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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Toviaz® / Fesoterodine

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT 00561951

PROTOCOL NO.: A0221005

PROTOCOL TITLE: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Finding Study to Evaluate the Efficacy, Tolerability and Safety of Fesoterodine in Comparison to Placebo in Patients with Overactive Bladder

Study Center(s): Subjects were randomized at 69 centers (Hong Kong 3 centers, Japan 55 centers, Korea 5 centers, Taiwan 6 centers). One center in Taiwan did not enroll subjects and 1 center in Japan did not randomize subjects.

Study Initiation and Completion Dates: 27 November 2007 to 15 January 2009

Phase of Development: Phase 2

Study Objective(s):

The primary objective of the study was to assess the efficacy of fesoterodine 4 mg and 8 mg as compared to placebo in subjects with Overactive Bladder (OAB) syndrome after 12 weeks of treatment and to determine the recommended dose in subjects with OAB.

The secondary objectives were the following: to assess the safety and tolerability of fesoterodine 4 mg and 8 mg as compared to placebo in subjects with OAB after 12 weeks of treatment; to investigate pharmacokinetics of 5-HMT, the active metabolite of fesoterodine in patients with OAB who take fesoterodine 4 mg and 8 mg.

Comparisons of the results for efficacy and safety between this study and previous studies conducted to support registration in the US and Europe were also planned.

METHODS

Study Design: This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study. The trial consisted of a 2-week single-blind placebo run-in period and a 12-week double-blind treatment period and required a total of 6 in-clinic visits (Figure S1).

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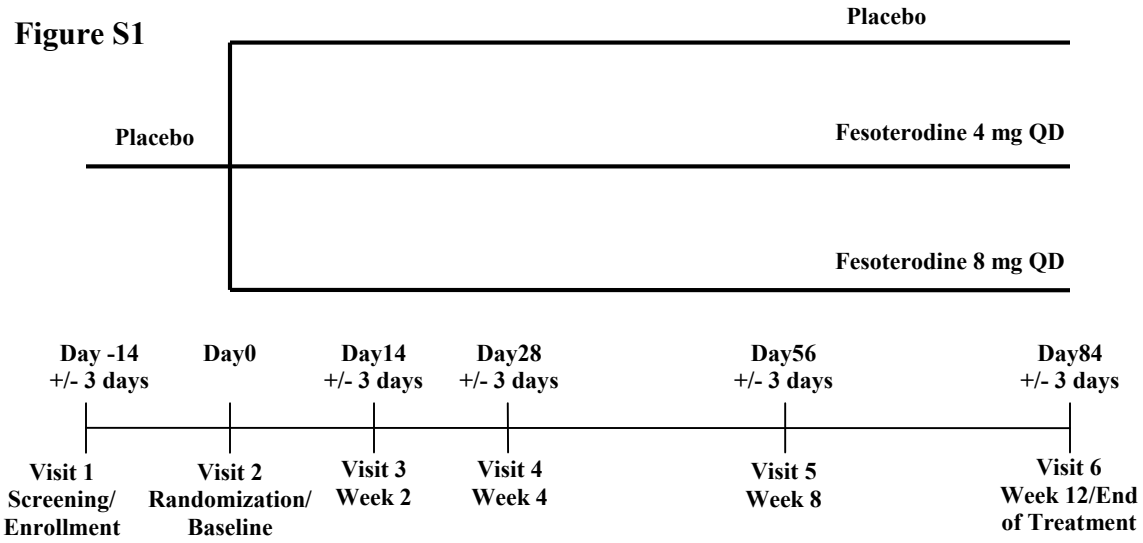
Subjects were initially screened at Visit 1 (Screening/Enrollment visit). Eligible subjects were enrolled at the same visit into the run-in period and received single-blind placebo for 2 weeks. The subject completed a 3-day micturition diary for 3 consecutive days during the 7 days prior to Visit 2 (Randomization/Baseline visit). The diary captured each micturition, including urgency urinary incontinence (UUI) episodes and urgency episodes, along with the corresponding time of the events. Each subject also measured and recorded the urine voided volume of any 1 day and the first micturition of the next day during 3-day diary period.

At Visit 2, the diary data and screening laboratory data were checked against the randomization criteria. Only OAB subjects with UUI defined as subjects with 3 UUI episodes during the 3-day diary period prior to randomization, who met the criteria were randomized to one of three treatment arms (fesoterodine 4 mg, fesoterodine 8 mg or placebo) in a 1:1:1 ratio. Randomized subjects received the assigned double-blind treatment for 12 weeks.

Figure S1



Number of Subjects (Planned and Analyzed): In this trial, 900 subjects were required for the analysis population. Six hundred subjects in Japan and 300 subjects in other Asian countries were planned to be enrolled. In total 951 subjects were analyzed for safety and 929 subjects met the required criteria to contribute to the efficacy analysis.

Diagnosis and Main Criteria for Inclusion: Adult males and females with a ≥6-month history of symptoms or signs of OAB syndrome with urinary urgency and increased urinary frequency were included in this study. Subjects had symptoms of UUI for ≥1 month prior to Visit 1. At least 3 UUI episodes documented during the 3-day micturition diary period and ≥8 micturitions per 24 hours confirmed on each day of the 3-day micturition diary period prior to Visit 2 were required for participation in the study.

Study Treatment: Fesoterodine 4 mg, 8 mg and a matching placebo were used. Fesoterodine placebo tablets were indistinguishable in appearance from fesoterodine 4 mg and 8 mg tablets. Subjects received one single blind fesoterodine placebo tablet orally for 2

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weeks from the morning of the day after Visit 1 with water every morning with or without food. Eligible subjects then received one double blind fesoterodine 4 mg tablet, 8 mg tablet, or placebo tablet orally from the morning of the day after Visit 2 with water every morning with or without food for a total of 12 weeks.

Efficacy Evaluations: Subjects completed a micturition diary for 3 consecutive days during the 7 days preceding each visit. In this diary, "a day" was defined as the period between the time subjects woke up in the morning to actively start the day through the time the subjects woke up the next morning. Subjects were also required to complete questionnaires including KHQ, OAB-q, and PPBC at Visits 2 and 6.

Pharmacokinetic Evaluations: For pharmacokinetic analysis, blood samples (4 mL) were collected in tubes containing lithium heparin at Visits 4 and 6. At each visit, 2 blood samples were taken at least 30 minutes apart. The investigator was to confirm the dosing time of the 3 administrations immediately prior to blood sampling at each visit.

Safety Evaluations: Adverse events were recorded on the case report form (CRF) from the time the subject took at least one dose of study treatment after randomization through the last subject visit. Serious adverse events required immediate notification to the sponsor or its designated representative beginning from the time that the subject provided informed consent, through and including 28 calendar days after the last administration of the study treatment. Clinical laboratory tests were performed by the central laboratory at Visits 1, 4, and 6. Blood pressure and pulse rate were recorded at all clinic visits. Twelve-lead electrocardiogram and residual urine volume measurements were performed at Visits 1, 2, 4, and 6.

Statistical Methods: The full analysis set (FAS) was the primary analysis set for the efficacy analyses. The FAS included all subjects who took at least one dose of study drug after randomization and had efficacy observations at both baseline and post baseline. The primary endpoint was change from baseline in mean number of UUI episodes per 24 hours at Week 12. The comparisons of fesoterodine 8 mg with placebo and fesoterodine 4 mg with placebo were tested by using analysis of covariance (ANCOVA) model with the treatment group, region (Japan, Korea, Taiwan and Hong Kong) as fixed effects and baseline values as a covariate. A closed testing procedure was used in order to control the probability of a type 1 error. Significance level was α=0.05. Last observation carried forward (LOCF) was used to impute missing data at Week 12 for the FAS analysis. The same analyses were performed for change from baseline in mean number of micturitions, urgency episodes, incontinence episodes, and night-time micturitions per 24 hours at Week 12. The descriptive statistics for the change from baseline to Week 12 were performed the primary endpoint and all secondary endpoints including micturition diary, KHQ, OAB-q, and PPBC.

The pharmacokinetic analysis set consisted of the safety set subjects who had pharmacokinetic data recorded. For each subject, 4 plasma samples to measure plasma 5-HMT concentration were obtained during the trial. Two samples were taken at each of the following visits: Visit 4 (Day 28 ± 3), and Visit 6/early termination (Day 84 ± 3). All concentration data collected during the trial were listed. Population pharmacokinetic analysis of 5-HMT was planned.

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The safety analysis set included all subjects who took at least one dose of study drug after randomization. The safety assessment was based on the incidence, severity and nature of treatment emergent adverse events recorded during the treatment period. However, subjects who were not randomized but received the randomized study drug were included in the safety analysis set, if they have post-dosing safety data. Safety data were evaluated using descriptive statistics. Standard output tables were produced for adverse events, vital signs, ECG data and lab data in accordance with Pfizer Data Standards (PDS). The Medical Dictionary for Regulatory Activities (MedDRA), version 11.1 was used for coding of adverse events.

The analysis plan and report for comparisons of the results for efficacy and safety between this study and previous studies conducted to support registration in the US and Europe which was one of the objectives of this study were generated separately from this report.

RESULTS

Subject Disposition and Demography: A total of 1232 subjects were enrolled and entered the placebo run-in period. Out of them, 951 subjects were assigned to the double-blind treatment. All 951 subjects were treated. There was 1 subject (ID 10051026) who was not randomized but took the study drugs for the double-blind treatment period. This subject was counted as being assigned to the double-blind treatment and was also included in the safety analysis set. All other 950 subjects were randomized (Table S1).

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Table S1. Subject Disposition and Subjects Evaluated [Number (%) of Subjects]

	Placebo	Fesoterodine 4 mg	Fesoterodine 8 mg
Enrolled in placebo run-in= 1232			
Assigned to double-blind treatment[a]	318	320	313
Treated	318	320	313
Completed study	285 (89.6)	286 (89.4)	281 (89.8)
Discontinued study	33 (10.4)	34 (10.6)	32 (10.2)
Adverse events[b]	12 (3.8)	15 (4.7)	15 (4.8)
Lack of efficacy	5 (1.6)	3 (0.9)	2 (0.6)
Lost to follow-up	1 (0.3)	1 (0.3)	0
Subject no longer willing to participate in study	10 (3.1)	9 (2.8)	10 (3.2)
Other	5 (1.6)	6[c] (1.9)	5 (1.6)
Analyzed for efficacy			
FAS	309 (97.2)	314 (98.1)	306 (97.8)
Analyzed for pharmacokinetics	312 (98.1)	312 (97.5)	310 (99.0)
Analyzed for safety			
Adverse events	318 (100.0)	320 (100.0)	313 (100.0)
Laboratory data	315 (99.1)	314 (98.1)	312 (99.7)

[a] Included the subjects who were randomized and took at least 1 dose of study drug and 1 subject in the placebo group who was not randomized but took the study drugs for the double-blind treatment period during the run-in period due to being wrongly dispensed.
[b] Consisted of subjects who discontinued due to no treatment emergent adverse event (1 subject each in all treatment groups) and treatment emergent adverse event.
[c] One subject (fesoterodine 4 mg) who met a withdrawal criterion was counted as discontinuation due to 'Other reason'. This event was also reported as treatment emergent adverse event (ie. electrocardiogram QT prolonged). Therefore, the study drug action for this adverse event was reported as permanently discontinued.

All demographic characteristics were comparable across the 3 treatment groups (Table S2)

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Table S2. Demographic Characteristics in the Safety Analysis Set [Number (%) of Subjects]

	Placebo	Fesoterodine 4 mg	Fesoterodine 8 mg	Total
Sex [n (%)]	318	320	313	951
Male	67 (21.1)	69 (21.6)	58 (18.5)	194 (20.4)
Female	251 (78.9)	251 (78.4)	255 (81.5)	757 (79.6)
Age (years)				
<18	0	0	0	0
18-44	62 (19.5)	73 (22.8)	41 (13.1)	176 (18.5)
45-64	165 (51.9)	144 (45.0)	155 (49.5)	464 (48.8)
≥65	91 (28.6)	103 (32.2)	117 (37.4)	311 (32.7)
Mean (SD)	56.7 (13.5)	57.2 (14.2)	58.8 (13.4)	57.6 (13.7)
Range	20-88	21-86	20-87	20-88
Race [n (%)]				
Asian	318 (100.0)	320 (100.0)	313 (100.0)	951 (100.0)
Region [n (%)]				
Japan	248 (78.0)	250 (78.1)	249 (79.6)	747 (78.5)
Korea	45 (14.2)	46 (14.4)	44 (14.1)	135 (14.2)
Taiwan	21 (6.6)	21 (6.6)	19 (6.1)	61 (6.4)
Hong Kong	4 (1.3)	3 (0.9)	1 (0.3)	8 (0.8)
Weight (kg)				
Mean (SD)	57.6 (10.6)	57.2 (10.4)	57.9 (10.6)	57.6 (10.5)
Range	34.0-104.0	34.7-93.5	31.2-107.0	31.2-107.0
Height (cm)				
Mean (SD)	157.2 (8.3)	158.1 (8.0)	156.1 (7.5)	157.2 (8.0)
Range	137.0-186.1	137.0-177.8	133.1-177.5	133.1-186.1
Body Mass Index				
Mean (SD)	23.3 (3.8)	22.8 (3.5)	23.7 (3.9)	23.3 (3.7)
Range	15.5-38.2	14.7-35.0	14.6-39.7	14.6-39.7

Descriptive summaries of the mean number of UUI episodes and micturitions per 24 hours at baseline are provided in Table S3. Those values at baseline were comparable across the 3 treatment groups.

Table S3. Mean Number of UUI Episodes and Micturitions per 24 hours at Baseline, FAS

	Placebo		Fesoterodine 4 mg		Fesoterodine 8 mg	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Number of UUI Episodes per 24 hours	309	2.24 (1.872)	314	2.23 (1.814)	306	2.26 (1.788)
Number of Micturitions per 24 hours	309	11.13 (2.494)	314	11.32 (2.576)	306	11.36 (2.560)

SD= standard deviation, UUI= urgency urinary incontinence.

Efficacy Results: Both fesoterodine 4 mg/day and 8 mg/day demonstrated statistically significant decreases in the mean number of UUI episodes per 24 hours at Week 12 (primary endpoint) compared to placebo. Dose dependent responses to fesoterodine 4 mg/day and 8 mg/day were also observed (Table S4).

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Table S4. ANCOVA of Change from Baseline in Mean Number of UUI Episodes per 24 Hours at Week 12, FAS-LOCF

Treatment (N)	LS Mean	95% CI for the LS Mean	Contrast	Treatment difference	95% CI for the difference	p-value[a]
Placebo (309)	−1.01	(−1.31, −0.71)	—	—	—	—
Fesoterodine 4 mg (314)	−1.35	(−1.65, −1.05)	4 mg vs Placebo	−0.34	(−0.56, −0.13)	0.002
Fesoterodine 8 mg (306)	−1.40	(−1.70, −1.09)	8 mg vs Placebo	−0.39	(−0.60, −0.17)	<0.001

ANCOVA=analysis of covariance, CI=confidence interval, FAS=full analysis set, LOCF=last observation carried forward, LS=least squares, UUI= urgency urinary incontinence, vs=versus.
Baseline value for each subject was defined as a value of Week 0.
Analysis of covariance model with the treatment group, region as fixed effects and baseline values as a covariate was used.
[a] The closed testing procedure was used in order to control the probability of a type 1 error. The significance level was 0.05 (2-sided).

Both fesoterodine 4 mg/day and 8 mg/day demonstrated statistically significant decreases in the mean number of micturitions per 24 hours at Week 12 compared to placebo. Dose dependent responses to fesoterodine 4 mg/day and 8 mg/day were also observed. Numerical improvements were observed with fesoterodine 4 mg/day and 8 mg/day in other secondary micturition diary endpoints compared to placebo. Out of them, the mean numbers of urgency and incontinence episodes per 24 hours at Week 12 were statistically significant (Table S5). Fesoterodine 4 mg/day and 8 mg/day increased (improved) mean voided volume per micturition in a dose-dependent manner during this study.

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Table S5. ANCOVA of Change from Baseline in Mean Number of Micturitions, Urgency Episodes, Incontinence Episodes, and Night-Time Micturitions per 24 Hours at Week 12, FAS-LOCF

Treatment (N)	LS Mean	95% CI for the LS Mean	Contrast	Treatment difference	95% CI for the difference	p-value [a]
Micturitions						
Placebo (309)	−0.59	(−1.08, −0.10)	—	—	—	—
Fesoterodine 4 mg (314)	−1.15	(−1.64, −0.67)	4 mg vs Placebo	−0.56	(−0.91, −0.22)	0.002
Fesoterodine 8 mg (306)	−1.25	(−1.75, −0.76)	8 mg vs Placebo	−0.66	(−1.01, −0.32)	<0.001
Urgency Episodes						
Placebo (309)	−1.00	(−1.60, −0.40)	—	—	—	—
Fesoterodine 4 mg (314)	−1.65	(−2.25, −1.05)	4 mg vs Placebo	−0.65	(−1.07, −0.22)	0.003
Fesoterodine 8 mg (306)	−1.66	(−2.27, −1.05)	8 mg vs Placebo	−0.66	(−1.09, −0.23)	0.002
Incontinence Episodes						
Placebo (309)	−0.88	(−1.22, −0.54)	—	—	—	—
Fesoterodine 4 mg (314)	−1.27	(−1.61, −0.93)	4 mg vs Placebo	−0.39	(−0.63, −0.14)	0.002
Fesoterodine 8 mg (306)	−1.15	(−1.50, −0.80)	8 mg vs Placebo	−0.27	(−0.52, −0.03)	0.030
Night-Time Micturitions						
Placebo (243)	−0.18	(−0.41, 0.06)	—	—	—	—
Fesoterodine 4 mg (256)	−0.21	(−0.44, 0.02)	4 mg vs Placebo	−0.04	(−0.18, 0.11)	0.624
Fesoterodine 8 mg (257)	−0.29	(−0.52, −0.05)	8 mg vs Placebo	−0.11	(−0.26, 0.03)	0.129

ANCOVA=analysis of covariance, CI=confidence interval, FAS=full analysis set, LOCF=last observation carried forward, LS=least squares, vs=versus.
Baseline value for each subject was defined as a value of Week 0.
Analysis of covariance model with the treatment group, region as fixed effects and baseline values as a covariate was used.
[a] The significance level was 0.05 (2-sides).

In each domain of KHQ, subjects receiving fesoterodine demonstrated improvement from baseline that was greater than that of placebo, except for general health perception. In each domain of OAB-q, the improvement in the symptom bother score was more marked in the fesoterodine 4 and 8 mg groups than the placebo group. An improvement in all 4 HRQL domains (coping, concern, sleep, and social) and total HRQL score was also more marked in the fesoterodine 4 and 8 mg groups than the placebo group. The minimum PPBC score at baseline was "some moderate problems, score 4" across the 3 treatment groups due to one of the inclusion criteria. At Week 12, "some minor problems, score 3" or "some very minor problems, score 2" or even "no problems at all, score 1" were found in 71.2% in the placebo group, and in 77.7% and 78.1% in the fesoterodine 4 and 8 mg/day groups, respectively.

Pharmacokinetic Results: Population pharmacokinetic analysis results will be summarized in a separate report.

Safety Results: Overall summary of adverse events is shown in Table S6.

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Table S6. Overall Summary of Treatment-Emergent Adverse Events

	Placebo N=318	Fesoterodine 4 mg N=320	Fesoterodine 8 mg N=313
Number of adverse events			
All causality	215	320	397
Treatment-related	112	203	304
Number (%) of subjects			
Adverse events			
All causality	130 (40.9)	192 (60.0)	222 (70.9)
Treatment-related	81 (25.5)	150 (46.9)	192 (61.3)
Serious adverse events			
All causality	5 (1.6)	3 (0.9)	0
Treatment-related	2 (0.6)	1 (0.3)	0
Severe adverse events			
All causality	4 (1.3)	6 (1.9)	3 (1.0)
Treatment-related	2 (0.6)	4 (1.3)	3 (1.0)
Discontinuations due to adverse events			
All causality	11 (3.5)	15 (4.7)	14 (4.5)
Treatment-related	8 (2.5)	9 (2.8)	13 (4.2)
Temporary discontinuations due to adverse events			
All causality	1 (0.3)	6 (1.9)	6 (1.9)
Treatment-related	0	2 (0.6)	2 (0.6)

Subjects were counted only once per treatment in each row, except for the number of adverse events.
One subject, who was not randomized but took the study drugs for the double-blind treatment period during the run-in period due to being wrongly dispensed, was summarized in the actual treatment (placebo group).

All-causality adverse events that occurred in ≥2% of subjects in any treatment group are summarized in Table S7.

Table S7 Adverse Events Reported by ≥2% of Subjects in Any Treatment Group [Number (%) of Subjects]

MedDRA System Organ Classes Preferred Term (version 11.1)	Placebo N=318	Fesoterodine 4 mg N=320	Fesoterodine 8 mg N=313
Gastrointestinal disorders			
Constipation	15 (4.7)	17 (5.3)	33 (10.5)
Diarrhoea	3 (0.9)	7 (2.2)	3 (1.0)
Dry mouth	31 (9.7)	93 (29.1)	158 (50.5)
Infections and infestations			
Cystitis	4 (1.3)	12 (3.8)	7 (2.2)
Nasopharyngitis	21 (6.6)	19 (5.9)	22 (7.0)
Nervous system disorders			
Dizziness	1 (0.3)	7 (2.2)	2 (0.6)
Headache	5 (1.6)	10 (3.1)	4 (1.3)
Renal and urinary disorders			
Dysuria	0	2 (0.6)	14 (4.5)
Residual urine	5 (1.6)	7 (2.2)	2 (0.6)

If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row.

Most of the all-causality adverse events were mild or moderate in severity. The percentage of subjects with severe adverse events was low and similar among groups. The percentage of subjects who permanently discontinued the study due to adverse events was similar among

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the treatment groups. The adverse events leading to discontinuation are summarized in Table S8.

Table S8 Adverse Events Leading to Discontinuation [Number (%) of Subjects]

MedDRA System Organ Classes Preferred Term (version 11.1)	Placebo N=318	Fesoterodine 4 mg N=320	Fesoterodine 8 mg N=313
Cardiac disorders			
Palpitations	1 (0.3)	0	0
Eye disorders			
Vision blurred	2 (0.6)	0	0
Visual acuity reduced	0	0	1 (0.3)
Gastrointestinal disorders			
Abdominal discomfort	1 (0.3)	0	0
Abdominal pain	1 (0.3)	0	0
Diarrhoea	1 (0.3)	2 (0.6)	1 (0.3)
Dry mouth	2 (0.6)	1 (0.3)	7 (2.2)
Nausea	0	1 (0.3)	0
Vomiting	0	1 (0.3)	0
General disorders and administration site conditions			
Chest pain	0	1 (0.3)	0
Malaise	1 (0.3)	0	0
Pain	0	0	1 (0.3)
Hepatobiliary disorders			
Hepatic function abnormal	0	0	1 (0.3)
Infections and infestations			
Cystitis	0	1 (0.3)	0
Tinea pedis	1 (0.3)	0	0
Urinary tract infection	0	2 (0.6)	0
Injury, poisoning and procedural complications			
Pelvic fracture	0	1 (0.3)	0
Investigations			
Alanine aminotransferase increased	2 (0.6)	0	1 (0.3)
Aspartate aminotransferase increased	1 (0.3)	0	0
Blood creatine phosphokinase increased	0	1 (0.3)	0
Electrocardiogram QT prolonged	0	2 (0.6)	0
Nervous system disorders			
Autonomic nervous system imbalance	1 (0.3)	0	0
Cerebral infarction	1 (0.3)	0	0
Dizziness	0	2 (0.6)	0
Headache	1 (0.3)	1 (0.3)	0
Somnolence	1 (0.3)	0	0
Psychiatric disorders			
Depression	0	2 (0.6)	0
Renal and urinary disorders			
Dysuria	0	0	2 (0.6)
Respiratory, thoracic and mediastinal disorders			
Asthma	0	1 (0.3)	0
Dyspnoea	1 (0.3)	0	0
Skin and subcutaneous tissue disorders			
Eczema	0	0	1 (0.3)

The serious adverse events are summarized in Table S9.

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Table S9 Serious Adverse Events [Number (%) of Subjects]

MedDRA System Organ Classes Preferred Term (version 11.1)	Placebo N=318	Fesoterodine 4 mg N=320	Fesoterodine 8 mg N=313
Gastrointestinal disorders			
Abdominal pain	1 (0.3)	0	0
Diarrhoea	1 (0.3)	0	0
Vomiting	1 (0.3)	0	0
General disorders and administration site conditions			
Pyrexia	1 (0.3)	0	0
Infections and infestations			
Abscess	1 (0.3)	0	0
Cellulitis	1 (0.3)	0	0
Urinary tract infection	0	1 (0.3)	0
Injury, poisoning and procedural complications			
Pelvic fracture	0	1 (0.3)	0
Road traffic accident	0	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma	1 (0.3)	0	0
Nervous system disorders			
Cerebral infarction	1 (0.3)	0	0
Reproductive system and breast disorders			
Pelvic pain	0	1 (0.3)	0

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Only 1 serious adverse event (urinary tract infection) out of the 3 serious adverse events that occurred in the fesoterodine treated subjects was considered to be treatment-related by the investigator. This event resolved. No deaths were reported in this study.

Overall, the frequency of laboratory test abnormalities was low and similar among the treatment groups. The number of subjects who permanently discontinued the study due to adverse events associated with laboratory test abnormalities was small and similar among the treatment groups (2 subjects in the placebo group, and 1 subject each in the fesoterodine 4 and 8 mg groups, respectively). There were no adverse events leading to temporary discontinuations or serious adverse events, which were associated with laboratory test abnormalities.

No clinically relevant changes or trends were apparent in the mean changes from baseline for systolic blood pressure and diastolic blood pressure. A small increase from baseline in the mean pulse rate and heart rate at Week 12 was observed in subjects receiving fesoterodine. An increase in heart rate is a known effect of antimuscarinic drugs. ECG results did not suggest evidence of an increased risk following treatment with fesoterodine. The mean increases in residual urine volume were small and not clinically significant in each treatment group (3.54 mL in the placebo group, and 8.62 mL and 10.47 mL in the fesoterodine 4 and 8 mg groups, respectively).

CONCLUSION(S): This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study in subjects with OAB.

Both fesoterodine 4 mg/day and 8 mg/day demonstrated statistically significant decreases in the mean number of UUI episodes (primary endpoint) and micturitions per 24 hours at Week

12 compared to placebo and dose dependent responses to fesoterodine 4 mg/day and 8 mg/day were observed. Fesoterodine 4 mg/day and 8 mg/day were also found to be more effective in most of the secondary endpoints compared to placebo.

Fesoterodine 4 mg/day and 8 mg/day had a favorable safety profile and were generally well tolerated compared to placebo in this study. The percentage of subjects who permanently discontinued study due to adverse events was similar among the treatment groups and was less than 5%. Most of the adverse events were mild or moderate in severity. The most frequently reported adverse events included known adverse events for antimuscarinic drugs including dry mouth and constipation. These adverse events were more common in subjects treated with fesoterodine than placebo and were more frequently reported in the fesoterodine 8 mg group than the 4 mg group.

Overall, both fesoterodine 4 mg/day and 8 mg/day demonstrated a greater treatment effect than placebo. Both fesoterodine doses were generally well tolerated compared to placebo in this study. The safety and efficacy results in this study support the conclusion that fesoterodine 4 mg/day and fesoterodine 8 mg/day could be recommended for OAB patients.

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