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Incontinence

Clinical Efficacy, Safety, and Tolerability of Once-Daily Fesoterodine in Subjects with Overactive Bladder

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Abstract

Objective: To determine the efficacy, tolerability, and safety of fesoterodine in subjects with overactive bladder (OAB).
Methods: This was a multicentre, randomised, double-blind, placebo- and active-controlled trial with tolterodine extended release (ER) to assess the efficacy and safety of fesoterodine. Eligible subjects (≥18 yr) with increased micturition frequency and urgency and/or urgency urinary incontinence (UUI) were randomised to placebo, fesoterodine 4 mg, fesoterodine 8 mg, or tolterodine ER 4 mg for 12 wk. The primary efficacy variable was a change from baseline to week 12 in micturitions per 24 h. Co-primary end points included change from baseline to week 12 in UUI episodes per 24 h and Treatment Response (''yes'' or ''no,'' based on four-point treatment benefit scale). Secondary efficacy variables included mean volume voided per micturition, continent days per week, and number of urgency episodes.
Results: At the end of treatment, subjects taking fesoterodine 4 and 8 mg had significant ($p < 0.05$) and clinically relevant improvements versus placebo in the primary, co-primary, and most secondary efficacy variables. Tolterodine ER (active control) also provided significantly greater improvement than placebo for most efficacy variables, confirming the sensitivity of the study design. A more pronounced effect was observed with fesoterodine 8 mg at most end points.
Conclusions: Both doses of fesoterodine were significantly better than placebo in improving the symptoms of OAB and produced a significantly greater Treatment Response versus placebo. Efficacy was more pronounced with fesoterodine 8 mg compared with the other treatments. Active treatments were well tolerated.

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1. Introduction

Overactive bladder (OAB) syndrome is a collection of symptoms, in particular, urinary urgency with or without urgency urinary incontinence (UUI), usually accompanied by increased micturition frequency and nocturia [1]. OAB is a chronic condition occurring in both men and women, with a prevalence that increases with advancing age [2]. A recent population-based study performed in over 19,000 individuals in four European countries and Canada (the EPIC study [3]), using current International Continence Society definitions, determined the overall prevalence of OAB to be 12%, ranging from 7% to 10% in individuals <39 yr of age to almost 20% in those ≥60 yr of age.

Because the underlying cause of OAB is multifactorial and often undetermined, treatment modalities focus on symptomatic relief. Current treatment regimens include nonpharmacological (behavioural therapy, coping strategies, protective garments, barrier devices, pelvic floor stimulation, or sacral nerve stimulation) and pharmacological components [4]. The primary pharmacological treatments considered the mainstay for the relief of OAB symptoms are antimuscarinic drugs, which have demonstrated efficacy in improving OAB symptoms, but are associated with dose-dependent increases in antimuscarinic adverse effects, such as dry mouth, constipation, and blurred vision.

Data from phase 2 trials have suggested that fesoterodine, a new antimuscarinic drug in development, is an effective and well-tolerated therapy for OAB [5]. Fesoterodine acts functionally as a prodrug. It is rapidly and extensively hydrolysed by nonspecific esterases to 5-hydroxymethyl tolterodine. The conversion is rapid and virtually complete such that, after oral dosing, only the metabolite, not the parent compound, can be detected in patient plasma [6]. This active metabolite, responsible for the antimuscarinic activity of fesoterodine [7], is also the active metabolite of tolterodine, 5-hydroxymethyl tolterodine (5-HMT) [8–10]. Tolterodine is converted to 5-HMT by the cytochrome P450 (CYP) 2D6 enzyme system. Thus, the efficacy of conversion of tolterodine to 5-HMT is dependent on the activity and expression of CYP2D6 in patients. In contrast to tolterodine, the conversion of fesoterodine to 5-HMT bypasses the CYP system, although CYP3A4 and CYP2D6 are involved in subsequent inactivation of the active metabolite [11].

The objective of this trial was to investigate the efficacy, tolerability, and safety of fesoterodine 4 and 8 mg versus placebo in subjects with OAB. The study included a tolterodine ER 4 mg arm as an active control.

2. Methods

2.1. Study design

In this randomised, 12-wk treatment, double-blind, double-dummy, placebo- and active-controlled, parallel-arm, multicentre study, the efficacy, tolerability, and safety of fesoterodine were assessed in men and women with OAB. This phase 3 study was conducted at 150 sites in 19 countries (Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Spain, Sweden, Ukraine, the United Kingdom, South Africa, Australia, and New Zealand). The study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. The protocol was approved by respective ethics committees or institutional review boards, and all subjects gave written informed consent before the start of the study.

Subjects entered a 2-wk placebo run-in phase during which they received one capsule (tolterodine placebo) and one tablet (fesoterodine placebo) of placebo medication in the morning (Fig. 1). To ensure adequate blinding, placebo had to be given in both forms in the run-in phase. Once eligibility was established, subjects were randomised 1:1:1:1 to double-blind treatment (once daily in the morning) in one of the treatment arms for 12 wk: tolterodine ER 4 mg, fesoterodine 4 mg, fesoterodine 8 mg, or matching placebo. In the double-blind phase, placebo was given as a capsule to the fesoterodine group and as a tablet to the tolterodine group.

2.2. Subjects

2.2.1. Inclusion criteria

Subjects must have had a medical history of OAB symptoms with urinary urgency for ≥6 mo to enrol. Subjects had to be at least 18 yr of age with ≥8 micturitions per 24 h and either ≥6 urgency episodes or ≥3 UUI episodes per 24 h (symptoms were recorded in a 3-d diary). In addition, subjects had to indicate on a Likert scale that the condition caused them at least moderate

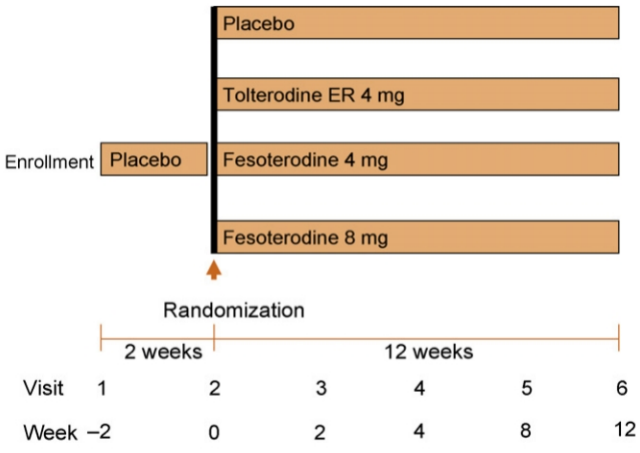

Fig. 1 – Study design. ER, extended release.

problems, which is almost identical to the subject perception of bladder condition [12]. After the start of the trial, the protocol was amended to ensure enrollment of the planned 80% of subjects with UUI at baseline; the amendment required ≥3 UUI episodes per 24 h in all remaining subjects. Women participating in the trial had to have a negative pregnancy test and use adequate contraception throughout the trial.

2.2.2. *Exclusion criteria*

Subjects were excluded who had lower urinary tract pathology that could, in the investigator's opinion, be responsible for urgency or incontinence (eg, genuine stress incontinence, bladder stones, interstitial cystitis, urothelial tumours), pelvic prolapse of grade III or higher, clinically relevant bladder outlet obstruction, polyuria (>3 l per 24 h), symptomatic or recurrent urinary tract infections, or postvoid residual (PVR) urine volume >100 ml. Subjects who were currently receiving treatment, were treated within 2 wk of screening visit with antimuscarinic agents, were treated within the past 4 wk with electrostimulation for bladder training, or had an active urinary tract infection or an underlying neurological disease responsible for their OAB were not included. Subjects who had clinically relevant cardiac arrhythmia and/or unstable angina or a QTcB interval >500 ms were not included.

2.3. *Efficacy analyses*

For assessment of efficacy, subjects were asked to complete a 3-d micturition diary during the placebo run-in phase before visit 2 and on the days immediately preceding treatment visits 3, 5, and 6. Subjects were also asked to record their micturition volumes on one of these 3 d. In the diaries, subjects recorded the time of each micturition and/or urgency episode, urine volume with each micturition, any episode of incontinence, and the severity of urgency: 1 = none (normal voiding); 2 = mild (could have postponed micturition for as long as necessary without fear of wetting myself); 3 = moderate (could have postponed micturition for a short while without fear of

Table 1 – Definitions of bladder diary variables

Measurement	Definition
Number of micturitions (frequency) per 24 h	Number of times a subject passed urine (including incontinence episodes).
Treatment Response, yes/no	Treatment Response was derived from a four-point treatment benefit scale: "My condition has been: 1 = greatly improved; 2 = improved; 3 = not changed; 4 = worsened, during treatment. 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.
Number of UUI episodes per 24 h (among incontinent subjects)	Number of times a subject recorded a UUI episode per day within the 3-d collection period.
MVV per micturition	MVV (ml) during the 1-d collection period.
Number of micturitions during daytime	Number of times a subject voluntarily passed urine during daytime (including incontinence episodes) per day within the 3-d 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 micturitions during sleeping time (nocturia)	Number of times a subject voluntarily passed urine during sleeping time (including incontinence episodes) per day within the 3-d 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 h	The number of times a subject recorded an urgency episode with or without incontinence per day within the 3-d collection period.
Severity of urinary urgency	Each episode was graded using the following four-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." The number of occurrences of each grade for each valid day during the 3-d collection period was counted and expressed as a percentage of the total number of episodes recorded on those valid days. The grade for the visit was set equal to the grade with the highest percentage of occurrences for that visit. If two or more grades had equal percentages, then the grade with the highest severity was used.
Number of continent days per week (among incontinent subjects)	Number of times a subject had no incontinence episodes in a day within the 3-d collection period, normalized to a 7-d period.

UUI, urgency urinary incontinence; MVV, mean volume voided.

wetting myself); 4 = severe (could not postpone micturition, had to rush to the toilet in order not to wet myself).

Primary efficacy end points were change from baseline to week 12 in micturitions per 24 h, change from baseline to week 12 in UUI episodes per 24 h, and Treatment Response. Treatment Response was derived from a four-category treatment benefit scale, whereby a score of 1 (greatly improved) or 2 (improved) was considered "yes," and a score of 3 (not changed) or 4 (worsened) was considered "no." The definition of Treatment Response and all other efficacy end points are listed in Table 1.

Secondary efficacy end points included mean volume voided per micturition, daytime micturitions per 24 h, nocturnal micturitions per 24 h, urgency episodes per 24 h, and continent days per week (calculated based on a 3-d diary).

2.4. *Safety and tolerability*

Safety and tolerability were assessed on the basis of the observation and assessment of adverse events (AEs). Seriousness, severity, and relatedness to treatment were assessed by the investigator. Safety assessments were conducted at each visit and after the safety follow-up.

Safety laboratory parameters included haematology and serum chemistry with hepatic and renal parameters. Changes deemed of clinical relevance were recorded as AEs. In addition, urinalysis parameters, vital signs, centrally read electrocardiogram (ECG), physical examination and urological/urogynecological examination, residual urinary volume (ml), and subject assessment of treatment tolerance using a four-grade scale were recorded.

2.5. *Statistical analyses*

The primary subject population for statistical analyses of efficacy was the full analysis set, which was defined as all subjects who were randomised, received any study medication, and for whom baseline and double-blind micturition data were available. Safety analyses were conducted on the safety set, which was defined as all subjects who took at least one dose of trial medication after randomisation. Demographic characteristics are also presented for this population.

Parametric analysis for continuous variables (change in micturition frequency, UUI episodes, etc) was performed with the use of an analysis of covariance model with treatment and region as factors and baseline value as a covariate; nonparametric sensitivity analysis was conducted with the use of Wilcoxon rank sum test. Binary data (Treatment Response) were analysed with the use of the normal approximation method. In an exploratory analysis, median percentage change from baseline to week 12 was calculated for diary end points, and statistical hypothesis testing was conducted for secondary end points.

A sequentially rejective closed-test procedure was applied to the primary variables to adequately account for multiplicity. A sequentially rejective closed-test procedure is one that performs the hypothesis tests in a sequential manner, and steps to the next test only if the previous test was significant and stops if the previous test was not significant. This kind of test procedure is a closed test if the multiple significance level α can be preserved. According to the requirements suggested by the US Food and Drug Administration, the test procedure started with micturition frequency per 24 h, performed the test of fesoterodine 8 mg compared with placebo for this variable, stepped down to test fesoterodine 4 mg versus placebo if the first test demonstrated statistical significance, and continued with the respective tests for the number of UUI episodes per 24 h. According to the requirements of the European Agency for the Evaluation of Medicinal Products, the test procedure considered micturition frequency per 24 h and Treatment Response simultaneously, tested fesoterodine 8 mg versus placebo for both variables first, and, in the case of a statistically significant result, continued to test the 4-mg dose versus placebo for both variables.

3. Results

3.1. *Subjects*

Subject disposition of the trial is shown in Fig. 2, and subject demographics are shown in Table 2. Of the 1135 subjects who entered the double-blind treatment phase, 1132 received study medication (two subjects from the placebo and one subject from the fesoterodine 8 mg were not treated); therefore, demographics were captured from the 1132 subjects enrolled and treated in the study. The population in this trial corresponded to the general clinical OAB populations in studies that have been previously reported. Subjects were approximately 57 yr of age and most were women (80%), with 75–81% of subjects reporting UUI in baseline diary. The mean time since first diagnosis or onset of OAB was 8–9 yr. Only 5–8% of subjects in any group had been diagnosed with OAB for less than 1 yr before enrollment; therefore, the population in this trial primarily comprised subjects with long-term, established OAB.

3.2. *Efficacy*

In subjects receiving tolterodine ER, changes from baseline in most end points, as well as Treatment Response, were statistically significantly greater than placebo, which demonstrated the sensitivity of the study design. Similarly, changes from baseline were statistically significant versus placebo for the primary and both co-primary efficacy variables, as well as most secondary end points in subjects receiving fesoterodine 4 or 8 mg. Efficacy end point data are shown in Table 3.

At the end of treatment, the mean number of micturitions per 24 h was significantly reduced from baseline in subjects receiving tolterodine ER (−1.73; $p = 0.001$ vs. placebo), fesoterodine 4 mg (−1.76; $p < 0.001$ vs. placebo), and fesoterodine 8 mg (−1.88; $p < 0.001$ vs. placebo).

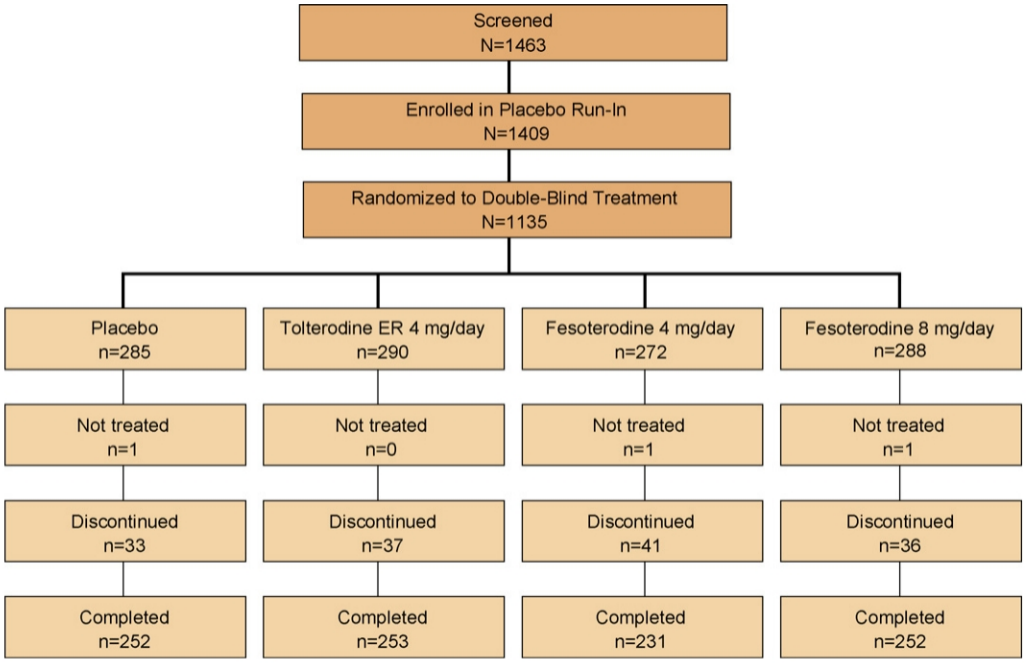

Fig. 2 – Subject disposition throughout the trial. ER, extended release.

Treatment with tolterodine ER resulted in significantly greater proportion of subjects who responded to treatment compared with placebo ($p < 0.001$). The proportion of subjects reporting a positive Treatment Response was significantly greater among subjects receiving fesoterodine 4 mg ($p < 0.001$) and fesoterodine 8 mg ($p < 0.001$) than placebo.

At the end of treatment, the mean reduction from baseline in UUI episodes per 24 h was significantly greater for subjects receiving tolterodine ER (−1.74;

Table 2 – Baseline demographics and clinical characteristics*

Parameter	PBO (n = 283)	TOL ER 4 mg (n = 290)	FESO 4 mg (n = 272)	FESO 8 mg (n = 287)
Age, yr (mean ± SD)	56.0 ± 13.7	57.7 ± 14.6	57.1 ± 13.2	55.6 ± 14.1
Sex, % (M/W)	19/81	22/78	19/81	19/82
Race, %				
White	98	98	96	98
Black	<1	0	0	1
Asian	2	2	2	1
Other	<1	<1	3	0
BMI, kg/m^2 (mean ± SD)	27.2 ± 5.2	27.5 ± 5.2	27.5 ± 5.5	27.1 ± 5.2
Duration of OAB symptoms, yr (mean ± SD)	7.9 ± 9.6	8.7 ± 10.1	9.0 ± 11.2	7.6 ± 8.4
Incontinence, %†	76	79	75	81
Previous drug treatment for OAB, n (%)	112 (40)	135 (47)	102 (38)	118 (41)
Oxybutynin	73 (26)	99 (34)	74 (27)	85 (30)
Tolterodine	47 (17)	48 (17)	40 (15)	37 (13)
Propiverine	12 (4)	17 (6)	9 (3)	15 (5)
Trospium	15 (5)	17 (6)	8 (3)	8 (3)
Flavoxate hydrochloride	5 (2)	5 (2)	2 (<1)	3 (1)

PBO, placebo; TOL ER, tolterodine extended release; FESO, fesoterodine; BMI, body mass index; OAB, overactive bladder; SD, standard deviation.

* Based on safety population, that is, all subjects who took ≥ 1 dose of medication.

† Based on FAS population.

Table 3 – Baseline* and change from baseline† to end of treatment (LOCF) in bladder diary efficacy variables

	Treatment group			
	PBO	TOL ER 4 mg	FESO 4 mg	FESO 8 mg
Primary end point				
Micturitions/24 h				
n	279	283	265	276
Baseline mean (SD)	12.0 (3.7)	11.5 (2.9)	11.6 (3.2)	11.9 (3.8)
LS mean (SE) change	−0.95 (0.16)	−1.73 (0.16)	−1.76 (0.17)	−1.88 (0.16)
p value		0.001	<0.001	<0.001
Median % change**	−11.1	−13.8	−16.7	−18.6
p value**		0.005	<0.001	<0.001
Co-primary end points				
Treatment Response, %				
n	279	283	265	276
Yes	53	72	75	79
p value		<0.001	<0.001	<0.001
UUI/24 h§				
n	211	223	199	223
Baseline mean (SD)	3.7 (3.1)	3.8 (3.1)	3.8 (3.4)	3.7 (3.0)
LS mean (SE) change	−1.14 (0.16)	−1.74 (0.16)	−1.95 (0.17)	−2.22 (0.16)
p value		0.008	0.001	<0.001
Median % change**	−50.0	−70.0	−80.0	−87.5
p value**		0.105	0.001	<0.001
Secondary end points				
MVV, ml				
n‡	278	282	265	275
Baseline mean (SD)	150.2 (52.0)	154.3 (52.9)	160.0 (59.5)	153.9 (56.9)
LS mean (SE) change	9.37 (3.33)	23.64 (3.31)	27.72 (3.41)	33.62 (3.35)
p value		0.002	<0.001	<0.001
Daytime micturitions/24 h				
n	279	283	265	276
Baseline mean (SD)	10.1 (3.5)	9.5 (2.7)	9.6 (2.9)	9.9 (3.2)
LS mean (SE) change	−0.60 (0.14)	−1.35 (0.14)	−1.37 (0.15)	−1.48 (0.14)
p value		<0.001	<0.001	<0.001
Median % change**	−9.5	−13.6	−14.3	−16.9
p value**		0.003	0.001	<0.001
Nocturnal micturitions/24 h				
n‡	279 (254)	283 (266)	265 (247)	276 (255)
Baseline mean (SD)	1.8 (1.2)	2.0 (1.2)	1.9 (1.3)	2.0 (1.6)
LS mean (SE) change	−0.32 (0.06)	−0.40 (0.06)	−0.39 (0.06)	−0.39 (0.06)
p value		0.336	0.394	0.418
Median % change**	−26.8	−25.0	−28.6	−23.1
p value**		0.815	0.982	0.896
Number of urgency episodes/24 h				
n‡	279	283	265 (264)	276
Baseline mean (SD)	11.4 (4.0)	11.0 (3.4)	11.0 (4.2)	11.5 (4.2)
LS mean (SE) change	−1.07 (0.19)	−2.03 (0.19)	−1.88 (0.20)	−2.36 (0.20)
p value		<0.001	0.003	<0.001
Median % change**	−11.1	−16.0	−17.6	−19.1
p value**		0.004	0.002	<0.001
Continent days per week§,***				
n	211	223	199	223
Baseline mean (SD)	0.8 (1.5)	0.6 (1.3)	0.8 (1.6)	0.6 (1.3)
LS mean (SE) change	2.07 (0.20)	2.48 (0.20)	2.84 (0.21)	3.32 (0.19)
p value		0.139	0.007	<0.001

LOCF, last observation carried forward; PBO, placebo; TOL ER, tolterodine extended release; FESO, fesoterodine; SD, standard deviation; LS, least squares; SE, standard error; UUI, urinary urgency incontinence; MVV, mean volume voided per micturition.
Based on FAS population. All median % values and related statistical comparisons are derived from an exploratory analysis.
* Baseline values are presented as mean ± SD.
† Change from baseline is presented as LS means ± SE.
‡ *n* = number of subjects from mean change analysis; (*n*) = number of subjects from median % change analysis.
** Exploratory analysis.
§ Analysis included only subjects with at least one urgency incontinence episode at baseline.
*** Weekly calculation was based on estimates from 3-d diary data.

Table 4 – Treatment-emergent adverse events occurring in ≥ 2% of subjects in any group*

Adverse event, *n* (%)	PBO (*n* = 283)	TOL ER 4 mg (*n* = 290)	FESO 4 mg (*n* = 272)	FESO 8 mg (*n* = 287)
Any adverse event	107 (38)	144 (50)	135 (50)	167 (58)
Dry mouth	20 (7.1)	49 (16.9)	59 (21.7)	97 (33.8)
Constipation	4 (1.4)	8 (2.8)	9 (3.3)	13 (4.5)
Headache	14 (4.9)	14 (4.8)	12 (4.4)	7 (2.4)
Dry eye	0	1 (<1)	6 (2.2)	12 (4.2)
Nasopharyngitis	7 (2.5)	10 (3.4)	8 (2.9)	5 (1.7)
Fatigue	1 (<1)	10 (3.4)	1 (<1)	1 (<1)
Influenza	6 (2.1)	2 (<1)	9 (3.3)	2 (<1)
Dry throat	0	3 (1)	1 (<1)	8 (2.8)
Dizziness	7 (2.5)	4 (1.4)	4 (1.5)	3 (1.0)
↑Alanine aminotransferase	1 (<1)	0	2 (<1)	6 (2.1)
Nausea	1 (<1)	6 (2.1)	1 (<1)	4 (1.4)

PBO, placebo; TOL ER, tolterodine extended release; FESO, fesoterodine.
* Based on safety population, that is, all subjects who took ≥ 1 dose of medication.

$p = 0.008$ vs. placebo), fesoterodine 4 mg (−1.95; $p = 0.001$ vs. placebo), and fesoterodine 8 mg (−2.22; $p < 0.001$ vs. placebo).

Active treatment significantly increased mean volume voided (MVV) from baseline ($p \leq 0.002$) compared with placebo. The increases in MVV were 2.5, 3.0, and 3.6 times greater than placebo in subjects receiving tolterodine ER, fesoterodine 4 mg, or fesoterodine 8 mg, respectively.

Statistically significant improvements were also observed in active treatment groups versus placebo in daytime micturitions and number of urgency episodes. Significant improvements in change from baseline compared with placebo in number of continent days per week were observed in subjects receiving fesoterodine 4 mg or 8 mg (Table 3).

3.3. *Safety and tolerability*

All treatment-emergent AEs, irrespective of relationship to study medication are shown in Table 4. The most frequent AE in all treatment groups was dry mouth, which was mild or moderate in most cases, except for 3% of subjects taking fesoterodine 8 mg, who reported severe dry mouth. Other than dry mouth, no AE occurred in more than 5% of subjects. In this trial, no episodes of acute urinary retention requiring catheterisation were reported. There were no clinically relevant changes in vital signs, such as heart rate or blood pressure, laboratory, or ECG parameters. Mean change in heart rate was 2.8 bpm in the tolterodine ER group, 3.3 bpm in the fesoterodine 4-mg group, and 3.9 bpm in the fesoterodine 8-mg group. The change in heart rate in the placebo group was 0.8 bpm.

Overall, 3.2% of subjects (36 of 1132) discontinued the study prematurely owing to an AE: placebo, 2% (6 of 283); tolterodine ER 4 mg, 3% (9 of 290); fesoterodine 4 mg, 3% (7 of 272); and fesoterodine 8 mg, 5% (14 of 287) during the treatment phase. No single AE resulted in withdrawal of ≥1% of subjects in any treatment group. Among the reasons for discontinuation was urinary retention, which occurred in <1% (1 of 272) and 1% (2 of 287), respectively, in the fesoterodine 4 mg and fesoterodine 8 mg groups but led to discontinuation in only 1 subject (receiving fesoterodine 4 mg). One subject in the tolterodine ER 4-mg group and 1 subject in the fesoterodine 8-mg group withdrew because of dry mouth. Two patients in the fesoterodine 8-mg group withdrew because of unspecified mucosal dryness.

4. Discussion

This trial has demonstrated that treatment with fesoterodine 4 and 8 mg resulted in statistically significant and clinically relevant improvements in bothersome OAB symptoms and end points, including increased micturition frequency, urgency, UUI, and MVV, and the treatment was associated with a significantly greater Treatment Response rate compared with placebo. Treatment effects appeared to be more pronounced with fesoterodine 8 mg than with tolterodine ER 4 mg or fesoterodine 4 mg, especially regarding UUI episodes and volume voided per micturition, which may have clinical relevance considering the similar tolerability profiles among active treatment groups.

Fesoterodine 4 and 8 mg were generally well tolerated, and discontinuations because of an AE were low in all groups. AEs observed in any of the active treatment groups were low and similar to placebo, except for dry mouth, which occurred at a higher rate with fesoterodine 8 mg. However, only 1 subject each from the fesoterodine 8 mg and tolterodine ER 4 mg groups withdrew from the trial because of dry mouth. As expected with

antimuscarinic therapy, dry mouth and constipation [13], respectively, were the first and second most common adverse events reported. Dry mouth was the most frequently reported class effect in this trial, occurring in 7%, 17%, 22%, and 34% of subjects treated with placebo, tolterodine ER 4 mg, fesoterodine 4 mg, and fesoterodine 8 mg, respectively; most cases were mild. Because constipation may cause or exacerbate urinary symptoms [14], consideration of this AE is important in the treatment of OAB. In this study, the incidence of constipation was low, with 1.4% in subjects receiving placebo, 2.8% in subjects receiving tolterodine ER 4 mg, 3.3% in subjects receiving fesoterodine 4 mg, and 4.5% in subjects receiving fesoterodine 8 mg. With other antimuscarinic agents, the incidence of constipation in phase 3 trials is reported as 7–13% in subjects receiving immediate-release oxybutynin [15], 6% treated with tolterodine ER [16], 5–13% in subjects treated with solifenacin [17], and 8–21% in subjects receiving darifenacin [18]. The higher rates of constipation in subjects treated with darifenacin compared with other antimuscarinic agents is most likely attributable to its relative selectivity for the M_3 receptor [19], which mediates contraction of intestinal smooth muscle [18].

In this trial, an apparent placebo effect was observed, whereby treatment with placebo for 12 wk resulted in marked (albeit not significant) improvements from baseline. In contrast, significant effects from baseline to end point were observed among active treatment groups for the primary and co-primary efficacy variables. A marked placebo effect on treatment outcomes is generally expected in similarly designed, randomised controlled trials in OAB subjects [20]. These effects, although more strongly correlated with subjective rather than objective measures, may be due at least in part to the use of micturition diaries, which draws attention to micturition habits [20]. Trials with run-in periods, such as the present trial, often show less of a placebo effect than those without run-in periods, perhaps because the initial attention required to fill out the micturition diary is attenuated by the time the active treatment begins [20].

Data regarding subjects with OAB of neurogenic origin treated with fesoterodine were not collected in this study. Studies in a broader subject population, including looking at greater ethnic diversity, more men, the very frail elderly (although this study did not specify an upper age limit), and the paediatric population would be helpful in providing greater breadth of knowledge relevant to real-life clinical practice. An ongoing, long-term, open-label extension trial will provide additional information regarding long-term continuous use of fesoterodine under clinical conditions closer to real life.

5. Conclusions

Fesoterodine 4 and 8 mg demonstrated statistically significant and clinically relevant improvements in most OAB symptoms and were associated with a significantly higher Treatment Response compared with placebo. Efficacy results were generally more pronounced with the 8-mg dose. Tolterodine ER 4 mg was also more effective than placebo on most end points, confirming the sensitivity of the study design. Both doses of fesoterodine were safe and well tolerated, with a low overall incidence of AEs, which was similar to that with tolterodine ER. The incidence of dry mouth was higher in subjects receiving fesoterodine 8 mg; however, most cases were mild to moderate. Discontinuations because of adverse events were low. These findings are in line with expectations based on the pharmacological relationship between fesoterodine and tolterodine [7]. The availability of two doses of fesoterodine presents an additional clinical benefit in that dose flexibility allows OAB treatment to be tailored to individual subject needs.

Conflicts of interest

Professor Chapple is a consultant/investigator/speaker for Astellas (Yamanouchi), Pfizer Inc, Novartis, and Schwarz BioSciences GmbH, and has acted as a consultant for UCB. Professor Van Kerrebroeck is an investigator and lecturer for Astellas, Eli-Lilly, Ferring, Pfizer Inc, and Novartis. Professor Tubaro is a consultant/investigator/lecturer for Pfizer Inc, GlaxoSmithKline, and Novartis. Drs. Haag-Molkenteller, Forst, and Massow were all employees of Schwarz BioSciences GmbH at the time the study was performed. Drs. Wang and Brodsky are employees of Pfizer Inc.

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