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

PROTOCOL NO.: A0221007

PROTOCOL TITLE: A 12-Week, Multicenter, Open-Label, Single-Arm Study to Evaluate the Effects of Fesoterodine on Treatment Satisfaction and Symptom Relief in Overactive Bladder Patients

Study Centers: A total of 59 centers took part in the study and randomized subjects 23 centers in United States, 7 centers in Germany, 6 centers in Republic of Korea, 5 centers each in Belgium, Slovakia, and Ukraine, 4 centers in Czech Republic, 2 centers each in Costa Rica and Poland.

Study Initiation Date and Final Completion Date: 18 January 2007 to 11 October 2007

Phase of Development: Phase 3b

Study Objectives: Primary Objective:

- To evaluate the effect of fesoterodine on subject satisfaction and overactive bladder (OAB) symptom relief in OAB subjects who were dissatisfied with their prior therapy with tolterodine.

Secondary Objectives:

- To evaluate the effects of fesoterodine on quality of life (QoL) and secondary micturition diary endpoints in OAB subjects who were dissatisfied with their prior therapy with tolterodine.

- To evaluate tolerability and safety of fesoterodine in OAB subjects who were dissatisfied with their prior therapy with tolterodine.

METHODS

Study Design: This was a 12-week, multicenter, international, open-label, single-arm study with flexible dose escalation. Following a 2-week Screening period, subjects with persistent OAB symptoms (as defined by their diary responses) who were dissatisfied with their previous treatment with tolterodine or tolterodine extended release (ER) during the 2 years prior to Screening and were at least moderately bothered by OAB symptoms at Baseline and met all other entry criteria were enrolled. Subjects were treated with fesoterodine 4 mg once

daily (QD) for the first 4 weeks of treatment. At Week 4, based upon a discussion between the subjects and the Investigators of efficacy and tolerability as reported by the subjects, the Investigator either increased the dose of fesoterodine to 8 mg QD for those who desired greater symptom improvement and reported good tolerability, or continued the subjects on the 4 mg QD dose, for the remaining 8 weeks of the study. No dose adjustments were allowed during the remaining 8 weeks of the study. The study required 5 in-clinic visits including a Screening visit, Baseline/Enrollment visit, Week 1 visit, Week 4 visit, and end-of-study visit (Week 12 or early termination [ET]). The timing of procedures and visits is summarized in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

Activities & Forms to be Completed	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening Week -2 (±5 Days)	Baseline Week 0	End of Week 1 (-1 to +3 Days)	End of Week 4 (±5 Days)	End of Study Week 12 (±5 Days) or Early Termination
Written informed consent	X				
Demographics & medical history	X				
Sitting blood pressure & pulse rate	X	X	X	X	X
Physical exam & 12-lead ECG	X				
Inclusion/exclusion criteria	X	X			
Blood draw (hematology and chemistry)	X				
Urine dipstick test	X				
Urine pregnancy test for women of child bearing potential	X				
Prior treatment satisfaction question (pTSQ)	X				
Treatment satisfaction question (TSQ)					X
"Satisfaction with OAB Control" module of OAB-S					X
Patient perception of bladder condition (PPBC)		X		X	X
Urgency perception scale (UPS)		X		X	X
Overactive bladder questionnaire (OAB-q)		X			X
Dispense bladder diary (5-day)	X	X	X	X	
Evaluation of bladder diary (5-day)		X	X	X	X
Adverse events[a]		X	X	X	X
Concomitant medication	X	X	X	X	X
Concomitant non-drug treatment/procedures	X	X	X	X	X
Assess overall compliance			X	X	X
Dose assessment[b]				X	
Dispense study medication		X		X	
Study medication return/count			X	X	X
Subject disposition page					X

CRF = case report form; ECG = electrocardiogram; OAB = overactive bladder; QD = once daily.

a. Serious adverse events were to be reported once informed consent had been obtained. Serious and non-serious adverse events were collected (recorded on CRF) once the subject had taken at least 1 dose of study medication.

b. Based upon a discussion between the subjects and the investigators of efficacy and tolerability reported by the subjects, the investigator either increased the dose to 8 mg QD for those who desired greater symptom improvement and reported good tolerability, or continued the subjects on 4 mg QD dose, for the remaining 8 weeks of the study.

Number of Subjects (Planned and Analyzed): Assuming that 90% of enrolled subjects would contribute data to the full analysis set, a total of 400 subjects were planned to be enrolled into this study. A total of 595 subjects were actually screened, and 516 subjects were randomized to treatment. Due to rapid enrollment the number of final enrolled subjects was higher than originally targeted.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 years and older with OAB who presented with OAB symptoms (≥8 micturitions and ≥3 urgency episodes per 24 hours documented in the Baseline micturition diary) who were dissatisfied with their prior therapy with tolterodine.

Subjects with any contraindication to fesoterodine usage, eg, urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or known hypersensitivity to the drug or its ingredients, subjects with significant hepatic and renal disease or other significant unstable diseases, and subjects with OAB symptoms caused by neurological conditions, known pathologies of urinary tract, etc were excluded from the study.

Study Treatment: This was an open-label study. Fesoterodine was supplied as 4 mg tablets and 8 mg tablets in blister packages. All enrolled subjects were treated with fesoterodine 4 mg QD for 4 weeks, followed by either 4 mg QD or 8 mg QD for the remaining 8 weeks of the study. The decision to maintain or increase the dose was based on a discussion between the subject and the Investigator regarding drug efficacy and tolerability.

Efficacy Endpoints: Primary Endpoints:

- Percentage of subjects reporting satisfaction (including 'very satisfied' and 'somewhat satisfied') with their current OAB treatment using the treatment satisfaction question at Week 12.
- Change in mean number of micturition episodes per 24 hours at Week 12 relative to Baseline.
- Change in mean number of urgency urinary incontinence (UUI) episodes per 24 hours at Week 12 relative to the Baseline in subjects with a Baseline of UUI ≥1 episode(s) during the 5-day micturition diary period.
- Change in mean number of urgency episodes per 24 hours at Week 12 relative to Baseline (Urgency episodes are defined as those with Bladder Sensation Scale rating of ≥3 in the diary).

Secondary Endpoints:

- Micturition Diary:
    - Change in mean number of micturitions per 24 hours at Weeks 1 and 4 relative to Baseline.

- Percent change of micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of nighttime micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Percent change of nighttime micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of UUI episodes per 24 hours at Weeks 1 and 4 relative to Baseline in subjects with a Baseline of UUI ≥1 episode(s) during the 5-day micturition diary period.
- Percent change of UUI episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline in subjects with a Baseline of UUI ≥1 episode(s) during the 5-day micturition diary period.
- Change in mean number of urgency episodes per 24 hours at Weeks 1 and 4 relative to Baseline (Urgency episodes are defined as those with Bladder Sensation Scale rating of ≥3 in the diary).
- Percent change of urgency episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline (Urgency episodes are defined as those with Bladder Sensation Scale rating of ≥3 in the diary).
- Change in the mean and sum rating on the Bladder Sensation Scale at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of severe urgency episodes per 24 hours (severe urgency episodes are defined as those with bladder sensation scale rating ≥4) at Weeks 1, 4, and 12 relative to Baseline.
- Percent change of severe urgency episodes per 24 hours (severe urgency episodes are defined as those with bladder sensation scale rating ≥4) at Weeks 1, 4, and 12 relative to Baseline.

- Patient Perception of Bladder Condition (PPBC):
  - Change in PPBC at Weeks 4 and 12 relative to Baseline.
- Patient Perception of Urgency Scale (PPUS):
  - Change in PPUS at Weeks 4 and 12 relative to Baseline.
- Overactive Bladder Questionnaire (OAB-q):
  - Change in total score of OAB-q at Week 12 relative to Baseline.

  - Change in total score of each domain of OAB-q at Week 12 relative to Baseline.

- "Satisfaction with OAB Control" module of OAB treatment satisfaction questionnaire (OAB-S):

  - Total score at Week 12.

Safety Evaluations: Incidence of adverse events was monitored from first dose of study medication until 7 days after last dose of study medication. All serious adverse events (SAEs) were recorded from signing of informed consent until 30 days post-study participation. Vital signs (blood pressure and pulse rate) were measured at each visit. Physical examination, electrocardiogram, and blood samples for hematology and serum chemistry were performed at screening only.

Statistical Methods: The Full analysis set (FAS) included all subjects who took at least 1 dose of assigned study drug and contributed data to at least 1 Baseline or post-baseline efficacy assessment. The Safety set included all subjects who took at least 1 dose of study drug. The analysis of efficacy parameters was based on the FAS. The analysis of the first primary endpoint was also performed on the safety set to support the robustness of conclusions drawn from the primary analysis based on the FAS.

A 2-sided paired t-test was performed at the 5% level of significance for each of the 3 diary primary endpoints. Efficacy was claimed only when all 3 diary endpoints demonstrated statistical significance in change from Baseline to Week 12.

The treatment satisfaction endpoint was summarized by frequency and percentage with a 95% confidence interval (CI) around the point estimate.

Secondary endpoints were defined to analyze the results obtained with the micturition diary, PPBC, UPS, OAB-q and OAB-S in more detail. Descriptive summary statistics and paired t-tests for the change from Baseline to Week 12 were performed as appropriate.

Safety data were evaluated using descriptive statistics. The Medical Dictionary for Regulatory Activities (MedDRA), Version 10.1 was used for coding of adverse events.

RESULTS

Subject Disposition and Demography: Of the 595 subjects screened, 516 subjects were assigned to and received study treatment (Table 2). Of those, 463 subjects (89.7%) completed the study. A total of 257 subjects (about 50%) opted to increase to fesoterodine 8 mg QD at the Week 4 visit.

A total of 53 subjects (10.3%) were discontinued from the study. The most frequent reasons for discontinuation (for 5.6% of subjects) were adverse events related to the study drug.

All 516 treated subjects were included in the FAS and the Safety set for analysis.

Table 2. Subject Disposition

Variables	Number (%) of Subjects	
Screened	595	
Assigned to study treatment	516	
Treated[a]	516	(100)
Completed	463	(89.7)
Discontinued[b]	53	(10.3)
Related to study drug	33	(6.4)
Adverse event	29	(5.6)
Lack of efficacy	4	(0.8)
Not related to study drug	20	(3.9)
Adverse event	7	(1.4)
Lost to follow-up	2	(0.4)
Other[c]	4	(0.8)
Subject defaulted[d]	7	(1.4)

a. Received at least 1 dose of study treatment.
b. Discontinuations occurring outside the lag period (30 days) have been attributed to the last study treatment received.
c. Other: "protocol violation".
d. Subject defaulted: "subject no longer willing to participate in study".

The majority of subjects were white (76.6%), female (77.1%) and non-smokers (66.1%; Table 3). The average age was 59.6 years, with females being about 6 years younger than males (58.3 versus 64.0 years). The average weights were 84.0 kg and 73.4 kg for males and females, respectively. Most of the female subjects had been pregnant at least once and were menopausal at the time of entering the study.

Table 3. Demographic Characteristics

Variables	Male		Female		Total	
Number of Subjects [n, (%)]	118	(22.9)	398	(77.1)	516	(100)
Age (years)						
<18 [n, (%)]	0		0		0	
18-44 [n, (%)]	6	(5.1)	70	(17.6)	76	(14.7)
45-64 [n, (%)]	49	(41.5)	176	(44.2)	225	(43.6)
≥65 [n, (%)]	63	(53.4)	152	(38.2)	215	(41.7)
Mean (SD)	64.0	(11.9)	58.3	(13.8)	59.6	(13.6)
Range	19-83		19–90		19–90	
Race [n, (%)]						
White	92	(78.0)	303	(76.1)	395	(76.6)
Black	5	(4.2)	5	(1.3)	10	(1.9)
Asian	21	(17.8)	76	(19.1)	97	(18.8)
Other	0		14	(3.5)	14	(2.7)
Weight (kg)[a]						
Mean (SD)	84.0	(16.5)	73.4	(16.9)	75.8	(17.4)
Range	44.0-140.6		41.0-158.7		41.0–158.7	
Body Mass Index (kg/m²)[a]						
Mean (SD)	27.6	(4.8)	28.0	(6.1)	27.9	(5.8)
Range	16.4–47.8		16.6–54.9		16.4–54.9	
Smoking status [n, (%)]						
Never smoked	51	(43.2)	290	(72.9)	341	(66.1)
Smoker	20	(16.9)	39	(9.8)	59	(11.4)
Ex-Smoker	47	(39.8)	69	(17.3)	116	(22.5)
Menstrual status [n, (%)]						
Menarche			71	(17.8)		
Perimenopause			22	(5.5)		
Menopause			304	(76.4)		
Obstetrical history [n, %][b]						
Pregnancies			348	(87.4)		
Vaginal deliveries			317	(79.7)		
C-sections			42	(10.6)		
UUI based on diary at Baseline [n, (%)]						
UUI episodes =0	96	(81.4)	164	(41.2)	260	(50.4)
UUI episodes >0	22	(18.6)	234	(58.8)	256	(49.6)

n = number of subjects with pre-specified criteria; N = total number of subjects; SD = standard deviation; UUI = urgency urinary incontinences.
a. N for weight and body mass index was 513 (116 male and 397 female).
b. n for obstetrical history: number of subjects with at least 1 event.

Efficacy Results:

Primary Endpoints: Changes from Baseline to Week 12 were statistically significant for the 3 primary micturition diary endpoints (change in mean number of micturitions, UUI episodes, and urgency episodes per 24 hours; Table 4). The magnitude of improvement (both mean changes and median percent changes from Baseline) increased from Week 1 through Week 12.

Table 4. Change in Mean Number of Micturitions, UUI Episodes and Urgency Episodes per 24 Hours at Week 12 Relative to Baseline

Micturitions	**N=514[a]**	
Baseline mean (SD)	12.7	(3.9)
Week 12 mean (SD)	9.7	(3.4)
Numerical change from Baseline to Week 12		
Mean (SD)	-3.0	(3.1)
95% CI for mean	-3.2, -2.7	
p-value[b]	<0.0001	
UUI episodes	**N=256[a,c]**	
Baseline mean (SD)	2.3	(2.8)
Week 12 mean (SD)	0.6	(1.3)
Numerical change from Baseline to Week 12		
Mean (SD)	-1.7	(2.4)
95% CI for mean	-2.0, -1.4	
p-value[b]	<0.0001	
Urgency episodes	**N=514[a]**	
Baseline mean (SD)	10.0	(4.5)
Week 12 mean (SD)	5.0	(4.7)
Numerical change from Baseline to Week 12		
Mean (SD)	-5.0	(4.8)
95% CI for mean	-5.4, -4.5	
p-value[b]	<0.0001	

CI = confidence interval; LOCF = last observation carried forward; SD = standard deviation; UUI = urgency urinary incontinence.

a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 12 (LOCF).

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

c. Restricted to subjects with UUI at Baseline >0.

Nearly 80% of subjects responding reported satisfaction with their current OAB treatment with fesoterodine 4 mg or 8 mg QD at Week 12 (Table 5).

Table 5. Percentage of Subjects Reporting Satisfaction With Their Current OAB Treatment at Week 12

Treatment Satisfaction Question	**Primary Endpoint Analysis N=474[a]**	
	N	**%**
Satisfied (95% confidence interval)	378	79.7 (75.8, 83.3)
Neither dissatisfied nor satisfied	42	8.9
Dissatisfied	54	11.4

N = total number of subjects; n = number of subjects with pre-specified criteria.

a. Number of subjects in the full analysis set with non-missing value at Week 12.

Secondary Endpoints:

Change in Number of Micturitions per 24 Hours Relative to Baseline: A numerical decrease in mean number of micturitions per 24 hours relative to Baseline was visible already at Week 1 and Week 4. The magnitude of changes increased from Week 1 to Week 4 and Week 12 (Table 6).

Table 6. Change in Micturitions per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline

Week 1	**N=503[a]**	
Baseline mean (SD)	12.6	(3.6)
Week 1 mean (SD)	11.2	(3.6)
Mean numerical change from Baseline (SD)	-1.3	(2.2)
Median percent change from Baseline (min, max)	-9.5%	(-62.5, 49.3)
Week 4	**N=514[a]**	
Baseline mean (SD)	12.7	(3.9)
Week 4 mean (SD)	10.3	(3.7)
Mean numerical change from Baseline (SD)	-2.3	(2.7)
Median percent change from Baseline (min, max)	-17.0%	(-69.3, 45.2)
Week 12	**N=514[a]**	
Baseline mean (SD)	12.7	(3.9)
Week 12 mean (SD)	9.7	(3.4)
Mean numerical change from Baseline (SD)	-3.0	(3.1)
p-value[b]	<0.0001	
Median percent change from Baseline (min, max)	-22.4%	(-84.6, 96.4)

LOCF = last observation carried forward; min = minimum; max = maximum; SD = standard deviation.
a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 (LOCF) or Week 12 (LOCF).
b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Percent changes in micturitions per 24 hours at Weeks 1, 4 and 12 relative to Baseline were also calculated. The number of micturitions decreased by a median percentage of 9.5% at Week 1, 17.0% at Week 4 and 22.4% at Week 12.

Change in Number of Nocturnal Micturitions per 24 Hours Relative to Baseline: A numerical decrease in mean number of nocturnal micturitions per 24 hours relative to Baseline was visible at all 3 time points. The magnitude of change increased from Week 1 to Week 4 and Week 12 (Table 7).

Table 7. Change in Nocturnal Micturitions per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline

Week 1	**N=503[a]**	
Baseline mean (SD)	2.6	(1.5)
Week 1 mean (SD)	2.2	(1.5)
Mean numerical change from Baseline (SD)	-0.4	(0.9)
Median percent change from Baseline (min, max)	-13.0%	(-100.0, 366.7)
Week 4	**N=514[a]**	
Baseline mean (SD)	2.6	(1.6)
Week 4 mean (SD)	1.9	(1.5)
Mean numerical change from Baseline (SD)	-0.7	(1.1)
Median percent change from Baseline (min, max)	-25.0%	(-100.0, 600.0)
Week 12	**N=514[a]**	
Baseline mean (SD)	2.6	(1.6)
Week 12 mean (SD)	1.8	(1.4)
Mean numerical change from Baseline (SD)	-0.8	(1.2)
p-value[b]	<0.0001	
Median percent change from Baseline (min, max)	-31.3%	(-100.0, 600.0)

LOCF = last observation carried forward; min = minimum; max = maximum; SD = standard deviation.

a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 and Week 12 (LOCF).

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Percent changes in nocturnal micturitions per 24 hours at Week 1, Week 4 and Week 12 relative to Baseline were also calculated. The number of nocturnal micturitions decreased by a median percentage of 13.0% at Week 1, 25.0% at Week 4 and 31.3% at Week 12.

Change in Number of UUI Episodes per 24 Hours: A numerical decrease in mean number of UUI episodes (ie, micturitions with Urinary Sensation Scale rating =5) per 24 hours relative to Baseline was visible already at Week 1 and Week 4. This analysis included only subjects with UUI >0 at Baseline. The magnitude of changes increased from Week 1 to Week 4 and Week 12 (Table 8).

Table 8. Change in UUI Episodes per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline

Week 1		**N=251[a]**
Baseline mean (SD)	2.2	(2.8)
Week 1 mean (SD)	1.3	(2.7)
Mean numerical change from Baseline (SD)	-1.0	(1.8)
Median percent change from Baseline (min, max)	-75.0%	(-100.0, 1500.0)
Week 4		**N=256[a]**
Baseline mean (SD)	2.3	(2.8)
Week 4 mean (SD)	0.8	(1.8)
Mean numerical change from Baseline (SD)	-1.4	(2.1)
Median percent change from Baseline (min, max)	-100.0%	(-100.0, 471.4)
Week 12		**N=256[a]**
Baseline mean (SD)	2.3	(2.8)
Week 12 mean (SD)	0.6	(1.3)
Mean numerical change from Baseline (SD)	-1.7	(2.4)
p-value[b]	<0.0001	
Median percent change from Baseline (min, max)	-100.0%	(-100.0, 1400.0)

LOCF = last observation carried forward; min = minimum; max = maximum; SD = standard deviation; UUI = urgency urinary incontinence.

a. Number of subjects in the full analysis set with Baseline UUI >0 and non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 (LOCF).

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Percent changes relative to Baseline were also calculated. The number of UUI episodes per 24 hours decreased by a median percentage of 75.0% at Week 1 and 100.0% at Weeks 4 and 12.

Change in Number of Urgency Episodes per 24 Hours Relative to Baseline: A numerical decrease in mean numbers of urgency episodes per 24 hours relative to Baseline was visible already at Week 1 and Week 4. The magnitude of change increased from Week 1 to Week 4 and Week 12 (Table 9 and Table 4).

Table 9. Change in Urgency Episodes per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline

Week 1		**N=503[a]**
Baseline mean (SD)	9.9	(4.3)
Week 1 mean (SD)	7.8	(4.8)
Mean numerical change from Baseline (SD)	-2.1	(3.4)
Median percent change from Baseline (min, max)	-21.1%	(-100.0, 159.1)
Week 4		**N=514[a]**
Baseline mean (SD)	10.0	(4.5)
Week 4 mean (SD)	6.3	(4.9)
Mean numerical change from Baseline (SD)	-3.7	(4.0)
Median percent change from Baseline (min, max)	-36.3%	(-100.0, 172.2)
Week 12		**N=514[a]**
Baseline mean (SD)	10.0	(4.5)
Week 12 mean (SD)	5.0	(4.7)
Mean numerical change from Baseline (SD)	-5.0	(4.8)
p-value[b]	<0.0001	
Median percent change from Baseline (min, max)	-56.8%	(-100.0, 116.7)

LOCF = last observation carried forward; min = minimum; max = maximum; SD = standard deviation.

a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 (LOCF).

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Percent changes relative to Baseline were also calculated. The number of urgency episodes per 24 hours decreased by a median percentage of 21.1% at Week 1, 36.3% at Week 4 and 56.8% at Week 12.

Change in Number of Severe Urgency Episodes per 24 Hours Relative to Baseline: Severe urgency episodes were defined as those with Urinary Sensation Scale rating ≥4. A numerical decrease in mean number of episodes relative to Baseline was evident at all-time points assessed. The magnitude of change increased from Week 1 to Week 4 and Week 12 (Table 10).

Table 10. Change in Severe Urgency Episodes per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline

Week 1		**N=435[a]**
Baseline mean (SD)	5.0	(4.4)
Week 1 mean (SD)	3.2	(4.2)
Mean numerical change from Baseline (SD)	-1.8	(3.1)
Median percent change from Baseline (min, max)	-50.0%	(-100.0, 3300.0)
Week 4		**N=442[a]**
Baseline mean (SD)	5.0	(4.4)
Week 4 mean (SD)	2.2	(3.4)
Mean numerical change from Baseline (SD)	-2.8	(3.8)
Median percent change from Baseline (min, max)	-79.2%	(-100.0, 3000.0)
Week 12		**N=442[a]**
Baseline mean (SD)	5.0	(4.4)
Week 12 mean (SD)	1.5	(2.7)
Mean numerical change from Baseline (SD)	-3.5	(4.1)
p-value[b]	<0.0001	
Median percent change from Baseline (min, max)	-93.5%	(-100.0, 2100.0)

LOCF = last observation carried forward; min = minimum; max = maximum; SD = standard deviation.
a. Number of subjects in the full analysis set with Baseline severe urgency episodes >0 and non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 and Week 12 (LOCF).
b. The p-value was based on a paired t-test comparing Baseline with post-baseline values.

Percent changes relative to Baseline were also calculated. The number of severe urgency episodes per 24 hours decreased by a median percentage of 50.0% at Week 1, 79.2% at Week 4 and 93.5% at Week 12.

Change in the Mean and Sum Rating on the Urinary Sensation Scale Relative to Baseline:
Subjects were asked to rate their feeling of urgency associated with each micturition episode using the Urinary Sensation Scale provided in their diaries. The scale ranges from 1 "no feeling of urgency" to 5 "unable to hold, leak urine." A decrease in rating thus indicated an improvement with respect to urgency symptoms. The mean rating was calculated as the sum of rating scores on the Urinary Sensation Scale divided by the total number of micturitions with non-missing rating at that visit. The sum rating per 24 hours was calculated as the mean rating score on the Urinary Sensation Scale multiplied by the mean number of micturitions per 24 hours at that visit.

A numerical decrease in sum and mean ratings relative to Baseline was evident at all-time points assessed. The magnitude of change for both sum rating and mean rating increased from Week 1 to Week 4 and Week 12 (Table 11).

Table 11. Change in Sum Rating and Mean Rating on the Urinary Sensation Scale at Weeks 1, 4 and 12 Relative to Baseline

Variables	Sum Rating		Mean Rating	
Week 1		**N=503[a]**		
Baseline mean (SD)	40.1	(15.1)	3.2	(0.6)
Week 1 mean (SD)	33.2	(15.4)	2.9	(0.6)
Mean numerical change from Baseline (SD)	-6.9	(10.3)	-0.3	(0.5)
Week 4		**N=514[a]**		
Baseline mean (SD)	40.4	(15.6)	3.2	(0.6)
Week 4 mean (SD)	28.7	(14.3)	2.7	(0.7)
Mean numerical change from Baseline (SD)	-11.7	(12.3)	-0.5	(0.6)
Week 12		**N=514[a]**		
Baseline mean (SD)	40.4	(15.6)	3.2	(0.6)
Week 12 mean (SD)	25.2	(13.2)	2.5	(0.7)
Mean numerical change from Baseline (SD)	-15.2	(14.2)	-0.7	(0.7)
p-value[b]	<0.0001		<0.0001	

LOCF = last observation carried forward; SD = standard deviation.
a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 1 (no LOCF possible) or Week 4 and Week 12 (LOCF).
b. The p-value was based on a paired t-test comparing Baseline with post-baseline values.

Change in PPBC score relative to Baseline: Subjects were asked to describe their perception of problems related to their bladder condition at Baseline, Week 4, and Week 12. The PPBC score ranges from 1 "no problems at all" to 6 "many severe problems." A decrease in score thus indicates an improvement.

The following 3 variables were used to summarize the results of PPBC for each visit: numerical change in score (Table 12), categorized change in score (improvement, no change, deterioration) and magnitude of improvement (major improvement, minor improvement, no change, deterioration; Table 13).

Table 12. Numerical Change in Patient Perception of Bladder Condition Score at Week 4 and Week 12 Relative to Baseline

Week 4		N=484[a]	
Baseline mean (SD)	4.9		(0.7)
Week 4 mean (SD)	3.7		(1.1)
Mean numerical change from Baseline (SD)	-1.1		(1.0)
Week 12		**N=487[a]**	
Baseline mean (SD)	4.9		(0.7)
Week 12 mean (SD)	3.1		(1.2)
Mean numerical change from Baseline (SD)	-1.8		(1.3)
p-value[b]	<0.0001		

LOCF = last observation carried forward; SD = standard deviation.
a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 4 (no LOCF possible) or Week 12 (LOCF).
b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Table 13. Categorical Change in Patient Perception of Bladder Condition Score at Week 4 and Week 12 Relative to Baseline

Variables	Number (%) of Subjects	
Change at Week 4 relative to Baseline[a]	**N=484[b]**	
Improvement	340	70.2
Major improvement	158	32.6
Minor improvement	182	37.6
No change	135	27.9
Deterioration	9	1.9
Change at Week 12 relative to Baseline[a]	**N=487[b]**	
Improvement	405	83.2
Major improvement	287	58.9
Minor improvement	118	24.2
No change	72	14.8
Deterioration	10	2.1

LOCF = last observation carried forward.

a. Improvement: negative score change.
Major improvement: negative score change ≥2.
Minor improvement: negative score change =1.
no change: score change =0.
deterioration: positive score change.

b. Number of subjects in the full analysis set with non-missing change from Baseline to Week 4 (no LOCF possible) or Week 12 (LOCF).

Change in UPS relative to Baseline: Subjects were asked to describe their perception of urinary urgency using the UPS. Change in UPS was assessed at Week 4 and Week 12 relative to Baseline. The UPS scores used in the present study for the purpose of data entry and analysis range from 0 ("I am usually not able to hold urine") to 2 ("I am usually able to finish what I am doing before going to the toilet [without leaking]"). An increase thus indicated an improvement. The following 2 variables were used to summarize the scores from the UPS for each visit: numerical change in score (Table 14) and categorical change in score (improvement, no improvement; Table 15).

Table 14. Numerical Change in Urgency Perception Scale at Week 4 and Week 12 Relative to Baseline

Week 4	N=481[a]	
Baseline mean (SD)	0.8	(0.5)
Week 4 mean (SD)	1.2	(0.6)
Mean numerical change from Baseline (SD)	0.4	(0.6)
Week 12	**N=485[a]**	
Baseline mean (SD)	0.8	(0.5)
Week 12 mean (SD)	1.4	(0.6)
Mean numerical change from Baseline (SD)	0.5	(0.7)
p-value[b]	<0.0001	

LOCF = last observation carried forward; SD = standard deviation.

a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 4 (no LOCF possible) or Week 12 (LOCF).

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

Table 15. Categorical Change in Urgency Perception Scale at Week 4 and Week 12 Relative to Baseline

Variable	Number (%) of Subjects	
Change at Week 4 relative to Baseline[a]	**N=481[b]**	
Improvement	189	39.3
No improvement	292	60.7
Change at Week 12 relative to Baseline[a]	**N=485[b]**	
Improvement	237	48.9
No improvement	248	51.1

LOCF = last obersavtion carried forward.
a. Improvement: positive score change.
No improvement: 0 or negative score change.
b. Number of subjects in the full analysis set with non-missing change from Baseline to Week 4 (no LOCF possible) or Week 12 (LOCF).

Change in OAB-q Relative to Baseline: The OAB-q was used to assess how much subjects have been bothered by selected bladder symptoms and to assess the effect on their health related quality of life (HRQL) during the previous 4 weeks. It consists of 2 distinct components. The first 8 questions contribute to the Symptom Bother Score. Questions 9 to 33 cover the HRQL component, which includes the domains of Concern, Coping, Sleep, and Social Interaction. The questionnaire was administered at Baseline and Week 12 (or early termination). Table 16 summarizes the numerical changes from Baseline to Week 12. To be able to compare scores the different raw ranges were transformed to a scale from 0 to 100. A positive effect of treatment with fesoterodine was evident for all components and domains.

Table 16. Numerical Change in Overactive Bladder Questionnaire at Week 12 Relative to Baseline

HRQL Concern domain	**N=470[a]**	
Baseline mean (SD)	50.5	(25.3)
Week 12 mean (SD)	79.1	(21.2)
Mean numerical change from Baseline to Week 12 (SD)	28.6	(26.4)
p-value[b]	<0.0001	
HRQL Coping domain	**N=470[a]**	
Baseline mean (SD)	44.7	(25.3)
Week 12 mean (SD)	75.3	(24.3)
Mean numerical change from Baseline to Week 12 (SD)	30.6	(26.6)
p-value[b]	<0.0001	
HRQL Sleep domain	**N=470[a]**	
Baseline mean (SD)	47.4	(25.5)
Week 12 mean (SD)	72.3	(23.3)
Mean numerical change from Baseline to Week 12 (SD)	24.9	(27.3)
p-value[b]	<0.0001	
HRQL Social Interaction domain	**N=470[a]**	
Baseline mean (SD)	71.3	(23.5)
Week 12 mean (SD)	88.1	(18.6)
Mean numerical change from Baseline to Week 12 (SD)	16.8	(21.1)
p-value[b]	<0.0001	
Total HRQL scale	**N=470[a]**	
Baseline mean (SD)	52.2	(21.8)
Week 12 mean (SD)	78.3	(20.2)
Mean numerical change from Baseline to Week 12 (SD)	26.1	(22.8)
p-value[b]	<0.0001	
Symptom Bother scale	**N=470[a]**	
Baseline mean (SD)	57.4	(18.7)
Week 12 mean (SD)	28.6	(20.2)
Mean numerical change from Baseline to Week 12 (SD)	-28.7	(22.7)
p-value[b]	<0.0001	

HRQL = health related quality of life; SD = standard deviation.

a. Number of subjects in the full analysis set with non-missing numerical change from Baseline to Week 12.

b. The p-value is based on a paired t-test comparing Baseline with post-baseline values.

"Satisfaction with OAB Control" Module of OAB-S: Table 17 provides a summary for all subjects, as well as separately for subjects satisfied or not satisfied with their OAB treatment based on the Treatment Satisfaction Question (TSQ) at Week 12. The responses to the 10 questions were coded on a scale of 1 (very satisfied) to 5 (very dissatisfied). Note that the coding was reversed by subtracting the initial response value of each item from 6 (ie, 6 – initial response value) so that a higher final response value is associated with better satisfaction with OAB control. The achievable range for the total score was 0 to 100. The mean total score for all subjects was 74.7, indicating a high level of satisfaction with OAB symptom control at Week 12.

Table 17. "Satisfaction with OAB Control" Module of OAB Treatment Satisfaction Questionnaire (OAB-S) at Week 12

All subjects	N
N	473[a]
Mean (SD)	74.7 (22.3)
Subjects satisfied on TSQ[b]	
N	377[a]
Mean (SD)	82.7 (14.0)
Subjects not satisfied on TSQ[c]	
N	96[a]
Mean (SD)	43.6 (21.5)

OAB = overactive bladder; SD = standard deviation; TSQ = Treatment Satisfaction Questionnaire.
a. Number of subjects with non-missing values on OAB-S at Week 12.
b. Includes subjects responding "very satisfied" or "somewhat satisfied" to the TSQ at Week 12.
c. Includes subjects responding "very dissatisfied", "somewhat dissatisfied" or "neither dissatisfied nor satisfied" to the TSQ at Week 12.

Safety Results: A summary of treatment-emergent AE (all causalities) reported by ≥1% of subjects is presented in Table 18.

Table 18. Treatment-Emergent Adverse Events (All Causalities) - Safety Analysis Set For Events Having Frequency of ≥1%

System Organ Class and MedDRA Preferred Term	Fesoterodine (N=516) n (%)
Eye disorders	13 (2.5)
Dry eye	6 (1.2)
Gastrointestinal disorders	160 (31.0)
Abdominal pain upper	11 (2.1)
Constipation	25 (4.8)
Diarrhoea	12 (2.3)
Dry mouth	120 (23.3)
Nausea	6 (1.2)
Infections and infestations	28 (5.4)
Urinary tract infection	7 (1.4)
Nervous system disorders	30 (5.8)
Dizziness	6 (1.2)
Headache	19 (3.7)
Renal and urinary disorders	17 (3.3)
Dysuria	6 (1.2)

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 is taken.
Subjects are counted only once in each row.
In this case, the reported severity is summarized. Missing Baseline severities are imputed as mild.
Includes data up to 7 days after last dose of study drug.
MedDRA (v10.1) coding dictionary applied.
MedDRA = medical dictionary of regulatory activities.

Treatment-emergent AEs (treatment-related) are summarized in Table 19.

Table 19. Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and MedDRA Preferred Term	Fesoterodine n (%)
Ear and labyrinth disorders	1 (0.2)
Tinnitus	1 (0.2)
Eye disorders	12 (2.3)
Dry eye	6 (1.2)
Lacrimation increased	2 (0.4)
Vision blurred	3 (0.6)
Visual disturbance	1 (0.2)
Gastrointestinal disorders	153 (29.7)
Abdominal distension	1 (0.2)
Abdominal pain	1 (0.2)
Abdominal pain lower	1 (0.2)
Abdominal pain upper	10 (1.9)
Chapped lips	2 (0.4)
Constipation	25 (4.8)
Diarrhoea	6 (1.2)
Dry mouth	120 (23.3)
Dyspepsia	3 (0.6)
Flatulence	3 (0.6)
Gastric disorder	1 (0.2)
Gastrooesophageal reflux disease	1 (0.2)
Nausea	3 (0.6)
Oesophagitis	1 (0.2)
Stomatitis	1 (0.2)
Vomiting	1 (0.2)
General disorders and administration site conditions	6 (1.2)
Fatigue	2 (0.4)
Oedema peripheral	1 (0.2)
Suprapubic pain	1 (0.2)
Thirst	2 (0.4)
Infections and infestations	1 (0.2)
Cystitis	1 (0.2)
Investigations	1 (0.2)
Blood glucose increased	1 (0.2)
Metabolism and nutrition disorders	2 (0.4)
Dehydration	1 (0.2)
Fluid retention	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.6)
Back pain	3 (0.6)
Nervous system disorders	21 (4.1)
Balance disorder	1 (0.2)
Dizziness	4 (0.8)
Dysgeusia	1 (0.2)
Headache	14 (2.7)
Paraesthesia	1 (0.2)
Somnolence	2 (0.4)
Psychiatric disorders	3 (0.6)
Euphoric mood	1 (0.2)
Insomnia	1 (0.2)
Sleep disorder	1 (0.2)
Renal and urinary disorders	14 (2.7)
Dysuria	5 (1.0)
Residual urine	1 (0.2)

Table 19. Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and MedDRA Preferred Term	Fesoterodine n (%)
Urinary hesitation	1 (0.2)
Urinary retention	3 (0.6)
Urine flow decreased	4 (0.8)
Respiratory, thoracic and mediastinal disorders	4 (0.8)
Bronchitis chronic	1 (0.2)
Cough	1 (0.2)
Nasal dryness	1 (0.2)
Pharyngolaryngeal pain	1 (0.2)
Skin and subcutaneous tissue disorders	4 (0.8)
Erythema	1 (0.2)
Hyperhidrosis	2 (0.4)
Rash	1 (0.2)
Vascular disorders	1 (0.2)
Hypertension	1 (0.2)

Subjects are counted only once in each row.
Includes data up to 7 days after last dose of study drug.
SAEs and AEs are not seprated out in this table.
MedDRA (v10.1) coding dictionary applied.
AE = adverse events; MedDRA = medical dictionary of regulatory activities; n = number of subjects with adverse events; SAE = serious adverse events.

Nine subjects experienced 10 non-fatal SAEs while receiving treatment or within 7 days of the last dose in this study (Table 20). None of these SAEs was considered to be treatment-related.

Table 20. Serious Adverse Events

Serial Number	Fesoterodine Dose[a]	MedDRA Preferred Term	SAE Start day	Drug Stop day	Action Taken[b]	Sponsor/ Investigator Causality	Outcome
1	4 mg	Appendicitis	53	85[c]	no action taken	no/other	recovered
2	8 mg	Renal mass	48[d]	84[c]	no action taken	no/other	not recovered
3	8 mg	Deafness unilateral	78	83[c]	no action taken	no/other	recovered
4	4 mg	Hypertension	27	82	stopped temporarily	no/other illness	recovered
5	8 mg	Upper respiratory tract infection	41	85[c]	no action taken	no/other illness	recovered
6	8 mg	Asthenia	83	90	permanently discontinued	no/other	recovered
7	8 mg	Joint sprain	37	84[c]	no action taken	no/other	recovered
		Radius fracture	37	84[c]	no action taken	no/other	recovered[e]
8	8 mg	Pyrexia	44	83[c]	no action taken	no/other illness	recovered
9	4 mg	Pyelonephritis acute	27	27	permanently discontinued	no/other	recovered

Reversible unilateral deafness in one subject was due to diving; asthenia in 1 subject was related to a fall; and pyrexia in one subject was "fever of unknown origin".
MedDRA = medical dictionary of regulatory activities; SAE = serious adverse event.
a. Dose at onset of adverse event.
b. Action taken on study drug.
c. Day of last dose taken from study database.
d. Day 44.
e. Ongoing.

AEs leading to permanent discontinuation are summarized in Table 21.

Table 21. Adverse Events Contributing to Permanent Discontinuation of Study Medication

MedDRA System Organ Class Preferred Term	Number (%) of Subjects N=516			
	All Causalities		Treatment-Related	
Gastrointestinal disorders	14	(2.7)	12	(2.3)
Constipation	3	(0.6)	3	(0.6)
Dry mouth	3	(0.6)	3	(0.6)
Abdominal pain upper	2	(0.4)	2	(0.4)
Abdominal distension	1	(0.2)	1	(0.2)
Diarrhea	1	(0.2)	1	(0.2)
Dyspepsia	1	(0.2)		
Gastritis	1	(0.2)		
Nausea	1	(0.2)	1	(0.2)
Oesophagitis	1	(0.2)	1	(0.2)
Nervous system disorders	6	(1.2)	6	(1.2)
Headache	3	(0.6)	3	(0.6)
Balance disorder	1	(0.2)	1	(0.2)
Dizziness	1	(0.2)	1	(0.2)
Dysgeusia	1	(0.2)	1	(0.2)
Renal and urinary disorders	6	(1.2)	6	(1.2)
Dysuria	4	(0.8)	4	(0.8)
Urinary retention	2	(0.4)	2	(0.4)
Infections and infestations	2	(0.4)	1	(0.2)
Cystitis	1	(0.2)	1	(0.2)
Pyelonephritis acute[a]	1	(0.2)		
Metabolism and nutrition disorders	2	(0.4)	2	(0.4)
Dehydration	1	(0.2)	1	(0.2)
Fluid retention	1	(0.2)	1	(0.2)
Psychiatric disorders	2	(0.4)	2	(0.4)
Euphoric mood	1	(0.2)	1	(0.2)
Insomnia	1	(0.2)	1	(0.2)
Injury, poisoning and procedural complications	1	(0.2)		
Back injury	1	(0.2)		
Investigations	1	(0.2)	1	(0.2)
Blood glucose increased	1	(0.2)	1	(0.2)
Musculoskeletal and connective tissue disorders	1	(0.2)		
Muscular weakness[a]	1	(0.2)		
Respiratory, thoracic and mediastinal disorders	1	(0.2)	1	(0.2)
Cough	1	(0.2)	1	(0.2)
Reproductive system and breast disorders	1	(0.2)		
Genital haemorrhage	1	(0.2)		
Skin and subcutaneous tissue disorders	1	(0.2)	1	(0.2)
Hyperhidrosis	1	(0.2)	1	(0.2)

Note that 3 subjects had 2 events and 1 subject had an event prior to intake of study medication (N=39)
a. Serious adverse event

There were no deaths among subjects who participated in this study.

CONCLUSIONS:

- This open-label, flexible dosing study demonstrated the efficacy of fesoterodine 4 mg or 8 mg QD on OAB symptom relief and patient satisfaction in OAB patients who were

dissatisfied with their prior therapy with tolterodine or tolterodine ER. At Week 12 all 3 primary diary variables (change in mean number of micturitions, UUI episodes and urgency episodes per 24 hours) showed statistically significant improvement from Baseline. Approximately 80% of subjects were satisfied with fesoterodine treatment after 12 weeks.

- Similarly, all secondary bladder diary and HRQL endpoints showed statistically significant improvement from Baseline at Week 12.

- Fesoterodine had a favorable safety profile and was generally well tolerated in this study. The most frequently reported AEs were consistent with the known AE profile for fesoterodine and were mostly mild or moderate in intensity.