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

PROTOCOL NO: A0221046

PROTOCOL TITLE: 12-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, Multicenter Trial to Evaluate the Efficacy and Safety of Fesoterodine in Comparison to Tolterodine ER in Patients With Overactive Bladder

Study Centers: A total of 210 centers in 25 countries took part in the study and randomized subjects; 5 each in Costa Rica, Spain, Ukraine, Slovakia, Lithuania, Greece, Hungary and Brazil; 6 each in Sweden, India, Korea Republic of and Bulgaria; 8 in Canada; 1 each in Singapore, Ireland and Latvia; 10 in Germany; 3 in Estonia; 7 each in South Africa and Poland; 4 in Romania; 2 each in Colombia and Malaysia; 11 in Russian Federation and 89 in the United States (US).

Study Initiation Date and Final Completion Date: 04 April 2008 to 20 October 2009

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To compare the efficacy of fesoterodine with that of placebo and of tolterodine extended release (ER) in subjects with overactive bladder (OAB), after 12 weeks of treatment.

Secondary Objectives:

- To compare the effect of fesoterodine with that of placebo on patient reported outcomes (PROs) in subjects with OAB, after 12 weeks of treatment.
- To compare the efficacy of fesoterodine 4 mg once daily (QD) with that of placebo in subjects with OAB after 1 week of treatment.
- To summarize safety data for 12 weeks of treatment with either fesoterodine, tolterodine ER, or placebo in subjects with OAB.

Study Design: This was a 12-week, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study to compare the efficacy of fesoterodine to placebo and tolterodine ER in subjects with OAB. The study consisted of a 2-week single-blind placebo run-in period and a 12-week double-blind treatment period, and required a total of

5 in-clinic visits: Screening/Enrollment Visit, Randomization/Baseline Visit, Week 1 Visit, Week 4 Visit, and End-of-Study Visit (Week 12 or early termination [ET]).

Subjects were initially screened at the Screening/Enrollment Visit and eligible subjects were enrolled into the run-in period, and received placebo for 2 weeks in a single-blind fashion. The subject completed a 3-day bladder diary for 3 consecutive days prior to the Randomization/Baseline Visit. Only OAB subjects with urgency incontinence, defined as subjects with an average of at least 1 urgency urinary incontinence (UUI) episode per 24 hours during the 3-day diary period prior to randomization and who met the entrance criteria were randomized to 1 of 3 treatment arms (fesoterodine, tolterodine, and placebo) in a 2:2:1 ratio. Randomized subjects received the assigned treatment in a double-blind, double-dummy fashion for 12 weeks.

Study procedures are detailed in Table 1.

Table 1. Schedule of Activities

Activities and Forms to be Completed	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening/ Enrollment, Week-2 (±5 Days)	Randomization/ Baseline, Week 0	End of Week 1 (-1 to +3 Days)	End of Week 4 (±7 Days)	End of Study Week 12 or Early Termination (±7 Days)
Written informed consent	X				
Demographics & medical history	X				
Sitting blood pressure & pulse rate	X	X	X	X	X
Physical examination & 12-lead ECG	X				
Inclusion/exclusion criteria	X	X			
Blood draw (hematology and chemistry)	X				X
Urine dipstick test	X				
Urine pregnancy test for women of child bearing potential	X				
PPBC		X	X	X	X
UPS (formerly known as PPUS)[a]		X	X	X	X
OAB-q		X			X
Dispense bladder diary (3-day)	X	X	X	X	
Evaluation of bladder diary (3-day)		X	X	X	X
AEs[b]		X	X	X	X
Concomitant medication	X	X	X	X	X
Concomitant non-drug treatment/procedures	X	X	X	X	X
Access Impala[c]	X	X		X	X
Dispense study medication	X	X		X	
Study medication return/count		X		X	X
Assess overall compliance		X	X	X	X

AE = adverse event; ECG = electrocardiogram; OAB-q = Overactive Bladder Questionnaire; PPBC = Patient's Perception of Bladder Condition; PPUS = Patient Perception of Urgency Scale; SSID = single subject identification number; UPS = Urgency Perception Scale.

a. UPS was formerly known as the Patient Perception of Urgency Scale [PPUS].

b. 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.

c. Impala was a centralized randomization system used to obtain the subject's SSID, randomization number, and randomization assignment. It also functioned to document subject's status, eg completion, discontinuation, etc, and to predict and trigger drug re-supply for a site.

Number of Subjects (Planned and Analyzed): Approximately 2160 subjects were planned to be randomized in this study. Of the total 4136 subjects screened in this study, 3745 received single-blind placebo during the run-in period out of which 2417 subjects were randomized to receive double-blind study treatment (8 in Spain, 46 in Brazil, 174 in Bulgaria, 24 in Canada, 21 in Colombia, 106 in Costa Rica, 29 in Estonia, 120 in Germany, 30 in Greece, 68 in Hungary, 94 in India, 3 in Ireland, 132 in Korea Republic of, 48 in Latvia, 178 in Lithuania, 84 in Poland, 6 in Malaysia, 30 in Romania, 114 in Russian Federation, 13 in Singapore, 97 Slovakia, 64 in South Africa, 54 in Sweden, 97 in Ukraine and 777 in US). Of the total 2417 subjects randomized, 2411 subjects received at least 1 confirmed double-blind study drug (placebo: 478; tolterodine ER: 973; fesoterodine: 960) and were analyzed.

Diagnosis and Main Criteria for Inclusion: Adult subjects with OAB symptoms (subject-reported) for ≥3 months prior to Screening/Enrollment Visit were eligible for enrollment in this study. In order to be randomized into double-blind study treatment, subjects had to have reported at least an average of 1 UUI episode per 24 hours and a mean urinary frequency of ≥8 micturitions per 24 hours in the 3-day bladder diary prior to the Randomization/Baseline Visit.

Study Treatment: During a 2-week run-in period, subjects were treated with placebo in a single-blind, double-dummy fashion. Eligible subjects were then randomized in a 2:2:1 ratio to receive either fesoterodine at 4 mg QD for 1 week then fesoterodine 8 mg QD for 11 weeks, or tolterodine ER at 4 mg QD for 12 weeks, or placebo QD for 12 weeks, respectively, in a double-blind, double-dummy fashion.

Fesoterodine was supplied as 4 mg or 8 mg ER tablets. Tolterodine was provided as 4 mg ER capsules. Placebo was provided as either a dummy tablet or a dummy capsule to match fesoterodine tablet and tolterodine capsule, respectively. To support the double-dummy model, each subject received both a blister pack of tablets (fesoterodine or placebo) and a bottle of capsules (tolterodine ER or placebo) at the Randomization/Baseline Visit and the Week 4 Visit. Subjects were instructed to swallow without chewing 1 tablet and 1 capsule with water every morning. Blister package medications were to be taken in number order to comply with the forced titration schedule in the fesoterodine treatment arm.

Efficacy Endpoints:

Primary Endpoint:

- Change in mean number of UUI episodes per 24 hours at Week 12 relative to the Baseline (UUI episodes were defined as those micturitions with USS rating of 5 in the diary).

Secondary Endpoints:

Bladder Diary

- Change in mean voided volume per micturition at Weeks 1, 4, and 12 relative to Baseline.

- Change in mean number of micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Percent change of micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of night time micturitions per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Percent change of night time (nocturnal) 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.
- Percent change of UUI episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of micturition-related urgency episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline (micturition-related urgency episodes were defined as those micturitions with USS rating of ≥3 in the diary).
- Percent change of micturition-related urgency episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in mean number of severe micturition-related urgency episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline (severe micturition-related urgency episodes were defined as those micturitions with USS rating ≥4).
- Percent change of severe micturition-related urgency episodes per 24 hours at Weeks 1, 4, and 12 relative to Baseline.
- Change in the mean and sum rating on the USS at Weeks 1, 4, and 12 relative to Baseline.
- Percentage of subjects who reported no UUI in the 3-day bladder diary at Weeks 1, 4, or 12 among those who reported >0 UUI episode at Baseline.

Patient's Perception of Bladder Condition (PPBC):

- Change in PPBC at Weeks 1, 4, and 12 relative to Baseline.

Patient Perception of Urgency Scale (PPUS):

- Change in PPUS at Weeks 1, 4, and 12 relative to Baseline.

Overactive Bladder Questionnaire (OAB-q):

- Change in OAB-q symptom bother score at Week 12 relative to Baseline.

- Change in scores of each Health-related Quality of Life (HRQL) domain of OAB-q at Week 12 relative to Baseline.

Safety Evaluations: Incidence of adverse events (AEs) was monitored for each subject once the subject had received 1 dose of study medication; the incidence of serious AEs (SAEs) was monitored for each subject once the subject had signed the informed consent through to the End-of-Study or ET Visit. Vital signs (blood pressure and pulse rate) were measured at each visit. Blood samples for hematology and serum chemistry were performed at screening and at the Week 12 Visit or ET Visit. Physical examination and electrocardiogram (ECG) were each performed at screening only. Additional laboratory and ECG measurements were allowed throughout the study at the discretion of the Investigator.

Statistical Methods:

Safety Analysis Set: included all subjects who took at least 1 dose of study drug.

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 postbaseline efficacy assessment.

Efficacy data were analyzed based on the FAS. Key efficacy endpoints were also analyzed based on the supporting FAS (SFAS; the FAS including subjects with unreliable efficacy data). Safety and Baseline characteristics were analyzed based on the safety analysis set.

The last valid postbaseline observation was carried forward to handle missing efficacy data at Week 4 and Week 12. Baseline data were not carried forward.

Regression diagnostics were performed to verify model assumptions and adequacy of the fitted model. Q-Q plots were provided to diagnose potential problems of non-normality or outliers. If the normality assumption was severely violated (proportion of non-normal residuals larger than 5%), a non-parametric analysis was to be conducted using Van Elteren's test (stratified Wilcoxon-Mann-Whitney test) stratified by Baseline quartile of the diary variable analyzed. Mean treatment changes were estimated with 5% Winsorized means. Based on the residual diagnostics the Van Elteren's test was used for the primary variable (UUI episodes per 24 hours, change from Baseline) and 2 secondary diary variables (mean voided volume per micturition and severe urgency micturition-related episodes per 24 hours, change from Baseline).

With regard to change from Baseline to Weeks 1, 4 and 12 in continuous efficacy endpoints, pairwise treatment comparisons of fesoterodine versus placebo, fesoterodine versus tolterodine ER and tolterodine ER versus placebo were performed. For data that did not violate model assumptions, pairwise comparisons were carried out using an analysis of covariance (ANCOVA) model that included Baseline value as a covariate with treatment and country as factors. All comparisons were performed with 2-sided testing at a 5% significance level. The results that were generated included p-value from pairwise treatment comparisons, the least squares mean (LSMean) and standard error (SE) for change from Baseline for each treatment, the LSMean difference and SE between treatments, and the 95% confidence interval (CI) of the LSMean difference. ANCOVA models were repeated with

2 additional interaction terms, treatment by Baseline and treatment by center. These interaction terms were assessed at the 5% significance level. If an interaction term was significant, the relationship between the covariates and the response was not the same in each treatment group. In these cases further analyses were to be performed to address the nature of the 'non-parallelism' or interaction.

The Cochran-Mantel-Haenszel (CMH) test with modified ridit scoring was used for ordinal variables (PPBC 4-category analysis, UPS 3-category analysis), and the CMH general association test was used for nominal variables (PPBC 2-category analysis, diary dry rate). The CMH analyses were stratified by country. For the diary dry-rate the CMH analysis was stratified by Baseline UUI quartile to be consistent with the primary analysis. Summary statistics including cell counts and percentages were generated.

Descriptive statistics were provided for all safety analyses.

RESULTS:

Subject Disposition and Demography: Subject disposition is presented in Table 2. Approximately 90% of subjects in each treatment group completed the study.

The primary cause of subject discontinuation in the active treatment groups was AEs, related and not related to the study drug, which was reported for 46 subjects (4.8%) in the fesoterodine group and 28 subjects (2.9%) in the tolterodine ER group compared to 9 subjects (1.9%) in the placebo group. Subjects in the placebo treatment group discontinued most frequently due to other reasons not related to the study drug (13 subjects [2.7%]) including protocol violations. Discontinuations due to lack of efficacy occurred in 11 subjects (2.3%) treated with placebo, 10 subjects (1.0%) treated with tolterodine ER and in 4 subjects (0.4%) treated with fesoterodine. For 2 subjects the study blind was broken.

Table 2. Subject Disposition

	Placebo	Tolterodine ER	Fesoterodine
Number (%) of subjects			
Screened: 4136			
Assigned to run-in 3867			
Treated in run-in: 3745			
Assigned to study treatment	480	974	963
Treated	478	973	960
Completed	431 (90.2)	885 (91.0)	862 (89.8)
Discontinued	47 (9.8)	88 (9.0)	98 (10.2)
Analyzed for efficacy:			
Full analysis set[a]	462 (96.7)	942 (96.8)	930 (96.9)
Supporting full analysis set	478 (100.0)	973 (100.0)	960 (100.0)
Analyzed for safety:			
Adverse events [b]	475 (99.4)	971 (99.8)	958 (99.8)
Laboratory data	439 (91.8)	899 (92.4)	883 (92.0)

Discontinuations occurring outside the lag period has been attributed to the last study treatment received
ER = extended-release formulation.
a. Included all randomized subjects who took at least 1 dose of assigned double-blind study drug and contributed data to at least 1 Baseline or postbaseline efficacy assessment excluding 77 subjects from 3 centers where reliability of efficacy data could not be established.
b. Adverse event data were not available for 3 subjects in the placebo group, 2 subjects in the tolterodine ER group and 2 subjects in the fesoterodine group from 1 of the 3 centers with unreliable data.

Demographic characteristics were comparable across the 3 treatment groups (Table 3). Subjects in the study were predominantly White (more than 77% in each treatment group) and female (more than 84% in each treatment group). The average age in all subjects was 58.3 years, with males being slightly older than females (60.6 years versus 57.9 years).

Table 3. Demographic Characteristics – Safety Analysis Set

	Placebo			Tolterodine ER			Fesoterodine		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Number (%) of subjects	68 (14.2)	410 (85.8)	478 (100.0)	155 (15.9)	818 (84.1)	973 (100.0)	144 (15.0)	816 (85.0)	960 (100.0)
Age (years)									
Mean (SD)	63.9 (13.2)	58.8 (13.0)	59.5 (13.2)	60.7 (15.0)	57.6 (13.5)	58.1 (13.8)	59.0 (15.2)	57.7 (13.2)	57.9 (13.5)
Range	28.0 – 84.0	18.0 – 89.0	18.0 – 89.0	19.0 – 85.0	18.0 – 89.0	18.0 – 89.0	21.0 – 89.0	18.0 – 90.0	18.0 – 90.0
<18 [n, (%)]	0	0	0	0	0	0	0	0	0
18-44 [n, (%)]	7 (10.3)	63 (15.4)	70 (14.6)	26 (16.8)	131 (16.0)	157 (16.1)	23 (16.0)	133 (16.3)	156 (16.3)
45-64 [n, (%)]	19 (27.9)	195 (47.6)	214 (44.8)	55 (35.5)	407 (49.8)	462 (47.5)	60 (41.7)	414 (50.7)	474 (49.4)
≥65 [n, (%)]	42 (61.8)	152 (37.1)	194 (40.6)	74 (47.7)	280 (34.2)	354 (36.4)	61 (42.4)	269 (33.0)	330 (34.4)
Race [n, (%)]									
White	47 (69.1)	337 (82.2)	384 (80.3)	111 (71.6)	647 (79.1)	758 (77.9)	98 (68.1)	646 (79.2)	744 (77.5)
Black	1 (1.5)	19 (4.6)	20 (4.2)	6 (3.9)	47 (5.7)	53 (5.4)	8 (5.6)	47(5.8)	55 (5.7)
Asian	17 (25.0)	30 (7.3)	47 (9.8)	33 (21.3)	66 (8.1)	99 (10.2)	28 (19.4)	73 (8.9)	101 (10.5)
Other	3 (4.4)	24 (5.9)	27 (5.6)	5 (3.2)	58 (7.1)	63 (6.5)	10 (6.9)	50 (6.1)	60 (6.3)

ER = extended-release formulation; n = number of subjects in the respective category; SD = standard deviation.

Efficacy Results:

Primary Endpoint Results: The results of the change in the mean number of UUI episodes per 24 hours at Week 12 relative to Baseline are presented in Table 4. The mean number of UUI episodes per 24 hours was comparable across the 3 treatment groups at Baseline (2.4 to 2.6 episodes per 24 hours), and decreased in all 3 treatment arms at Week 12 relative to Baseline. The Winsorized mean reduction was 1.95 episodes per 24 hours in the fesoterodine 8 mg group, 1.74 in the tolterodine ER 4 mg group and 1.62 in the placebo group. The reductions were statistically significantly greater in the fesoterodine 8 mg group compared with placebo ($p < 0.0001$) and tolterodine ER 4 mg ($p=0.0072$).

Table 4. Change in Mean Number of UUI Episodes per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Subjects Reporting This Symptom at Baseline)

Mean Number of UUI Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 12	n=448	n=926	n=908
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Change from Baseline to Week 12			
Mean (SEM)[a]	-1.62 (0.07)	-1.74 (0.06)	-1.95 (0.05)
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference	Mean difference[c]		p-value[d]
Fesoterodine vs placebo	-0.33		<0.0001
Tolterodine ER vs placebo	-0.12		0.0228
Fesoterodine vs tolterodine ER	-0.21		0.0072

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with Baseline UUI >0 per 24 hours and non-missing change from Baseline to Week 12 (LOCF); SD = standard deviation; SEM = standard error of the mean; UUI = urgency urinary incontinence; vs = versus.

a. Winsorized means (5% of the tails were censored, ie, replaced with the value at the 5th and 95th percentile respectively).

b. Based on Wilcoxon Signed-Rank test comparing Baseline with postbaseline values.

c. Differences between Winsorized means.

d. P-value based on Van Elteren's Test adjusted by Baseline UUI quartile.

Secondary Endpoint Results:

- Change in Mean Voided Volume per Micturition at Weeks 1, 4, and 12 Relative to Baseline: the mean voided volume per micturition was comparable across treatment groups at Baseline (142.1 mL to 147.3 mL), and increased in all 3 treatment arms at Weeks 1, 4 and 12 (Table 5).

Table 5. Change in Mean Voided Volume per Micturition at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean Voided Volume per Micturition (mL)	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=447**	**n=917**	**n=895**
Baseline mean (SD)	147.3 (54.9)	142.1 (55.5)	146.2 (54.5)
Mean change from Baseline to Week 1 (SEM)[a]	9.8 (1.92)	15.7 (1.43)	18.6 (1.55)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	8.8		0.0020
Tolterodine ER vs placebo	5.9		0.0519
Fesoterodine vs tolterodine ER	3.0		0.1503
Week 4	**n=452**	**n=927**	**n=909**
Baseline mean (SD)	147.6 (54.9)	141.8 (55.4)	146.6 (54.9)
Mean change from Baseline to Week 4 (SEM)[a]	14.3 (2.28)	26.4 (1.76)	32.3 (1.94)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	18.0		<0.0001
Tolterodine ER vs placebo	12.2		0.0002
Fesoterodine vs tolterodine ER	5.8		0.0130
Week 12	**n=452**	**n=930**	**n=912**
Baseline mean (SD)	147.6 (54.9)	142.0 (55.4)	146.6 (54.9)
Mean change from Baseline to Week 12(SEM)[a]	17.3 (2.40)	28.4 (1.82)	34.5 (2.06)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	17.1		<0.0001
Tolterodine ER vs placebo	11.1		0.0021
Fesoterodine vs tolterodine ER	6.0		0.0525

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SEM = standard error of the mean; vs = versus.

a. Winsorized means (5% of the tails were censored, ie, replaced with the value at the 5th and 95th percentile respectively).

b. Differences between Winsorized means.

c. P-value based on Van Elteren's Test adjusted by Baseline voided volume quartile.

- Change in Mean Number of Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: the mean number of micturitions per 24 hours was comparable across treatment groups at Baseline (11.7 to 11.9 per 24 hours), and decreased in all 3 treatment arms at Weeks 1, 4, and 12 (Table 6).

Table 6. Change in Mean Number of Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean Number of Micturitions per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=448**	**n=921**	**n=908**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Change from Baseline to Week 1			
LSMean (SE)	-0.8 (0.1)	-1.0 (0.1)	-1.0 (0.1)
95% CI for mean	-1.1, -0.7	-1.3, -1.0	-1.4, -1.0
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.3 (0.1)	-0.5, -0.1	0.0161
Tolterodine ER vs placebo	-0.2 (0.1)	-0.4, 0.0	0.0944
Fesoterodine vs tolterodine ER	-0.1 (0.1)	-0.3, 0.1	0.3613
Week 4	**n=454**	**n=931**	**n=916**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Change from Baseline to Week 4			
LSMean (SE)	-1.5 (0.1)	-1.8 (0.1)	-2.1 (0.1)
95% CI for mean	-1.8, -1.3	-2.2, -1.9	-2.4, -2.0
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.6 (0.1)	-0.9, -0.4	<0.0001
Tolterodine ER vs placebo	-0.4 (0.1)	-0.6, -0.1	0.0043
Fesoterodine vs tolterodine ER	-0.3 (0.1)	-0.5, -0.0	0.0186
Week 12	**n=454**	**n=935**	**n=916**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Change from Baseline to Week 12			
LSMean (SE)	-2.0 (0.1)	-2.3 (0.1)	-2.6 (0.1)
95% CI for mean	-2.4, -1.9	-2.6, -2.3	-2.9, -2.6
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.6 (0.1)	-0.9, -0.4	<0.0001
Tolterodine ER vs placebo	-0.3 (0.1)	-0.6, -0.0	0.0407
Fesoterodine vs tolterodine ER	-0.4 (0.1)	-0.6, -0.1	0.0016

CI = confidence interval; ER = extended-release formulation; LOCF = last observation carried forward; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SE = standard error; vs = versus.

a. Based on a paired t-test comparing Baseline with postbaseline values.
b. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

- Percent Change of Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: at Week 1, the percent reductions of micturitions from Baseline were statistically significantly greater in the fesoterdine 4 mg group compared with placebo (p=0.0217; Table 7). At Weeks 4 and 12, the percent reductions were statistically significantly greater in the fesoterodine 8 mg group compared with both placebo (Weeks 4 and 12: p <0.0001) and tolterodine ER 4 mg (Week 4: p=0.0217, Week 12: p=0.0023).

Table 7. Percent Change of Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Percent Change of Micturitions per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Percent Change From Baseline to Week 1	**n=448**	**n=921**	**n=908**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Week 1 mean (SD)	10.8 (3.3)	10.7 (3.2)	10.5 (3.1)
Percent change median (min, max)	-7.1 (-70.6, 53.6)	-9.4 (-64.3, 74.2)	-9.0 (-61.9, 89.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0217	-	-
Tolterodine ER vs placebo	Not reported[b]	-	-
Fesoterodine vs tolterodine ER	Not reported[b]	-	-
Percent Change From Baseline to Week 4	**n=454**	**n=931**	**n=916**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Week 4 mean (SD)	10.1 (3.2)	9.8 (3.1)	9.5 (3.0)
Percent change median (min, max)	-13.4 (-64.4, 118.8)	-16.7 (-67.9, 64.0)	-18.9 (-68.8, 96.2)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0020	-	-
Fesoterodine vs tolterodine ER	0.0217	-	-
Percent Change From Baseline to Week 12	**n=454**	**n=935**	**n=916**
Baseline mean (SD)	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Week 12 mean (SD)	9.6 (3.3)	9.4 (3.1)	9.0 (2.9)
Percent change median (min, max)	-18.2 (-66.7, 118.8)	-20.8 (-67.5, 70.8)	-23.5 (-75.3, 64.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0421	-	-
Fesoterodine vs tolterodine ER	0.0023	-	-

ER = extended-release formulation; LOCF = last observation carried forward; min = minimum; max = maximum; N = number of subjects in the respective treatment group; n=number of subjects with non-missing percent change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; vs = versus.

a. Based on a ranked analysis of covariance model with country and treatment as factors, and ranked Baseline value as a covariate.

b. Statistical testing for percent change from Baseline to Week 1 for tolterodine vs placebo and fesoterodine vs tolterodine were not reported since the corresponding numerical change results were not statistically significant.

- Change in Mean Number of Nocturnal Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: the mean number of nocturnal micturitions per 24 hours was comparable across treatment groups at Baseline (2.1 to 2.3 episodes per 24 hours), and decreased in all 3 treatment arms at Weeks 1, 4, and 12 (Table 8).

Table 8. Change in Mean Number of Nocturnal Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean Number of Nocturnal Micturitions per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=432**	**n=879**	**n=871**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Change from Baseline to Week 1			
LSMean (SE)	-0.2 (0.1)	-0.3 (0.0)	-0.3 (0.0)
95% CI for mean	-0.3, -0.1	-0.4, -0.2	-0.4, -0.2
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.0 (0.1)	-0.1, 0.1	0.3823
Tolterodine ER vs placebo	-0.0 (0.1)	-0.1, 0.1	0.4802
Fesoterodine vs tolterodine ER	-0.0 (0.0)	-0.1, 0.1	0.8355
Week 4	**n=437**	**n=888**	**n=879**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Change from Baseline to Week 4			
LSMean (SE)	-0.4 (0.1)	-0.5 (0.0)	-0.5 (0.0)
95% CI for mean	-0.5, -0.3	-0.6, -0.5	-0.6, -0.5
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.1 (0.1)	-0.2, -0.0	0.0286
Tolterodine ER vs placebo	-0.1 (0.1)	-0.2, 0.0	0.0794
Fesoterodine vs tolterodine ER	-0.0 (0.0)	-0.1, 0.1	0.5906
Week 12	**n=437**	**n=892**	**n=879**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Change from Baseline to Week 12			
LSMean (SE)	-0.5 (0.1)	-0.6 (0.0)	-0.7 (0.0)
95% CI for mean	-0.6, -0.4	-0.7, -0.6	-0.8, -0.6
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.1 (0.1)	-0.3, -0.0	0.0134
Tolterodine ER vs placebo	-0.1 (0.1)	-0.2, 0.0	0.1759
Fesoterodine vs tolterodine ER	-0.1 (0.0)	-0.2, 0.0	0.1661

CI = confidence interval; ER = extended-release formulation; LOCF = last observation carried forward; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with Baseline nocturnal micturitions >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SE = standard error; vs = versus.

a. Based on a paired t-test comparing Baseline with postbaseline values.
b. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

- Percent Change of Nocturnal Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: the fesoterodine 4 mg versus placebo or tolterodine ER 4 mg comparisons at Week 1 were not statistically significant. At Week 4 and Week 12, there was a statistically significantly greater percent reduction in the fesoterodine 8 mg group than in the placebo group (Week 4: p=0.0021, Week 12: p=0.0200; Table 9). The fesoterodine 8 mg versus tolterodine 4 mg comparisons at Weeks 4 and 12, and the tolterodine versus placebo comparisons for Weeks 1, 4, and 12, were not statistically significant.

Table 9. Percent Change of Nocturnal Micturitions per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Percent Change of Nocturnal Micturitions per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Percent Change From Baseline to Week 1	**n=432**	**n=879**	**n=871**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Week 1 mean (SD)	1.9 (1.4)	2.0 (1.3)	1.9 (1.4)
Percent change median (min, max)	-7.7 (-100.0, 500.0)	-14.3 (-100.0, 500.0)	-12.5 (-100.0, 800.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	Not reported[b]	-	-
Tolterodine ER vs placebo	Not reported[b]	-	-
Fesoterodine vs tolterodine ER	Not reported[b]	-	-
Percent Change From Baseline to Week 4	**n=437**	**n=888**	**n=879**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Week 4 mean (SD)	1.7 (1.3)	1.7 (1.3)	1.7 (1.4)
Percent change median (min, max)	-20.0 (-100.0, 600.0)	-25.0 (-100.0, 400.0)	-25.0 (-100.0, 1600.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0021	-	-
Percent Change From Baseline to Week 12	**n=437**	**n=892**	**n=879**
Baseline mean (SD)	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Week 12 mean (SD)	1.6 (1.3)	1.6 (1.3)	1.5 (1.3)
Percent change median (min, max)	-27.3 (-100.0, 800.0)	-33.3 (-100.0, 350.0)	-33.3 (-100.0, 500.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0200	-	-

ER = extended-release formulation; LOCF = last observation carried forward; min = minimum; max = maximum; N = number of subjects in the respective treatment group; n = number of subjects with Baseline nocturnal micturitions >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; vs = versus.

a. Based on a ranked analysis of covariance model with country and treatment as factors, and ranked Baseline value as a covariate.

b. Statistical testing for percent change was not reported since the corresponding numerical change result was not statistically significant.

- Change in Mean Number of Urinary Urgency Incontinence Episodes per 24 Hours at Week 1 and Week 4 Relative to Baseline: the mean number of UUI episodes per 24 hours decreased in all 3 treatment arms at Week 1 and Week 4 (Table 10). At Week 1, the reduction was statistically significantly greater in the fesoterodine 4 mg group compared with placebo (p=0.0006). Fesoterodine 4 mg treatment compared with tolterodine ER 4 mg did not result in a statistically significant improvement (p=0.2126). At Week 4, the reduction in the fesoterodine 8 mg group was statistically significant compared to both placebo (p <0.0001) and tolterodine ER 4 mg (p=0.0148).

Table 10. Change in Mean Number of UUI Episodes per 24 Hours at Weeks 1 and 4 Relative to Baseline – Full Analysis Set (Subjects Reporting This Symptom at Baseline)

Mean Number of UUI Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=442**	**n=911**	**n=899**
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Mean change from Baseline to Week 1 (SEM)[a]	-0.80 (0.06)	-0.95 (0.05)	-1.03 (0.05)
Treatment difference	Mean difference[a]		p-value[b]
Fesoterodine vs placebo	-0.23		0.0006
Tolterodine ER vs placebo	-0.15		0.0202
Fesoterodine vs tolterodine ER	-0.08		0.2126
Week 4	**n=448**	**n=922**	**n=908**
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Mean change from Baseline to Week 4 (SEM)[a]	-1.31 (0.07)	-1.52 (0.05)	-1.68 (0.05)
Treatment difference	Mean difference[a]		p-value[b]
Fesoterodine vs placebo	-0.37		<0.0001
Tolterodine ER vs placebo	-0.20		0.0019
Fesoterodine vs tolterodine ER	-0.16		0.0148

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with Baseline UUI >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1 or Week 4 [LOCF]); SD = standard deviation; SEM = standard error of the mean; UUI = urgency urinary incontinence; vs = versus.

a. Winsorized means (5% of the tails were censored, ie, replaced with the value at the fifth and 95th percentile respectively).

b. P-value based on Van Elteren's Test adjusted by Baseline UUI quartile.

- Percent Change of UUI episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: at Week 1, the percent reduction from Baseline was statistically significantly greater in the fesoterodine 4 mg group compared with placebo (p=0.0012, Table 11). At Week 4 and Week 12, the percent reductions were statistically significantly greater in the fesoterodine 8 mg group compared with both placebo (Week 4: p <0.0001, Week 12: p=0.0001) and tolterodine ER 4 mg (Week 4: p=0.0219, Week 12: p=0.0093).

Table 11. Percent Change of UUI Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Percent Change of UUI Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Percent Change From Baseline to Week 1	**n=442**	**n=911**	**n=899**
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Week 1 mean (SD)	1.6 (2.0)	1.6 (2.1)	1.5 (1.9)
Percent change median (min, max)	-40.8 (-100.0, 966.7)	-50.0 (-100.0, 366.7)	-50.0 (-100.0, 633.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0012	-	-
Tolterodine ER vs placebo	0.0205	-	-
Fesoterodine vs tolterodine ER	Not reported[b]	-	-
Percent Change From Baseline to Week 4	**n=448**	**n=922**	**n=908**
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Week 4 mean (SD)	1.1 (2.0)	1.1 (1.8)	0.9 (1.6)
Percent change median (min, max)	-75.0 (-100.0, 1000.0)	-88.9 (-100.0, 900.0)	-100.0 (-100.0, 666.7)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0038	-	-
Fesoterodine vs tolterodine ER	0.0219	-	-
Percent Change From Baseline to Week 12	**n=448**	**n=926**	**n=908**
Baseline mean (SD)	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
Week 12 mean (SD)	0.8 (1.8)	0.8 (1.8)	0.6 (1.2)
Percent change median (min, max)	-100.0 (-100.0, 612.5)	-100.0 (-100.0, 687.5)	-100.0 (-100.0, 500.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0001	-	-
Tolterodine ER vs placebo	0.0805	-	-
Fesoterodine vs tolterodine ER	0.0093	-	-

ER = extended-release formulation; LOCF = last observation carried forward; min = minimum; max = maximum; N = number of subjects in the respective treatment group; n = number of subjects with Baseline UUI >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); UUI = urgency urinary incontinence; SD = standard deviation; vs = versus.

a. Based on a ranked analysis of covariance model with country and treatment as factors, and ranked Baseline value as a covariate.

b. Statistical testing for percent change from Baseline to Week 1 was not reported for fesoterodine vs tolterodine as the corresponding numerical change result was not statistically significant.

- Change in Mean Number of Micturition-Related Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: the mean number of urgency episodes per 24 hours was comparable for the treatment groups at Baseline (9.5 to 9.7 episodes per 24 hours), and decreased for subjects in all treatment groups at Weeks 1, 4 and 12 (Table 12).

Table 12. Change in Mean Number of Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean Number of Urgency Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=447**	**n=918**	**n=906**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Change from Baseline to Week 1			
LSMean (SE)	-0.8 (0.2)	-1.0 (0.1)	-1.2 (0.2)
95% CI for mean	-1.3, -0.7	-1.5, -1.1	-1.7, -1.2
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.4 (0.2)	-0.7, -0.0	0.0374
Tolterodine ER vs placebo	-0.2 (0.2)	-0.5, 0.2	0.3161
Fesoterodine vs tolterodine ER	-0.2 (0.1)	-0.5, 0.1	0.1817
Week 4	**n=453**	**n=929**	**n=915**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Change from Baseline to Week 4			
LSMean (SE)	-1.9 (0.2)	-2.5 (0.2)	-3.1 (0.2)
95% CI for mean	-2.4, -1.7	-3.0, -2.5	-3.6, -3.1
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-1.2 (0.2)	-1.6, -0.8	<0.0001
Tolterodine ER vs placebo	-0.6 (0.2)	-1.0, -0.2	0.0054
Fesoterodine vs tolterodine ER	-0.6 (0.2)	-0.9, -0.3	0.0005
Week 12	**n=453**	**n=933**	**n=915**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Change from Baseline to Week 12			
LSMean (SE)	-3.2 (0.2)	-3.5 (0.2)	-4.2 (0.2)
95% CI for mean	-3.6, -2.8	-3.9, -3.4	-4.7, -4.1
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-1.0 (0.2)	-1.5, -0.6	<0.0001
Tolterodine ER vs placebo	-0.3 (0.2)	-0.7, 0.1	0.1467
Fesoterodine vs tolterodine ER	-0.7 (0.2)	-1.1, -0.4	<0.0001

CI = confidence interval; ER = extended-release formulation; LOCF = last observation carried forward; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with Baseline urgency episodes >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SE = standard error; vs = versus.

a. Based on a paired t-test comparing Baseline with postbaseline values.
b. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

- Percent Change of Micturition-Related Urgency Episodes per 24 Hours at Weeks 1, 4 and 12 Relative to Baseline: at Week 1, the percent reductions from Baseline were not statistically significantly greater in the fesoterodine 4 mg group compared with placebo (p=0.0828; Table 13). At Weeks 4 and 12, the percent reductions were statistically significantly greater in the fesoterodine 8 mg group compared with both placebo (Weeks 4 and 12: p <0.0001) and tolterodine ER 4 mg (Week 4: p=0.0022, Week 12: p=0.0008).

Table 13. Percent Change of Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set (Subjects Reporting this Symptom at Baseline)

Percent Change of Urgency Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Percent Change From Baseline to Week 1	**n=447**	**n=918**	**n=906**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Week 1 mean (SD)	8.4 (4.1)	8.4 (4.0)	8.3 (4.1)
Percent change median (min, max)	-9.4 (-100.0, 385.7)	-12.0 (-100.0, 325.0)	-11.8 (-100.0, 433.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	0.0828	-	-
Tolterodine ER vs placebo	Not reported[b]	-	-
Fesoterodine vs tolterodine ER	Not reported[b]	-	-
Percent Change From Baseline to Week 4	**n=453**	**n=929**	**n=915**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Week 4 mean (SD)	7.4 (4.3)	6.9 (4.3)	6.4 (4.3)
Percent change median (min, max)	-17.2 (-100.0, 457.1)	-26.3 (-100.0, 350.0)	-32.1 (-100.0, 433.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0008	-	-
Fesoterodine vs tolterodine ER	0.0022	-	-
Percent Change From Baseline to Week 12	**n=453**	**n=933**	**n=915**
Baseline mean (SD)	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Week 12 mean (SD)	6.2 (4.5)	6.0 (4.3)	5.3 (4.2)
Percent change median (min, max)	-31.0 (-100.0, 385.7)	-37.5 (-100.0, 475.0)	-45.5 (-100.0, 266.7)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Fesoterodine vs tolterodine ER	0.0008	-	-

ER = extended-release formulation; LOCF = last observation carried forward; min = minimum; max = maximum; N = number of subjects in the respective treatment group; n = number of subjects with Baseline urgency episodes >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; vs = versus.

a. Based on a ranked analysis of covariance model with country and treatment as factors, and ranked Baseline value as a covariate.

b. Statistical testing for percent change was not reported since the corresponding numerical change result was not statistically significant.

- Change in Mean Number of Severe Micturition-Related Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: the mean number of severe urgency episodes per 24 hours was comparable across treatment groups at Baseline (6.0 to 6.4 episodes per 24 hours), and decreased in all 3 treatment arms at Weeks 1, 4, and 12 (Table 14).

Table 14. Change in Mean Number of Severe Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean Number of Severe Urgency Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=446**	**n=915**	**n=902**
Baseline mean (SD)	6.0 (3.5)	6.3 (3.5)	6.4 (4.0)
Mean change from Baseline to Week 1 (SEM)[a]	-1.14 (0.13)	-1.34 (0.10)	-1.58 (0.11)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	-0.44		0.0576
Tolterodine ER vs placebo	-0.20		0.2230
Fesoterodine vs tolterodine ER	-0.24		0.3555
Week 4	**n=452**	**n=926**	**n=911**
Baseline mean (SD)	6.0 (3.6)	6.2 (3.5)	6.4 (4.0)
Mean change from Baseline to Week 4 (SEM)[a]	-2.14 (0.16)	-2.71 (0.12)	-3.21 (0.12)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	-1.07		<0.0001
Tolterodine ER vs placebo	-0.57		0.0009
Fesoterodine vs tolterodine ER	-0.50		0.0071
Week 12	**n=452**	**n=930**	**n=911**
Baseline mean (SD)	6.0 (3.6)	6.2 (3.5)	6.4 (4.0)
Mean change from Baseline to Week 12 (SEM)[a]	-3.01 (0.17)	-3.39 (0.13)	-4.08 (0.13)
Treatment difference	Mean difference[b]		p-value[c]
Fesoterodine vs placebo	-1.07		<0.0001
Tolterodine ER vs placebo	-0.38		0.1764
Fesoterodine vs tolterodine ER	-0.69		0.0001

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with Baseline severe urgency episodes >0 and non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SEM = standard error of the mean; vs = versus.

a. Winsorized means (5% of the tails were censored, ie, replaced with the value at the 5th and 95th percentile respectively).
b. Differences between Winsorized means.
c. P-value based on Van Elteren's Test adjusted by Baseline severe urgency episodes quartile.

- Percent Change of Severe Micturition-Related Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline: The fesoterodine 4 mg versus placebo or tolterodine ER 4 mg comparisons at Week 1 were not statistically significant. At Weeks 4 and 12, the percent reductions were statistically significantly greater in the fesoterodine 8 mg group compared with both placebo (Weeks 4 and 12: p <0.0001) and tolterodine ER 4 mg (Week 4: p=0.0302, Week 12: p=0.0007; Table 15).

Table 15. Percent Change of Severe Urgency Episodes per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set (Subjects Reporting this Symptom at Baseline)

Percent Change of Severe Urgency Episodes per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Percent Change From Baseline to Week 1	**n=446**	**n=915**	**n=902**
Baseline mean (SD)	6.0 (3.5)	6.3 (3.5)	6.4 (4.0)
Week 1 mean (SD)	4.9 (3.8)	4.9 (3.8)	4.8 (3.9)
Percent change median (min, max)	-19.7 (-100.0, 575.0)	-24.1 (-100.0, 500.0)	-25.0 (-100.0, 475.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	Not reported[b]	-	-
Tolterodine ER vs placebo	Not reported[b]	-	-
Fesoterodine vs tolterodine ER	Not reported[b]	-	-
Percent Change From Baseline to Week 4	**n=452**	**n=926**	**n=911**
Baseline mean (SD)	6.0 (3.6)	6.2 (3.5)	6.4 (4.0)
Week 4 mean (SD)	3.8 (3.8)	3.6 (3.9)	3.2 (3.6)
Percent change median (min, max)	-41.7 (-100.0, 533.3)	-55.6 (-100.0, 800.0)	-61.1 (-100.0, 433.3)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0003	-	-
Fesoterodine vs tolterodine ER	0.0302	-	-
Percent Change From Baseline to Week 12	**n=452**	**n=930**	**n=911**
Baseline mean (SD)	6.0 (3.6)	6.2 (3.5)	6.4 (4.0)
Week 12 mean (SD)	3.0 (3.6)	2.9 (3.7)	2.3 (3.3)
Percent change median (min, max)	-61.0 (-100.0, 1850.0)	-69.2 (-100.0, 600.0)	-79.3 (-100.0, 440.0)
p-value for treatment difference[a]			
Fesoterodine vs placebo	<0.0001	-	-
Fesoterodine vs tolterodine ER	0.0007	-	-

ER = extended-release formulation; LOCF = last observation carried forward; min = minimum, max = maximum; N = number of subjects in the respective treatment group; n = number of subjects with Baseline severe urgency episodes >0 per 24 hours and non-missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation, vs = versus.

a. Based on a ranked analysis of covariance model with country and treatment as factors, and ranked Baseline value as a covariate.

b. Statistical testing for percent change was not reported since the corresponding numerical change result was not statistically significant.

- Change in the Mean and Sum Rating on the USS at Weeks 1, 4, and 12 Relative to Baseline: Mean USS rating per micturition was identical across treatment groups at Baseline (rating 3.5), and decreased in all 3 treatment arms at Weeks 1, 4, and 12 (Table 16). The Frequency-Urgency Sum (ie, sum rating on the USS) per 24 hours was comparable across the treatment groups at Baseline (score 40.8 to 41.8) and decreased in all 3 treatment arms at Weeks 1, 4, and 12 (Table 17).

Table 16. Change in Mean USS Rating per Micturition per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Mean USS Rating per Micturition per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=447**	**n=918**	**n=906**
Baseline mean (SD)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Change from Baseline to Week 1			
LSMean (SE)	-0.2 (0.0)	-0.2 (0.0)	-0.2 (0.0)
95% CI for mean	-0.2, -0.1	-0.3, -0.2	-0.3, -0.2
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.1 (0.0)	-0.1, 0.0	0.0701
Tolterodine ER vs placebo	-0.0 (0.0)	-0.1, 0.0	0.4823
Fesoterodine vs tolterodine ER	-0.0 (0.0)	-0.1, 0.0	0.1702
Week 4	**n=453**	**n=929**	**n=915**
Baseline mean (SD)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Change from Baseline to Week 4			
LSMean (SE)	-0.3 (0.0)	-0.4 (0.0)	-0.5 (0.0)
95% CI for mean	-0.4, -0.3	-0.5, -0.4	-0.7, -0.6
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.2 (0.0)	-0.3, -0.1	<0.0001
Tolterodine ER vs placebo	-0.1 (0.0)	-0.2, -0.0	0.0059
Fesoterodine vs tolterodine ER	-0.1 (0.0)	-0.2, -0.0	0.0014
Week 12	**n=453**	**n=933**	**n=915**
Baseline mean (SD)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Change from Baseline to Week 12			
LSMean (SE)	-0.6 (0.0)	-0.6 (0.0)	-0.7 (0.0)
95% CI for mean	-0.7, -0.5	-0.7, -0.6	-0.9, -0.8
p-value[a]	<0.0001	<0.0001	<0.0001
Treatment difference[b]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-0.2 (0.0)	-0.3, -0.1	<0.0001
Tolterodine ER vs placebo	-0.0 (0.0)	-0.1, 0.0	0.3110
Fesoterodine vs tolterodine ER	-0.1 (0.0)	-0.2, -0.1	0.0004

CI = confidence interval; ER = extended-release formulation; LOCF = last observation carried forward; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SE = standard error; USS = Urinary Sensation Scale; vs = versus.

a. Based on a paired t-test comparing Baseline with postbaseline values.
b. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

Table 17. Change in Frequency-Urgency Sum[a] per 24 Hours at Weeks 1, 4, and 12 Relative to Baseline – Full Analysis Set

Frequency-Urgency Sum per 24 Hours	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Week 1	**n=447**	**n=918**	**n=906**
Baseline mean (SD)	40.8 (13.5)	41.8 (12.9)	41.7 (15.0)
Change from Baseline to Week 1			
LSMean (SE)	-4.0 (0.6)	-4.8 (0.5)	-5.5 (0.5)
95% CI for mean	-5.8, -3.8	-6.7, -5.2	-7.4, -5.8
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-1.5 (0.6)	-2.7, -0.3	0.0136
Tolterodine ER vs placebo	-0.8 (0.6)	-2.0, 0.4	0.1918
Fesoterodine vs tolterodine ER	-0.7 (0.5)	-1.7, 0.3	0.1505
Week 4	**n=453**	**n=929**	**n=915**
Baseline mean (SD)	40.7 (13.5)	41.7 (12.8)	41.6 (15.0)
Change from Baseline to Week 4			
LSMean (SE)	-8.1 (0.7)	-10.1 (0.6)	-12.0 (0.6)
95% CI for mean	-9.9, -7.5	-12.0, -10.3	-13.9, 12.1
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-3.9 (0.7)	-5.2, -2.6	<0.0001
Tolterodine ER vs placebo	-2.0 (0.7)	-3.3, -0.7	0.0034
Fesoterodine vs tolterodine ER	-1.9 (0.5)	-3.0, -0.8	0.0006
Week 12	**n=453**	**n=933**	**n=915**
Baseline mean (SD)	40.7 (13.5)	41.7 (12.9)	41.6 (15.0)
Change from Baseline to Week 12			
LSMean (SE)	-12.0 (0.7)	-13.2 (0.6)	-15.6 (0.6)
95% CI for mean	-13.6, -11.0	-14.9, -13.1	-17.4, -15.5
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-3.7 (0.7)	-5.0, -2.3	<0.0001
Tolterodine ER vs placebo	-1.2 (0.7)	-2.5, 0.2	0.0859
Fesoterodine vs tolterodine ER	-2.5 (0.6)	-3.6, -1.4	<0.0001

CI = confidence interval; ER = extended-release formulation; LOCF = last observation carried forward; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); SD = standard deviation; SE = standard error; USS = Urinary Sensation Scale; vs = versus.

a. Synonymous with the Urinary Sensations Scale Sum.
b. Based on a paired t-test comparing Baseline with postbaseline values.
c. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

- Percentage of Subjects Who Reported no UUI in the 3-day Bladder Diary at Weeks 1, 4, or 12 Among Those Who Reported >0 UUI Episode at Baseline (Diary Dry Rates): the diary dry rate was defined as percentage of subjects who reported no UUI in the 3-day micturition diary at a postbaseline time point (Week 1, 4, or 12) among subjects who reported >0 UUI episode in the Baseline 3-day diary. At Week 1, the diary dry rate was statistically significantly higher in the fesoterodine 4 mg group than in the placebo group

(p=0.0008). At Weeks 4 and 12, fesoterodine 8 mg treatment resulted in a statistically significantly higher dry rate compared to both placebo and tolterodine ER 4 mg (Table 18).

Table 18. Diary Dry Rates at Weeks 1, 4, and 12 - Full Analysis Set

	Placebo N=478		Tolterodine ER N=973		Fesoterodine N=960	
Week 1	**n**	**%**	**n**	**%**	**n**	**%**
Subjects with Baseline UUI >0 per 24 hours[a]	442	100.0	911	100.0	899	100.0
Percentage of subjects reporting no UUI[b]	78	17.6	223	24.5	226	25.1
Treatment difference		%			p-value[c]	
Fesoterodine vs placebo		7.5			0.0008	
Tolterodine ER vs placebo		6.8			0.0024	
Fesoterodine vs tolterodine ER		0.7			0.6514	
Week 4	**n**	**%**	**n**	**%**	**n**	**%**
Subjects with Baseline UUI >0 per 24 hours[a]	448	100.0	922	100.0	908	100.0
Percentage of subjects reporting no UUI[b]	177	39.5	431	46.7	464	51.1
Treatment difference		%			p-value[c]	
Fesoterodine vs placebo		11.6			<0.0001	
Tolterodine ER vs placebo		7.2			0.0063	
Fesoterodine vs tolterodine ER		4.4			0.0494	
Week 12	**n**	**%**	**n**	**%**	**n**	**%**
Subjects with Baseline UUI >0 per 24 hours[a]	448	100.0	926	100.0	908	100.0
Percentage of subjects reporting no UUI[b]	241	53.8	538	58.1	574	63.2
Treatment difference		%			p-value[c]	
Fesoterodine vs placebo		9.4			0.0003	
Tolterodine ER vs placebo		4.3			0.0991	
Fesoterodine vs tolterodine ER		5.1			0.0169	

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with Baseline UUI >0 per 24 hours and non- missing change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); UUI = Urgency urinary incontinence; vs = versus.

a. Only subjects with non-missing Baseline and Week 1 values are included.
b. No urgency urinary incontinence episode reported in the 3 day diary at the respective time point.
c. Based on Cochran-Mantel-Haenszel test stratified by Baseline urgency urinary incontinence quartile.

- Change in PPBC at Weeks 1, 4, and 12 Relative to Baseline: the results for the 4-category analysis are presented by Weeks 1, 4 and 12 in Table 19. At Week 1, the composition of the categorical changes of PPBC from Baseline was statistically significant in favor of the fesoterodine 4 mg group versus placebo (p=0.0009). The comparison fesoterodine 4 mg versus tolterodine ER 4 mg did not show a statistically significant improvement (p=0.2817). At Weeks 4 and 12, the differences between fesoterodine 8 mg and both placebo and tolterodine ER 4 mg were statistically significant in favor of fesoterodine 8 mg (p <0.05).

Table 19. Change in Patient Perception of Bladder Condition at Weeks 1, 4, and 12 Relative to Baseline (4-Category Analyses) – Full Analysis Set

PPBC Category[a]	Number (%)[b] of Subjects		
	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Change From Baseline to Week 1	**n=452**	**n=931**	**n=913**
Major improvement	43 (9.5)	138 (14.8)	144 (15.8)
Minor improvement	144 (31.9)	278 (29.9)	280 (30.7)
No change	210 (46.5)	434 (46.6)	428 (46.9)
Deterioration	55 (12.2)	81 (8.7)	61 (6.7)
p-value for treatment difference[c]			
Fesoterodine vs placebo	0.0009	-	-
Tolterodine ER vs placebo	0.0279	-	-
Fesoterodine vs tolterodine ER	0.2817	-	-
Change From Baseline to Week 4	**n=455**	**n=937**	**n=918**
Major improvement	111 (24.4)	290 (30.9)	334 (36.4)
Minor improvement	124 (27.3)	298 (31.8)	280 (30.5)
No change	172 (37.8)	285 (30.4)	250 (27.2)
Deterioration	48 (10.5)	64 (6.8)	54 (5.9)
p-value for treatment difference[c]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0001	-	-
Fesoterodine vs tolterodine ER	0.0177	-	-
Change From Baseline to Week 12	**n=455**	**n=937**	**n=918**
Major improvement	166 (36.5)	379 (40.4)	440 (47.9)
Minor improvement	106 (23.3)	250 (26.7)	236 (25.7)
No change	133 (29.2)	249 (26.6)	189 (20.6)
Deterioration	50 (11.0)	59 (6.3)	53 (5.8)
p-value for treatment difference[c]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0107	-	-
Fesoterodine vs tolterodine ER	0.0005	-	-

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); PPBC = Patient Perception of Bladder Condition; vs = versus.

a. Major improvement=negative score change from Baseline in magnitude of 2 or more points; minor improvement=score change from Baseline is negative in magnitude of 1 point; no change = score change from Baseline is 0; deterioration=score change from Baseline is positive.
b. Based on n.
c. Based on Cochran-Mantel-Haenszel test with modified ridit scoring and stratified by country.

- Change in PPUS at Week 1, 4, and 12 Relative to Baseline: the results are presented by Weeks 1, 4 and 12 in Table 20. At Week 1, the distribution of the categorical changes of UPS from Baseline was statistically significant in favor of fesoterodine 4 mg compared to placebo (p=0.0011). Fesoterodine 4 mg compared with tolterodine ER 4 mg did not show statistically significance (p=0.3713). At Weeks 4 and 12, the differences between fesoterodine 8 mg and both placebo (Week 4: p=0.0002, Week 12: p <0.0001) and tolterodine ER 4 mg (Week 4: p=0.0040, Week 12: p=0.0016) were statistically significant in favor of fesoterodine 8 mg.

Table 20. Change in Urgency Perception Scale at Weeks 1, 4, and 12 Relative to Baseline (3-Category Analysis) – Full Analysis Set

UPS Score[a,b]	Number (%)[c] of Subjects		
	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Change From Baseline to Week 1	**n=452**	**n=932**	**n=913**
Improvement	97 (21.5)	264 (28.3)	267 (29.2)
No change	326 (72.1)	619 (66.4)	609 (66.7)
Deterioration	29 (6.4)	49 (5.3)	37 (4.1)
p-value for treatment difference[d]			
Fesoterodine vs placebo	0.0011	-	-
Tolterodine ER vs placebo	0.0072	-	-
Fesoterodine vs tolterodine ER	0.3713	-	-
Change From Baseline to Week 4	**n=455**	**n=938**	**n=918**
Improvement	161 (35.4)	376 (40.1)	421 (45.9)
No change	271 (59.6)	511 (54.5)	467 (50.9)
Deterioration	23 (5.1)	51 (5.4)	30 (3.3)
p-value for treatment difference[d]			
Fesoterodine vs placebo	0.0002	-	-
Tolterodine ER vs placebo	0.1485	-	-
Fesoterodine vs tolterodine ER	0.0040	-	-
Change From Baseline to Week 12	**n=455**	**n=938**	**n=918**
Improvement	183 (40.2)	440 (46.9)	495 (53.9)
No change	239 (52.5)	455 (48.5)	393 (42.8)
Deterioration	33 (7.3)	43 (4.6)	30 (3.3)
p-value for treatment difference[d]			
Fesoterodine vs placebo	<0.0001	-	-
Tolterodine ER vs placebo	0.0060	-	-
Fesoterodine vs tolterodine ER	0.0016	-	-

ER = extended-release formulation; LOCF = last observation carried forward; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to the respective postbaseline value (Week 1, Week 4 [LOCF], or Week 12 [LOCF]); UPS = Urgency Perception Scale; vs = versus.

a. Formerly known as the Patient Perception of Urgency Scale.
b. Improvement=positive score change from Baseline in magnitude of 1 or more points; no change = score change from Baseline is 0; deterioration = negative score change from Baseline in magnitude of 1 or more points.
c. Based on n.
d. Based on Cochran-Mantel-Haenszel test with modified ridit scoring and stratified by country.

- Overactive Bladder Questionnaire (OAB-q): change in OAB-q at Week 12 relative to Baseline is summarized in Table 21. The scores of the Symptom Bother Scale and the HRQL Scale and its domains were comparable across all 3 treatment arms at Baseline and improved in all arms from Baseline at Week 12. The improvement in the Symptom Bother Scale and each domain of HRQL Scale was statistically significantly greater for fesoterodine 8 mg compared with both placebo and tolterodine (all: $p < 0.05$).

Table 21. Change in Overactive Bladder Questionnaire at Week 12 Relative to Baseline – Full Analysis Set

HRQL Component	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
Symptom Bother Score[a]	**n=436**	**n=897**	**n=876**
Baseline mean (SD)	57.4 (18.1)	59.3 (19.5)	59.4 (19.1)
Change from Baseline to Week 12			
LSMean (SE)	-21.8 (1.3)	-24.3 (1.0)	-28.9 (1.1)
95% CI for mean	-24.5, -19.9	-27.6, -24.3	-32.3, -29.0
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	-7.1 (1.2)	-9.5, -4.7	<0.0001
Tolterodine ER vs placebo	-2.4 (1.2)	-4.8, -0.0	0.0458
Fesoterodine vs tolterodine ER	-4.6 (1.0)	-6.6, -2.7	<0.0001
HRQL Scale Total Score[a]	**n=431**	**n=892**	**n=873**
Baseline mean (SD)	54.9 (20.7)	53.3 (22.8)	53.4 (21.3)
Change from Baseline to Week 12			
LSMean (SE)	17.2 (1.2)	19.5 (1.0)	22.9 (1.0)
95% CI for mean	16.1, 20.5	20.1, 23.2	23.3, 26.4
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	5.6 (1.1)	3.4, 7.9	<0.0001
Tolterodine ER vs placebo	2.3 (1.1)	0.1, 4.6	0.0429
Fesoterodine vs tolterodine ER	3.3 (0.9)	1.5, 5.2	0.0003
HRQL Concern Domain[a]	**n=434**	**n=894**	**n=875**
Baseline mean (SD)	50.5 (23.5)	49.1 (26.0)	48.4 (24.9)
Change from Baseline to Week 12			
LSMean (SE)	20.2 (1.4)	22.5 (1.1)	26.8 (1.1)
95% CI for mean	18.6, 23.7	22.5, 26.1	27.0, 30.7
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	6.6 (1.3)	4.0, 9.2	<0.0001
Tolterodine ER vs placebo	2.3 (1.3)	-0.3, 4.9	0.0795
Fesoterodine vs tolterodine ER	4.2 (1.1)	2.1, 6.3	<0.0001
HRQL Coping Domain[a]	**n=433**	**n=892**	**n=875**
Baseline mean (SD)	48.2 (25.4)	46.2 (27.2)	46.1 (25.7)
Change from Baseline to Week 12			
LSMean (SE)	19.0 (1.4)	22.0 (1.1)	25.9 (1.2)
95% CI for mean	18.1, 23.2	23.1, 26.8	26.9, 30.6
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	7.0 (1.4)	4.3, 9.6	<0.0001
Tolterodine ER vs placebo	3.1 (1.3)	0.4, 5.7	0.0229
Fesoterodine vs tolterodine ER	3.9 (1.1)	1.7, 6.0	0.0004
HRQL Sleep Domain[a]	**n=433**	**n=894**	**n=875**
Baseline mean (SD)	53.4 (24.7)	51.3 (26.3)	52.2 (25.0)
Change from Baseline to Week 12			
LSMean (SE)	16.6 (1.3)	18.7 (1.1)	21.0 (1.1)
95% CI for mean	14.9, 19.7	18.9, 22.4	20.7, 24.1
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	4.5 (1.2)	2.0, 6.9	0.0003
Tolterodine ER vs placebo	2.1 (1.2)	-0.3, 4.5	0.0923
Fesoterodine vs tolterodine ER	2.4 (1.0)	0.4, 4.4	0.0180

Table 21. Change in Overactive Bladder Questionnaire at Week 12 Relative to Baseline – Full Analysis Set

HRQL Component	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
HRQL Social Interaction Domain[a]	**n=435**	**n=894**	**n=873**
Baseline mean (SD)	73.7 (23.2)	72.4 (24.3)	73.2 (23.2)
Change from Baseline to Week 12			
LSMean (SE)	10.8 (1.0)	12.0 (0.8)	13.9 (0.8)
95% CI for mean	9.4, 13.5	12.0, 14.9	13.5, 16.3
p-value[b]	<0.0001	<0.0001	<0.0001
Treatment difference[c]	LSMean difference (SE)	95% CI	p-value
Fesoterodine vs placebo	3.2 (1.0)	1.3, 5.1	0.0011
Tolterodine ER vs placebo	1.2 (1.0)	-0.7, 3.1	0.2208
Fesoterodine vs tolterodine ER	2.0 (0.8)	0.4, 3.5	0.0117

CI = confidence interval; ER = extended-release formulation; HRQL = health-related quality of life; LSMean = least squares mean; N = number of subjects in the respective treatment group; n = number of subjects with non-missing numerical change from Baseline to Week 12; SD = standard deviation; SE = standard error; vs = versus.

a. Negative change in symptom bother score indicated improvement; whereas an improvement in HRQL score indicated by a positive change.

b. Based on a paired t-test comparing Baseline with postbaseline values.

c. Based on an analysis of covariance model with country and treatment as factors, and Baseline value as a covariate.

Safety Results: An overall summary of treatment emergent AEs (TEAEs) that occurred after the first double-blind study drug administration and within 7 days after last dosing is provided in Table 22.

Table 22. Overall Summary of Treatment-Emergent Adverse Events

	Number (%) of Subjects					
	Placebo N=478		Tolterodine ER N=973		Fesoterodine N=960	
	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Number of TEAEs	236	90	633	341	818	556
Subjects with TEAEs	145 (30.3)	70 (14.6)	375 (38.5)	236 (24.3)	459 (47.8)	368 (38.3)
Subjects with TESAEs	8 (1.7)	0	6 (0.6)	0	13 (1.4)	2 (0.2)
Deaths (fatal TESAEs)	1 (0.2)	0	0	0	0	0
Non-fatal TESAEs	7 (1.5)	0	6 (0.6)	0	13 (1.4)	2 (0.2)
Subjects with severe TEAEs	9 (1.9)	0	19 (2.0)	8 (0.8)	38 (4.0)	29 (3.0)
Subjects discontinued from treatment or study due to TEAE	8 (1.7)	4 (0.8)	27 (2.8)	16 (1.6)	43 (4.5)	36 (3.8)
Subjects with dose reduced or temporary discontinuation of treatment due to TEAE	3 (0.6)	0	16 (1.6)	6 (0.6)	11 (1.1)	8 (0.8)

Data for TEAEs include both non serious adverse events (AEs) and serious AEs (SAEs) ie, AEs and SAEs are not separated out.

ER = extended-release formulation; N = number of subjects in the respective treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event (included data up to 7 days after last dose of study drug).

The TEAEs (all causality) that occurred in ≥1% of subjects in any treatment group are listed in Table 23, together with the corresponding System Organ Class (SOC) and their relationship to study drug. The most frequently reported non serious AEs in the fesoterodine group were dry mouth, constipation, and headache. Most of those 3 TEAEs were considered treatment related by the Investigators in every treatment group; summarized in Table 24.

Table 23. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Placebo	Tolterodine ER	Fesoterodine
	n (%)	n (%)	n (%)
Number (%) of subjects:			
Evaluable for adverse events	478	973	960
With adverse events	83 (17.4)	261 (26.8)	375 (39.1)
Number (%) of subjects with adverse events by:			
System Organ Class			
MedDRA (v12.1) Preferred Term			
Gastrointestinal disorders	38 (7.9)	170 (17.5)	304 (31.7)
Constipation	7 (1.5)	30 (3.1)	42 (4.4)
Diarrhoea	3 (0.6)	11 (1.1)	11 (1.1)
Dry mouth	26 (5.4)	130 (13.4)	265 (27.6)
Dyspepsia	2 (0.4)	10 (1.0)	21 (2.2)
Nausea	3 (0.6)	13 (1.3)	11 (1.1)
General disorders and administration site conditions	5 (1.0)	14 (14)	4 (0.4)
Oedema peripheral	5 (1.0)	14 (1.4)	4 (0.4)
Infections and infestations	20 (4.2)	51 (5.2)	33 (3.4)
Bronchitis	6 (1.3)	10 (1.0)	3 (0.3)
Influenza	1 (0.2)	12 (1.2)	5 (0.5)
Nasopharyngitis	6 (1.3)	9 (0.9)	8 (0.8)
Sinusitis	2 (0.4)	11 (1.1)	4 (0.4)
Urinary tract infection	5 (1.0)	12 (1.2)	14 (1.5)
Musculoskeletal and connective tissue disorders	6 (1.3)	9 (0.9)	8(0.8)
Back pain	6 (1.3)	9 (0.9)	8 (0.8)
Nervous system disorders	6 (1.3)	20 (2.1)	27 (2.8)
Headache	6 (1.3)	20 (2.1)	27 (2.8)
Renal and urinary disorders	12 (2.5)	32 (3.3)	39 (4.1)
Dysuria	2 (0.4)	8 (0.8)	10 (1.0)
Polyuria	10 (2.1)	24 (2.5)	29 (3.0)
Respiratory, thoracic and mediastinal disorders	3 (0.6)	5 (0.5)	21 (2.2)
Cough	3 (0.6)	4 (0.4)	12 (1.3)
Dry throat	0	2 (0.2)	11 (1.1)

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
ER = extended-release formulation; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the respective treatment group; v = version.

Table 24. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment Related)

Number (%) of Subjects With TEAEs	Number (%) of Subjects		
	Placebo N=478	Tolterodine ER N=973	Fesoterodine N=960
System Organ Class MedDRA (v12.1) preferred term			
Gastrointestinal disorders	35 (7.3)	163 (16.8)	304 (31.7)
Dry mouth	26 (5.4)	127 (13.1)	265 (27.6)
Constipation	6 (1.3)	28 (2.9)	41 (4.3)
Dyspepsia	1 (0.2)	6 (0.6)	15 (1.6)
Nausea	1 (0.2)	7(0.7)	10 (1.0)
Diarrhoea	1 (0.2)	7 (0.7)	6 (0.6)
Infections and infestations	3 (0.6)	8 (0.8)	10(1.0)
Urinary tract infection	1 (0.2)	2 (0.2)	4 (0.4)
Sinusitis	0	2 (0.2)	2 (0.2)
Renal and urinary disorders	8(1.7)	28 (2.9)	30 (3.1)
Polyuria	6(1.3)	16 (1.6)	12 (1.3)
Dysuria	1(0.2)	5 (0.5)	9 (0.9)
Nervous system disorders	5(1.0)	29 (3.0)	35 (3.6)
Headache	2(0.4)	14(1.4)	22 (2.3)
Dizziness	1(0.2)	5 (0.5)	7 (0.7)
Respiratory, thoracic and mediastinal disorders	3 (0.6)	10 (1.0)	24 (2.5)
Cough	1 (0.2)	3 (0.3)	6 (0.6)
Dry throat	0	2 (0.2)	11 (1.1)
General disorders and administration site conditions	8 (1.7)	13 (1.3)	12 (1.3)
Oedema peripheral	3 (0.6)	9 (0.9)	1 (0.1)

TEAEs include both non serious adverse events (AEs) and serious AEs (SAEs) ie, AEs and SAEs are not separated out.
MedDRA (v12.1) coding dictionary applied.
ER = extended-release formulation; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the respective treatment group; TEAE = treatment-emergent adverse event (included data up to 7 days after last dose of study drug); v = version.

Polyuria was assessed as treatment related, with a similar frequency in all treatment groups: 1.3% in the placebo group, 1.6% in the tolterodine ER group and 1.3% in the fesoterodine group. However, the reporting of polyuria was not based on the spontaneous reports by the subjects and/or Investigators, but rather triggered by a programmed database query procedure. It checked the total voided volume recorded in the 3-day diaries collected in the postrandomization visits and recorded all cases of voided volume greater than 3000 mL as AE polyuria.

All treatment emergent SAEs (TESAEs) are reported by SOC and preferred term in Table 25. None of the SAEs in the placebo or tolterodine ER treatment groups was considered treatment related. Two non-fatal TESAE cases (acute pyelonephritis and urinary retention) in the fesoterodine group were considered treatment related.

Table 25. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Placebo	Tolterodine ER	Fesoterodine
	n (%)	n (%)	n (%)
Number (%) of subjects:			
Evaluable for adverse events	478	973	960
With adverse events	8 (1.7)	6 (0.6)	13 (1.4)
Number (%) of subjects with adverse events by:			
System Organ Class			
MedDRA (v12.1) preferred term			
Cardiac disorders	1 (0.2)	0	2 (0.2)
Angina unstable	0	0	1 (0.1)
Atrial fibrillation	0	0	1 (0.1)
Atrial tachycardia	0	0	1 (0.1)
Cardiac failure chronic	0	0	1 (0.1)
Cardiac failure congestive	1 (0.2)	0	0
Mitral valve stenosis	1 (0.2)	0	0
Gastrointestinal disorders	1 (0.2)	0	0
Diverticulum intestinal haemorrhagic	1 (0.2)	0	0
Large intestine perforation	1 (0.2)	0	0
Peritonitis	1 (0.2)	0	0
General disorders and administration site conditions	0	0	1 (0.1)
Chest pain	0	0	1 (0.1)
Hepatobiliary disorders	1 (0.2)	0	0
Hepatitis acute	1 (0.2)	0	0
Infections and infestations	2 (0.4)	0	4 (0.4)
Bronchopneumonia	0	0	1 (0.1)
Cellulitis	1 (0.2)	0	0
Pneumonia	1 (0.2)	0	1 (0.1)
Pyelonephritis	0	0	1 (0.1)
Pyelonephritis acute	0	0	1 (0.1)
Sepsis	0	0	1 (0.1)
Injury, poisoning and procedural complications	2 (0.4)	2 (0.2)	1 (0.1)
Delayed recovery from anaesthesia	1 (0.2)	0	0
Fibula fracture	0	1 (0.1)	0
Lower limb fracture	1 (0.2)	0	0
Spinal compression fracture	0	1 (0.1)	0
Therapeutic agent toxicity	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	1 (0.1)	0
Osteoporotic fracture	0	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	3 (0.3)	1 (0.1)
Breast cancer	0	1 (0.1)	0
Colon cancer	0	1 (0.1)	1 (0.1)
Gastric cancer	0	1 (0.1)	0
Hepatic neoplasm	1 (0.2)	0	0
Nervous system disorders	0	0	3 (0.3)
Balance disorder	0	0	1 (0.1)
Dizziness	0	0	2 (0.2)
Ischaemic stroke	0	0	1 (0.1)

Table 25. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Placebo	Tolterodine ER	Fesoterodine
	n (%)	n (%)	n (%)
Psychiatric disorders	0	0	1 (0.1)
Bipolar disorder	0	0	1 (0.1)
Mania	0	0	1 (0.1)
Renal and urinary disorders	0	0	2 (0.2)
Renal failure acute	0	0	1 (0.1)
Urinary retention	0	0	1 (0.1)
Reproductive system and breast disorders	0	0	1 (0.1)
Postmenopausal haemorrhage	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)	0
Allergic respiratory disease	0	1 (0.1)	0
Skin and subcutaneous tissue disorders	0	0	1 (0.1)
Hyperhidrosis	0	0	1 (0.1)
Surgical and medical procedures	0	0	1 (0.1)
Cholecystectomy	0	0	1 (0.1)
Vascular disorders	1 (0.2)	0	0
Deep vein thrombosis	1 (0.2)	0	0

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
ER = extended-release formulation; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the respective treatment group; v = version.

Permanent Discontinuations: Discontinuations from the study due to TEAEs occurred in 8 subjects (1.7%) in the placebo group, 27 subjects (2.8%) in the tolterodine ER group, and 43 subjects (4.5%) in the fesoterodine group. All TEAEs that occurred during the double-blind treatment period and led to subject discontinuation from the study are shown in Table 26.

Table 26. Treatment-Emergent Adverse Events That led to Permanent Discontinuation – Safety Analysis Set

	Number (%) of Subjects					
	Placebo N=478		Tolterodine ER N=973		Fesoterodine N=960	
MedDRA Preferred Term[a,b]	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Subjects evaluable for TEAEs	478		973		960	
Subjects discontinued from the study due to TEAE	8 (1.7)	4 (0.8)	27 (2.8)	16 (1.6)	43 (4.5)	36 (3.8)
Subjects discontinued from the study due to severe TEAE	1 (0.2)	0	4 (0.4)	1 (0.1)	13 (1.4)	9 (0.9)
Dry mouth	0	0	4 (0.4)	4 (0.4)	10 (1.0)	10 (1.0)
Dysuria	0	0	0	0	5 (0.5)	5 (0.5)
Constipation	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	4 (0.4)	4 (0.4)
Urinary retention	0	0	1 (0.1)	1 (0.1)	3 (0.3)	3 (0.3)
Dyspepsia	1 (0.2)	1 (0.2)	0	0	2 (0.2)	2 (0.2)
Abdominal pain	0	0	0	0	2 (0.2)	2 (0.2)
Insomnia	0	0	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Vision blurred	0	0	0	0	1 (0.1)	1 (0.1)
Pubic pain	0	0	0	0	1 (0.1)	1 (0.1)
Pyelonephritis acute	0	0	0	0	1 (0.1)	1 (0.1)
Face oedema	0	0	0	0	1 (0.1)	1 (0.1)
Erythema	0	0	0	0	1 (0.1)	1 (0.1)
Cough	0	0	0	0	1 (0.1)	1 (0.1)
Palpitations	0	0	0	0	1 (0.1)	1 (0.1)
Strangury	0	0	0	0	1 (0.1)	1 (0.1)
Dry eye	0	0	0	0	1 (0.1)	1 (0.1)
Dizziness	0	0	0	0	1 (0.1)	1 (0.1)
Ischaemic stroke	0	0	0	0	1 (0.1)	0
Pyelonephritis	0	0	0	0	1 (0.1)	0
Sepsis	0	0	0	0	1 (0.1)	0
Therapeutic agent toxicity	0	0	0	0	1 (0.1)	0
Renal failure acute	0	0	0	0	1 (0.1)	0
Gastritis	0	0	0	0	1 (0.1)	0
Uterine haemorrhage	0	0	0	0	1 (0.1)	0
Cardiac failure chronic	0	0	0	0	1 (0.1)	0
Nausea	0	0	2 (0.2)	1 (0.1)	0	0
Rash	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)	0	0
Headache	0	0	1 (0.1)	1 (0.1)	0	0
Bladder pain	0	0	1 (0.1)	1 (0.1)	0	0
Oedema peripheral	0	0	1 (0.1)	1 (0.1)	0	0
Paraesthesia	0	0	1 (0.1)	1 (0.1)	0	0
Arthralgia	0	0	1 (0.1)	1 (0.1)	0	0
Abdominal pain upper	0	0	1 (0.1)	1 (0.1)	0	0
Colon cancer	0	0	1 (0.1)	0	0	0
Micturition urgency	0	0	1 (0.1)	0	0	0
Nephrolithiasis	0	0	1 (0.1)	0	0	0
Myalgia	0	0	1 (0.1)	0	0	0
Influenza	0	0	1 (0.1)	0	0	0
Myasthenia gravis	0	0	1 (0.1)	0	0	0
Urinary tract infection	0	0	1 (0.1)	0	0	0
Breast cancer	0	0	1 (0.1)	0	0	0
Gastric cancer	0	0	1 (0.1)	0	0	0

Table 26. Treatment-Emergent Adverse Events That led to Permanent Discontinuation – Safety Analysis Set

	Number (%) of Subjects					
	Placebo N=478		Tolterodine ER N=973		Fesoterodine N=960	
MedDRA Preferred Term[a,b]	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Respiratory disorder	0	0	1 (0.1)	0	0	0
Vomiting	1 (0.2)	1 (0.2)	0	0	0	0
Flushing	1 (0.2)	0	0	0	0	0
Meningioma	1 (0.2)	0	0	0	0	0
Sensory loss	1 (0.2)	0	0	0	0	0
Diverticulum intestinal haemorrhagic	1 (0.2)	0	0	0	0	0
Large intestine perforation	1 (0.2)	0	0	0	0	0
Peritonitis	1 (0.2)	0	0	0	0	0

ER = extended-release formulation; MedDRA = Medical Dictionary for Regulatory Activities (version 12.1); N = number of subjects in the respective treatment group; TEAE = treatment-emergent adverse event (included data up to 7 days after last dose of study drug); TESAE = treatment-emergent serious adverse event.
a. Sorted by descending frequency by TEAEs in the fesoterodine group and then in the tolterodine ER group (all causality).
b. Treatment discontinuation could be attributed to a single TEAE or to multiple events. Therefore, an individual subject might be counted more than once across the individual TEAEs.

There were no reports of dose reductions due to AEs. Temporary discontinuations of the study drug due to TEAEs were reported for 6 subjects (1.3%) in the placebo group, 16 subjects (1.6%) in the tolterodine ER group and 13 subjects (1.4%) in the fesoterodine group, respectively. Diarrhoea, dry mouth and dizziness were the only TEAEs leading to more than 1 case of temporary discontinuation of study drug in any treatment group. Three subjects in the tolterodine group and 2 subjects in the fesoterodine group temporarily discontinued study treatment due to diarrhea, for 1 subject in each group it was assessed as treatment related. Three subjects in the fesoterdine group discontinued the study drug temporarily due to dry mouth, all of these cases were assessed as treatment related. Two subjects in the tolterodine group temporarily discontinued due to dizziness, 1 of which was assessed as treatment related.

One death was reported in the placebo group during the study due to be hepatic neoplasm. The onset of the event was at Day 66, and the subject died at Day 95. There were no deaths in the tolterodine ER and fesoterodine groups.

CONCLUSIONS:

This was a 12-week, randomized, double-blind, double-dummy, placebo-controlled, superiority design study to compare the efficacy of fesoterodine to placebo and tolterodine ER in subjects with OAB. In this study, subjects were treated with either fesoterodine 4 mg for 1 week followed by fesoterodine 8 mg for 11 weeks, tolterodine ER 4 mg for 12 weeks, or placebo for 12 weeks.

- Superior efficacy of fesoterodine 8 mg over tolterodine ER 4 mg and placebo was demonstrated at Week 12 on the primary endpoint, ie, there was a statistically significantly greater reduction in UUI episodes from Baseline to Week 12. Fesoterodine 8 mg also showed a statistically significantly greater effect than placebo and tolterodine ER 4 mg on the secondary diary endpoints of decrease in mean number of micturitions, urgency and severe urgency episodes, diary dry rate, USS rating per micturition and frequency-urgency sum as well as on all PROs endpoints based on PPBC, UPS and all domains of OAB-q at Week 12.

    - Fesoterodine 8 mg showed a statistically significantly greater effect than placebo but not tolterodine ER 4 mg on the other secondary diary endpoints of mean voided volume per micturition and number of nocturnal micturitions.

    - Tolterodine ER 4 mg showed statistically significant efficacy over placebo in the primary endpoint UUI reduction from Baseline at Week 12 and in several secondary endpoints including mean voided volume per micturition, number of micturitions and selected PROs at Week 12.

- An early onset of superiority of fesoterodine 8 mg over tolterodine ER 4 mg on the UUI reduction was observed at Week 4 (3 weeks after titration of fesoterodine from 4 mg to 8 mg).

    - Fesoterodine 8 mg led to statistically significant improvements compared to tolterodine ER 4 mg in all bladder diary endpoints (except mean number of nocturnal micturitions), PPBC and UPS endpoints at Week 4.

- An early onset of efficacy of fesoterodine 4 mg at Week 1 was observed: fesoterodine 4 mg showed a statistically significantly greater effect than placebo in improving key diary efficacy measures, including those for UUI, diary dry rate, mean voided volume per micturition, number of micturitions, urgency episodes and frequency-urgency sum, and PPBC and UPS at Week 1.

- Fesoterodine 8 mg treatment for 11 weeks with a starting dose of 4 mg for 1 week was associated with a greater incidence of some anticholinergic TEAEs, primarily dry mouth, compared to placebo and tolterodine ER 4 mg. However, with low incidences of TESAEs, including urinary retention, and treatment discontinuation due to TEAEs, this fesoterodine regimen showed a good safety and tolerability profile. No unexpected safety risk was identified.