose of FESO, which would be expected based on the pharmacological relationship between tolterodine and FESO.

Dry mouth was the most commonly reported AE with increased incidence in the 8 mg FESO group. However, most occurrences were mild to moderate in nature and the rate of related discontinuations was low. The incidence of constipation with FESO was relatively low even at the higher FESO dose (5% and 8% for 4 and 8 mg, respectively, vs 3% for PBO). For example, in phase III trials of other antimuscarinics constipation was reported in 7% and 13% of subjects receiving 10 and 5 to 30 mg oxybutynin,[18] in 5% and 13% receiving 5 and 10 mg solifenacin (3% for PBO)[19] and in 15% and 21% receiving 7.5 and 15 mg darifenacin, respectively (6.2% for PBO).[20]

The limitations of this study are a lack of gender and ethnic diversity in a population that was primarily female and white. Efficacy and tolerability in other ethnic groups, a larger male population and subjects with neurogenic OAB must be confirmed in future studies. Similarly long-term efficacy and safety beyond 12 weeks must be determined and such trials are currently ongoing. The urgency scale used in the current trial allowed 4 choices, including none, mild, moderate and severe urgency with mild, moderate and severe counted equally as urgency episodes (see Appendix). Thus, an improvement in urgency from severe, as typically found in OAB, to mild, as in the normal desire to void, was not detected on analysis. The scale did not include UUI and, thus, the decrease in this ultimate expression of urgency was not measured. The robust efficacy of FESO for decreasing the number of UUI episodes and increasing MVV per micturition suggests that the smaller effect on the incidence of urgency was a reflection of how urgency was measured in this trial.

CONCLUSIONS

The 2 doses of FESO are safe and well tolerated. Each provides statistically significant and clinically relevant improvements in OAB symptoms, thus, allowing dose individualization. Furthermore, the higher 8 mg dose of FESO provides additional benefit compared with the lower dose, particularly for decreasing UUI episodes and increasing MVV per micturition, and it is well tolerated. Thus, FESO represents an alternative treatment modality in subjects with OAB.

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APPENDIX

Diary Definitions

Measurement	Definition
Number of micturitions (frequency) per 24 hours	Number of times a subject passed urine (*including* incontinence episodes) per day during the 3-day collection period.
Number of UUI episodes per 24 hours (among incontinent subjects)	Number of times a subject recorded a UUI episode per day within the 3-day collection period.
Treatment response, yes/no	The treatment response was derived from a 4-point Treatment Benefit scale: "My condition has been: 1=greatly improved; 2=improved; 3=not changed; 4=worsened, during treatment. The treatment response was set for "yes" if the answer was 1 or 2; response was set to "no" if the answer was 3 or 4.
MVV per micturition	MVV (ml) during the 1-day collection period.
Number of daytime micturitions	Number of times a subject passed urine during daytime (*including* incontinence episodes) per day within the 3-day collection period. Daytime was defined as the time between the subject getting up in the morning and the subject going to bed that evening. Any episodes occurring at the time of getting up in the morning or at the time of going to bed were attributed to daytime.
Number of nocturnal micturitions	Number of times a subject passed urine during sleeping time (*including* incontinence episodes) per day within the 3-day collection period. Sleeping time was defined as the time between the subject going to bed in the evening and getting up in the morning.
Number of urgency episodes per 24 hours	The number of times a subject recorded an urgency episode with or without incontinence per day within the 3-day collection period.
Severity of urinary urgency	Each episode was graded using the following 4-point scale: 1=None: Normal voiding, or "I felt no need to use the bathroom, but did." 2=Mild: "I could have postponed using the bathroom as long as necessary without fear of wetting myself." 3=Moderate: "I could have postponed using the bathroom for a short while without fear of wetting myself." 4=Severe: I could not postpone using the bathroom and had to rush to the bathroom in order not to wet myself."
Number of continence days per week (among incontinent subjects)	Number of times a subject had no incontinence episodes in a day within the 3-day collection period, normalized to a 7-day period.

Abbreviations and Acronyms

AE	=	adverse event
CYP	=	cytochrome P450
FESO	=	fesoterodine
5-HMT	=	5-hydroxymethyl tolterodine
LS	=	least squares
MVV	=	mean voided volume
OAB	=	overactive bladder
PBO	=	placebo
PVR	=	post-void residual urine
UUI	=	urgency urinary incontinence

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