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

PROTOCOL NO.: A0221094

PROTOCOL TITLE: A 14 Week Randomized Parallel Group Placebo-Controlled Double-Blind Multicentre Study of Fesoterodine 8 mg in Overactive Bladder Patients With Sub-Optimal Response to Tolterodine 4 mg ER

Study Centers: A total of 129 centers in 14 countries took part in the study and enrolled subjects: 5 centers each in Bulgaria and Sweden, 4 centers each in Czech Republic and Hungary, Germany (10 centers), Canada (6 centers), 1 center each in Egypt and South Africa, Hungary (4 centers), Mexico (2 centers), Russian Federation (7 centers), Ukraine (8 centers), Republic of Korea (3 centers), Poland (3 centers), Sweden (5 centers) and the United States (70 centers).

Study Initiation Date and Final Completion Date: 16 May 2011 to 25 May 2012

Phase of Development: Phase 4 (in some countries fesoterodine had not gained approval at the time of study and thus the study was designated as Phase 3 in those countries).

Study Objectives:

Primary Objective: To determine the efficacy of 8 mg fesoterodine on urgency urinary incontinence (UUI) reduction in overactive bladder (OAB) subjects with suboptimal response to tolterodine over time and in comparison with placebo.

Secondary Objectives:

- To determine the efficacy of 8 mg fesoterodine on frequency and urgency in OAB subjects with suboptimal response to tolterodine over time and in comparison with placebo;
- To determine the efficacy of 8 mg fesoterodine on quality of life subject reported outcomes in OAB subjects with suboptimal response to tolterodine, over time and in comparison with placebo;
- To determine the tolerability and safety of 8 mg fesoterodine in OAB subjects with suboptimal response to tolterodine.

METHODS

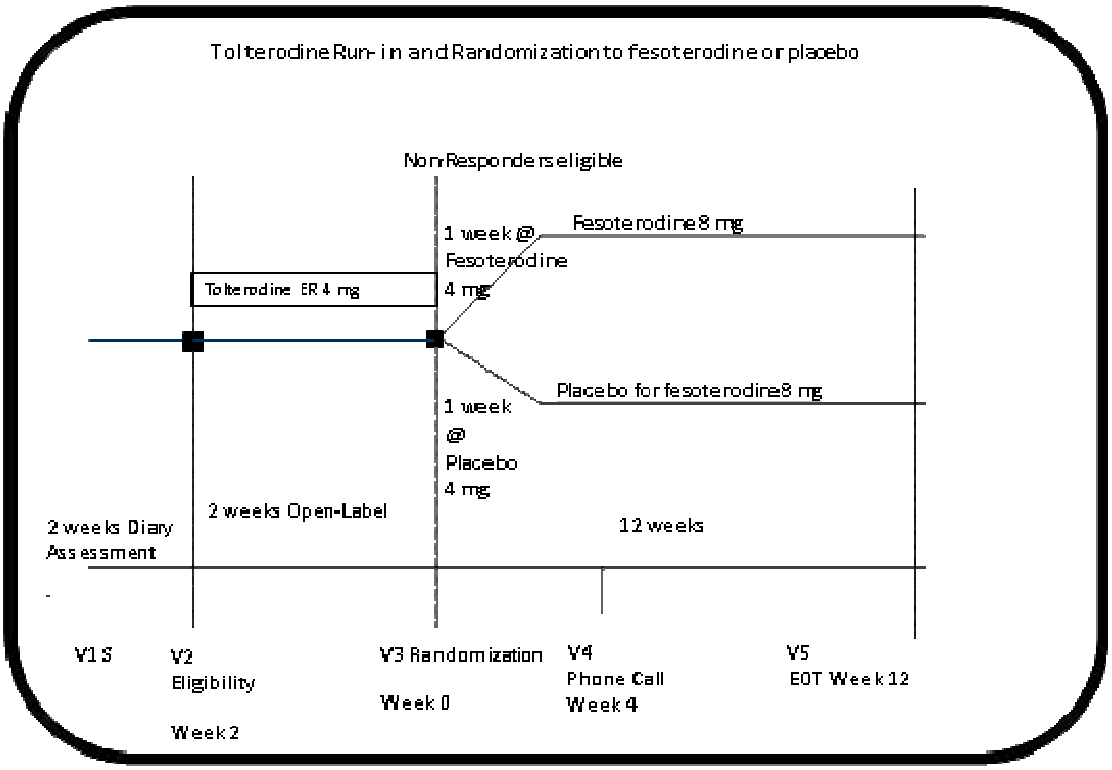
Study Design: This was a double-blind, placebo-controlled, parallel-group, multicenter study with a 2-week, open-label tolterodine run-in period, followed by randomization (for non-responders defined as subjects who had ≤50% change in UUI episode frequency during open-label run-in phase) to fesoterodine or placebo, for a 12-week treatment period.

For the first week of the randomized allocation period, subjects received fesoterodine 4 mg or matching placebo. After this week all subjects receiving 4 mg increased their dose to 8 mg and received 8 mg for the remainder of the study. Dose reduction was not permitted.

The assessment schedule was divided into 5 visits: Visit 1 (Screening and washout/Week -4); Visit 2 (tolterodine run-in/Week -2); Visit 3 (randomization/Week 0); Visit 4 (phone call assessment/Week 4); and Visit 5 (end of treatment or early termination/Week 12).

The study design is presented in Figure 1 and the schedule of activities is provided in Table 1.

Figure 1. Study Design



EOT = end of treatment; ER = extended release; V = visit.

Table 1. Schedule of Activity

Activities	Visit 1 Screening And Washout Week -4	Visit 2 Tolterodine Run-In Week -2 (-7 to +10 Days)	Visit 3 Randomization Week 0 (±5 Days)	Visit 4 Phone Call Week 4 (±7 Days)	Visit 5 EOT Week 12 or Early Termination (±7 Days)
Written informed consent	X				
Demographics and medical history	X				
Sitting blood pressure and pulse rate	X	X	X		X
Physical examination	X				
Inclusion/ exclusion criteria	X	X	X		
Urine dipstick test[a]	X	X			X
Urine pregnancy test for WOCBP[b]	X		X		
Patient's perception of bladder condition (PPBC)	X	X	X		X
Urgency perception scale (UPS)		X	X		X
Overactive bladder questionnaire (OAB-q)		X	X		X
Dispense bladder diary	X	X	X		
Collect and review bladder diary		X	X	X[c]	X
Calculate UUI and micturition frequency for eligibility		X	X		
Adverse events[d]	X[d]	X	X	X	X[e]
Concomitant medication	X	X	X	X	X
Concomitant non-drug treatment/ procedures	X	X	X	X	X
Dispense study medication		X	X		
Study medication return/count			X		X
Assess overall compliance			X	X	X
Phone call prior to visit[f]		X	X	X	X

CRF = case report form; EOT = end of treatment; UUI = urgency urinary incontinence; WOCBP = women of child bearing potential.

a. Any dipsticks positive for leukocyte esterase, protein, and/or nitrites were sent for culture and sensitivity at the site's local laboratory. The subject was excluded from the study if positive at Screening or Visit 2. If positive at end of study, then the subject was treated according to the site's usual standard of care.

b. A standard urine pregnancy test kit was used to test for pregnancy in female subjects of child bearing potential at Visit 1 and Visit 3, and those with a positive result were excluded.

c. The subjects were contacted 7 days prior to Week 4 and reminded to return their bladder diary (eg, by mail or unscheduled clinic visit). If bladder diary was not completed and returned within 1 week, subjects were contacted again and reminded to complete.

d. Serious adverse events were reported once Informed Consent had been obtained. Serious and non-serious adverse events were recorded on the CRF once the subject has taken at least 1 dose of study medication.

e. Adverse events that were still ongoing at the EOT visit were to be followed up with a phone call 1 week later, to determine a final status for the event.

f. A phone call was scheduled 7 days prior to each scheduled visit at which a 3-day bladder diary was to be completed, to remind the subject to complete it contemporaneously and make it available to the investigator.

Number of Subjects (Planned and Analyzed): A total of 452 evaluable subjects (226 subjects per arm) were planned. To achieve this, it was estimated that a total of 3143 subjects would need to be screened so that 566 subjects would be enrolled (283/arm) at Visit 3. A total of 2217 subjects were screened, of which 990 subjects took open-label

tolterodine in the run-in period. A total of 642 subjects were randomized to double-blind medication following the tolterodine run-period: 322 subjects in the fesoterodine group and 320 subjects in the placebo group. More subjects than planned (N=566) were randomized in the study, due to faster than anticipated enrollment rate. A total of 609 subjects were treated (308 with fesoterodine and 301 with placebo); all treated subjects were analyzed. The study enrolled a total of 642 subjects out of which 609 subjects were treated: 30 in Bulgaria, 24 in Canada, 7 in Czech Republic, 3 in Egypt, 51 in Germany, 18 in Hungary, 10 in Republic of Korea, 11 in Mexico, 22 in Poland, 54 in Russian Federation, 3 in South Africa, 17 in Sweden, 54 in Ukraine and 305 in the United States.

Diagnosis and Main Criteria for Inclusion: The study included healthy male and/or female subjects aged ≥18 years diagnosed with OAB symptoms (subject-reported) for ≥6 months prior to Screening Visit; moderate to severe incontinence episode frequency and subsequent sub-optimal response to tolterodine; females of child-bearing potential must not intend to become pregnant, be pregnant or producing breast milk at the time of study entry, and had to use contraception; no conditions or prior treatment that may also affect bladder function; no clinically significant urinary tract infection and no ongoing treatment with OAB medications (these could be stopped at the first visit to allow entry into the study).

Study Treatment: At Week 2 (Visit 2) eligible subjects were assigned to open-label oral tolterodine extended release (ER) 4 mg capsule, once daily (QD) every morning (with or without food), for the 2-week run-in period.

At Week 0 (Visit 3), non-responders identified in the run-in period were randomized in a 1:1 allocation to oral fesoterodine 8 mg tablet, or oral placebo for fesoterodine 8 mg in a double-blind fashion. For the first week of the randomized allocation period, subjects received oral fesoterodine 4 mg tablet or matching placebo, after which time the dose was increased to 8 mg. The study drug was taken QD every morning (with or without food) and was to be swallowed whole, without chewing.

Efficacy and Safety Endpoints:

Primary Endpoints: Change in mean number of UUI episodes per 24 hours at Week 12 (Visit 5) relative to Week 0 (Visit 3), defined as those micturitions with Urinary Sensation Scale rating of 5 in the diary.

Secondary Endpoints:

Efficacy:

- Change in mean number of micturitions (frequency) per 24 hours at Week 12 (Visit 5) relative to Week 0 (Visit 3).
- Change in mean number of micturition-related urgency episodes per 24 hours at Week 12 (Visit 5) relative to Week 0 (Visit 3), defined as those micturitions with Urinary Sensation Scale rating of ≥3 in the bladder diary.

- Change in Patient Perception of Bladder Condition (PPBC) at Week 12 (Visit 5) relative to Week 0 (Visit 3).

- Change in Urgency Perception Scale (UPS) at Week 12 (Visit 5) relative to Week 0.

- Change in OAB Questionnaire (OAB-q) symptom bother score and change in the Total Health-Related Quality of Life (HRQL) score of the OAB-q and score of each HRQL domain of the OAB-q at Week 12 (Visit 5) relative to Week 0 (Visit 3).

- Responder rates from Week -2 (Visit 2) to Week 12 (Visit 5) and from Week 0 (Visit 3) to Week 12 (Visit 5), defined as a >50% reduction in UUI episode frequency.

- Diary dry rate at Week 4 (Visit 4) and Week 12 (End of treatment).

Safety and tolerability: Adverse events (AEs); vital signs; and urinalysis and urine culture at Screening (Visit 1), Week 2 (Visit 2) and Week 12 (Visit 5).

Safety Evaluations: AEs were recorded throughout the study. Physical examinations, vital sign measurements (sitting blood pressure [BP] and pulse rate [PR]), urinalysis, urine culture and urine pregnancy tests were performed at specified time points throughout the study, as indicated in Table 1.

Statistical Methods:

Analysis Populations: The full analysis set (FAS) included all randomized subjects who took at least 1 dose of study drug and had baseline (Visit 3) or post-baseline efficacy assessment. Efficacy analysis was based on the FAS. The safety set included all randomized subjects who took at least 1 dose of study drug.

Primary Efficacy Measure: Change from baseline (Week 3) in number of UUI episodes per 24 hours at Week 12. Multiple statistical hypothesis testing was done in a hierarchical sequentially rejective manner using a step down procedure. The testing procedure started with the 1-sided test of superiority of reduction (within group mean change) for the primary endpoint at the 2.5% level of significance (equivalent to 2-sided test at 5% level of significance), using a paired t-test. If this test was statistically significant, a 1-sided test of superiority of the fesoterodine 8 mg dose versus placebo for the same variable was to be performed at the 2.5% level of significance (equivalent to 2-sided test at 5% level of significance) using an analysis of covariance (ANCOVA) model with terms for treatment, country, and baseline of UUI episodes per 24 hours.

This study was considered successful if the urge incontinence episodes variable showed significant outcome for the within group comparison.

Secondary Efficacy Measure: No adjustments were made for multiple comparisons and all tests were performed with a 2-sided test at significance level of 5%.

- Analysis of the Bladder Diary: A treatment group comparison was performed for change from baseline to 12 in micturition diary endpoints using the same ANCOVA model as for

the primary endpoint. A paired t-test was used for the within group mean changes. P-values were reported and the change scores were summarized with descriptive statistics by treatment group. If normality assumption was violated, a non-parametric analyses was to be performed using the van Elteren test (based on ranks of the data stratified by baseline quartiles) to test treatment differences. Examination of these data indicated no significant departure from normality for any of the primary or secondary diary endpoints. No significant interaction terms were found. Responder rate at Week 12 and diary dry rates at Weeks 4 and 12 were analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by country using modified ridit scores. Fesoterodine 8 mg was compared with placebo. Frequency tables for the categories were presented by treatment group. Empirical distribution function for responder rates were plotted and compared with a Kolmogorov-Smirnov 2-sample test.

- Analysis of the PPBC: Treatment group comparisons were carried out for the PPBC change categories at Week 12 using the CMH test controlling for country using modified ridit scores and the p-value was reported. Frequency tables for the categories were presented by treatment group. Wilcoxon signed rank test was applied to within group mean changes.

- Analysis of the UPS: Treatment group comparison was carried out for the UPS change scores and categories at Week 12 using the CMH test controlling using modified ridit scores for country and the p-value was reported. Frequency tables for the UPS data were presented by treatment group. Wilcoxon signed rank test was applied to within group mean changes.

- Analysis of the OAB-q: Treatment group comparison was performed for change in symptom bother score and change in scores of each individual domain of HRQL (coping, concern, sleep, and social interaction), and total HRQL scores at Week 12 relative to the baseline, using the same ANCOVA model as for the primary endpoint and the p-value was reported. In addition, the change scores were summarized with descriptive statistics by treatment group. A paired t-test was applied to within-group mean changes.

- Safety data were summarized using descriptive statistics. In addition, an exploratory 3-tier analysis of AEs was performed.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2.

Table 2. Evaluation Groups

	Tolterodine[a]	Fesoterodine N=322	Placebo N=320
Number (%) of subjects			
Screened 2217			
Assigned to Study Treatment	N/A	322	320
Treated during the study	990	308	301
Completed	611	281	255
Discontinued	379	27	46
Did not meet entrance criteria for randomization into the fesoterodine arm	314	0	2
Insufficient clinical response	4	2	4
Lost to follow-up	17	2	1
No longer willing to participate in study	16	6	14
Protocol violation	8	3	6
Adverse event	13	10	10
Unspecified	7	4	9
Analyzed for efficacy:			
Full analysis set	N/A	308 (95.7)	301 (94.1)
Analyzed for primary efficacy Week 12 (LOCF)	N/A	292	279
Analyzed for safety:			
Adverse events	974	308 (95.7)	301 (94.1)
Laboratory data	982	294 (91.3)	272 (85.0)

LOCF = last observed carried forward; N = number of subjects assigned to respective treatment group; N/A = not applicable.

a. The tolterodine group refers to subjects in the 2-week, open-label tolterodine run-in period, prior to the randomized, double-blind, fesoterodine versus placebo period.

The mean age of subjects receiving tolterodine during the open-label run-in period was 57.1 years. Most subjects were white (80.6%) and female (81.8%). The mean body mass index (BMI) was 30.2 kg/m^2, reflecting an over-weight study population. Among the female subjects, 74.9% subjects were postmenopausal at the time of the study.

The demographic characteristics of subjects receiving randomized, double-blind fesoterodine and placebo were similar. The mean ages were 57.3 and 58.2 years for the fesoterodine and the placebo group, respectively. Most subjects were white (81.5% versus 81.7%) and (83.0% versus 82.4%) for the fesoterodine and the placebo groups, respectively. The mean BMI was 29.8 kg/m^2 and 30.0 kg/m^2 for the fesoterodine and placebo groups, respectively. Among the female subjects, 75.9% and 74.3% in the fesoterodine and placebo groups, respectively, were postmenopausal at the time of the study

Efficacy Results:

Primary Endpoint: The primary endpoint in this study was the change in the mean number of UUI episodes per 24 hours at Week 12 (Visit 5) relative to baseline (Week 0, Visit 3). The decreases were statistically significant in both the fesoterodine and placebo arms (p<0.0001). The decrease was statistically significantly greater in the fesoterodine group, showing greater improvement compared to the placebo group (p=0.0079) of the study. Results are presented in Table 3.

Table 3. Change From Baseline in Mean Number of UUI Episodes per 24 Hours at Week 12-Full Analysis Set Subjects Reporting This Symptom at Baseline (ANCOVA)

	Fesoterodine	Placebo
N	292	279
Baseline		
Mean (SD)	3.93 (2.53)	3.83 (2.52)
Median (min, max)	3.29 (0.60, 15.67)	3.00 (1.00, 16.33)
Week 12		
Mean (SD)	1.60 (2.56)	2.07 (2.57)
Median (min, max)	0.33 (0.00, 15.33)	1.25 (0.00, 12.33)
Numerical change from baseline to Week 12		
Mean (SD)	-2.32 (2.67)	-1.76 (2.46)
Median (min, max)	-2.00 (-15.67, 6.67)	-1.50 (-10.00, 6.92)
LS mean (SE)	-2.37 (0.17)	-1.87 (0.17)
95% CI for mean	(-2.63,-2.02)	(-2.05,-1.47)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	-0.50 (0.19)	
95% CI	(-0.87,-0.13)	
p-value	0.0079	

* P-value was based on paired t-test comparing baseline with post-baseline values.
† Based on an ANCOVA model with terms for treatment and country with centered baseline value as a covariate.
The mean number of UUI episodes per 24 hours was calculated as the total number of micturitions with Urinary Sensation Scale = 5 divided by the total number of diary days collected at that visit.
ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; max = maximum; min = minimum; N = number of subjects with baseline UUI >0 per 24 hours (placebo: 301, fesoterodine: 304) and non-missing change from baseline to Week 12 (LOCF); SD = standard deviation; SE = standard error; UUI = urgency urinary incontinence.

Secondary Endpoints:

- Change in Mean Number of Micturitions (Frequency) Per 24 Hours at Week 12 Relative to Week 0: The change from baseline to Week 12 in the mean number of micturitions was not statistically significantly different with fesoterodine treatment compared to placebo (p-value=0.0931). Results are presented in Table 4.

Table 4. Change From Baseline in Mean Number of Micturitions per 24 Hours at Week 12-Full Analysis Set

	Fesoterodine	Placebo
N	292	279
Baseline		
Mean (SD)	12.44 (3.57)	12.48 (3.75)
Median (min, max)	12.00 (5.80, 30.00)	11.67 (5.67, 29.67)
Week 12		
Mean (SD)	10.51 (3.83)	10.92 (3.47)
Median (min, max)	9.67 (3.67, 30.00)	10.33 (4.67, 29.00)
Numerical change from baseline to Week 12		
Mean (SD)	-1.94 (3.15)	-1.57 (3.13)
Median (min, max)	-2.00 (-13.67, 12.00)	-1.33 (-13.67, 8.67)
LS mean (SE)	-2.04 (0.21)	-1.64 (0.21)
95% CI for mean	(-2.30,-1.58)	(-1.93,-1.20)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	-0.40 (0.24)	
95% CI	(-0.86,0.07)	
p-value	0.0931	

∗ P-value was based on paired t-test comparing baseline with post-baseline values.
† Based on an ANCOVA model with terms for treatment and country with centered baseline value as a covariate.
The mean number of micturitions per 24 hours was calculated as the total number of micturitions divided by the total number of diary days collected at that visit.
ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; max = maximum; min = minimum; N = number of subjects with baseline micturition frequency >0 per 24 hours (placebo: 301, fesoterodine: 305) and non-missing change from baseline Week 12 (LOCF), respectively; SD = standard deviation; SE = standard error; UUI = urgency urinary incontinence.

- Change in Mean Number of Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Week 0**:** The change from baseline to Week 12 in the mean number of micturition related urgency episodes was statistically significantly greater in the fesoterodine group, showing greater improvement compared to placebo (p-value=0.0438). Results are presented in Table 5.

Table 5. Change From Baseline in Mean Number of Micturition Related Urgency Episodes per 24 Hours at Week 12-Full Analysis Set Subjects Reporting This Symptom at Baseline

	Fesoterodine	Placebo
N	292	279
Baseline		
Mean (SD)	11.38 (3.98)	11.26 (4.01)
Median (min, max)	11.33 (1.00, 30.00)	10.67 (2.33, 24.33)
Week 12		
Mean (SD)	8.04 (5.01)	8.75 (4.30)
Median (min, max)	7.71 (0.00, 30.00)	8.67 (0.00, 22.67)
Numerical change from baseline to Week 12		
Mean (SD)	-3.33 (4.47)	-2.52 (4.45)
Median (min, max)	-3.00 (-21.67, 19.67)	-1.67 (-21.33, 14.00)
LS mean (SE)	-3.49 (0.31)	-2.79 (0.31)
95% CI for mean	(-3.85,-2.82)	(-3.04,-1.99)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	-0.70 (0.34)	
95% CI	(-1.37,-0.02)	
p-value	0.0438	

∗ P-value was based on paired t-test comparing baseline with post-baseline values.
† Based on an ANCOVA model with terms for treatment and country with centered baseline value as a covariate.
ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; max = maximum; min = minimum; N = number of subjects with baseline Urgency Episodes >0 per 24 hours (placebo: 301, fesoterodine: 305) and non-missing change from baseline to Week 12 (LOCF), respectively; SD = standard deviation; SE = standard error; UUI = urgency urinary incontinence.

- Responder Rates at Week 12, Compared to Week -2 (Before the Tolterodine Run-In Period) and Baseline (Week 0; After the Tolterodine Run-In Period and Before Randomized to Double-Blind Treatment with Fesoterodine or Placebo): There was a statistically significant difference in responder rates for UUI episode frequency (both 50% cut-off, defined as >50% reduction in UUI episode frequency and 70% cut-off, defined as 70% reduction in UUI episode frequency) in the fesoterodine group compared to the placebo group at Week 12 compared to Week -2 and baseline. Results are presented in Table 6 and Table 7.

Table 6. Responder Rate for Change in Mean Number of UUI Episodes per 24 Hours From Week -2 to Week 12-Full Analysis Set Subjects Reporting This Symptom at Week -2

	Responder Rate (50% Cut-Off)		Responder Rate (70% Cut-Off)	
	Fesoterodine n (%)	Placebo n (%)	Fesoterodine n (%)	Placebo n (%)
N	279 (100)	275 (100)	279 (100)	275 (100)
Proportion of subjects with >X% reduction in UUI episode frequency at Week 12	203 (72.8)	164 (59.6)	170 (60.9)	129 (46.9)
Treatment difference in rate (%)	13.2		14.0	
p-value*	0.0023		0.0020	

* The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) general association test and stratified by country.
Responder rate was defined as the proportion of subjects with >50% reduction in UUI frequency.
LOCF = last observation carried forward; LS = least squares; N = number of subjects with Week -2 UUI >0 per 24 hours (placebo: 295, fesoterodine: 291) and non-missing change from Week -2 to Week 12 (LOCF), respectively; n = number of subjects with observation; UUI = urgency urinary incontinence; X = 50% or 70%.

Table 7. Responder Rate for Change in Mean Number of UUI Episodes per 24 Hours From Baseline to Week 12-Full Analysis Set Subjects Reporting This Symptom at Baseline

	Responder Rate (50% Cut-Off)		Responder Rate (70% Cut-Off)	
	Fesoterodine n (%)	Placebo n (%)	Fesoterodine n (%)	Placebo n (%)
N	292 (100)	279 (100)	292 (100)	279 (100)
Proportion of subjects with >X% reduction in UUI episode frequency at Week 12	204 (69.9)	159 (57.0)	172 (58.9)	124 (44.4)
Treatment difference in rate (%)	12.9		14.5	
p-value*	0.0027		0.0010	

* The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) general association test and stratified by country.
Responder rate was defined as the proportion of subjects with >50% reduction in UUI frequency.
LOCF = last observation carried forward; LS = least squares; N = number of subjects with Baseline UUI >0 per 24 hours (placebo: 301, fesoterodine: 304) and non-missing change from baseline to Week 12 (LOCF), respectively; n = number of subjects with observation; UUI = urgency urinary incontinence; X = 50% or 70%.

- Diary Dry Rate (UUI=0) at Week 4 and Week 12: There was a statistically significantly improvement in the diary dry rate (UUI=0) in the fesoterodine group compared with the placebo group at Week 4 (p=0.0427). However, there was no statistically significantly difference in the diary dry rate (UUI=0) between fesoterodine treatment and placebo at Week 12. Results are presented in Table 8.

Table 8. Diary Dry Rate at Weeks 4 and 12 - Full Analysis Set Subjects Reporting This Symptom at Baseline

	Fesoterodine n (%)	Placebo n (%)
N1	279 (100)	265 (100)
Proportion of subjects with UUI = 0 at Week 4	71 (25.4)	47 (17.7)
Treatment difference in rate (%)	7.7	
p-value*	0.0427	
N2	292 (100)	279 (100)
Proportion of subjects with UUI = 0 at Week 12	114 (39.0)	90 (32.3)
Treatment difference in rate (%)	6.7	
p-value*	0.1461	

* The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) general association test and stratified by country.
Diary dry rate was defined as the proportion of subjects with UUI = 0.
n = number of subjects with observation; N1, N2 = number of subjects with baseline UUI >0 per 24 hours (placebo: 301, fesoterodine: 304) and non-missing change from baseline to Week 4 and Week 12 (LOCF), respectively; UUI = urgency urinary incontinence.

- Patient Perception of Bladder Condition (PPBC): The change from baseline to Week 12 in PPBC was statistically significantly greater in the fesoterodine group, showing a greater improvement compared to placebo (p-value=0.0009 based on the 2-category analysis [improved/didn't improve] and p-value <0.0001 based on the 4-category analysis). Results are presented in Table 9.

Table 9. Change From Baseline in PPBC at Week 12-Full Analysis Set

	Fesoterodine	Placebo
Patient Perception of Bladder Condition	**n (%)**	**n (%)**
N	291 (100.0)	267 (100.0)
Baseline		
My bladder condition does not cause me any problems at all	0 (0.0)	0 (0.0)
My bladder condition causes me some very minor problems	4 (1.4)	6 (2.2)
My bladder condition causes me some minor problems	15 (5.2)	9 (3.4)
My bladder condition causes me (some) moderate problems	60 (20.6)	75 (28.1)
My bladder condition causes me severe problems	147 (50.5)	141 (52.8)
My bladder condition causes me many severe problems	65 (22.3)	36 (13.5)
Week 12		
My bladder condition does not cause me any problems at all	21 (7.2)	5 (1.9)
My bladder condition causes me some very minor problems	39 (13.4)	19 (7.1)
My bladder condition causes me some minor problems	54 (18.6)	53 (19.9)
My bladder condition causes me (some) moderate problems	87 (29.9)	93 (34.8)
My bladder condition causes me severe problems	67 (23.0)	73 (27.3)
My bladder condition causes me many severe problems	23 (7.9)	24 (9.0)
2 Category: Improvement, No improvement		
Change from baseline		
No improvement	97 (33.3)	127 (47.6)
Improvement	194 (66.7)	140 (52.4)
Treatment difference versus placebo*	14.3	
p-value	0.0009	
Difference from baseline†		
p-value	<0.0001	<0.0001
4 Category: Magnitude of Improvement		
Change from baseline		
Deterioration	17 (5.8)	32 (12.0)
No change	s80 (27.5)	95 (35.6)
Minor improvement	84 (28.9)	83 (31.1)
Major improvement	110 (37.8)	57 (21.3)
Treatment difference versus placebo‡		
p-value	<0.0001	
Difference from baseline†		
p-value	<0.0001	<0.0001

* The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) general association test and stratified by country.
† The p-value was obtained from a Wilcoxon signed rank test comparing baseline with post-baseline values (within group changes).
‡ The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) test with modified ridit scoring controlling for country.
PPBC Scale: 1 = My bladder condition does not cause me any problems at all; 6 = My bladder condition causes me many severe problems.
No improvement = change from baseline is ≥0; Improvement = negative change from baseline.
Deterioration = positive change from baseline; No change = score change is 0; Minor improvement = score change is negative in magnitude of 1; Major improvement = score change is negative in magnitude of ≥2.
n = number of subjects with observation; N = number of subjects with non-missing baseline and Week 12 values;
PPBC = Patient perception of bladder condition.

- Urgency Perception Scale (UPS): The change from baseline to Week 12 in UPS was statistically significantly greater in the fesoterodine group, showing a greater improvement compared to placebo (p-value=0.0095). Results are presented in Table 10.

Table 10. Change From Baseline in UPS at Week 12-Full Analysis Set

	Fesoterodine	Placebo
Patient Perception of Bladder Condition	**n (%)**	**n (%)**
N*	291 (100.0)	267 (100.0)
Baseline		
I am usually not able to hold urine	126 (43.3)	99 (37.1)
I am usually able to hold urine until I reach a toilet	158 (54.3)	157 (58.8)
I am usually able to finish what I am doing before going to the toilet	7 (2.4)	11 (4.1)
Week 12		
I am usually not able to hold urine	71 (24.4)	73 (27.3)
I am usually able to hold urine until I reach a toilet	165 (56.7)	156 (58.4)
I am usually able to finish what I am doing before going to the toilet	55 (18.9)	38 (14.2)
Change from baseline		
Deterioration	17 (5.8)	31 (11.6)
No change	167 (57.4)	158 (59.2)
Improvement	107 (36.8)	78 (29.2)
Treatment difference versus placebo*		
p-value	0.0095	
Difference from baseline†		
p-value	<0.0001	<0.0001

* The p-value was obtained from a Cochran-Mantel-Haenszel (CMH) test with modified ridit scoring controlling for country.

† The p-value was obtained from a Wilcoxon signed rank test comparing baseline with post-baseline values (within group changes).

UPS Scale: 1 = I am usually not able to hold urine; 3 = I am usually able to finish what I am doing before going to the toilet (without leaking).

Deterioration = Negative change from baseline; No change = Score change is 0; Improvement = Positive change from baseline.

N = number of subjects; N = number of subjects with non-missing values for change from baseline to Week 12; UPS = urgency perception scale.

- Change in OAB-q Symptom Bother Score at Week 12 Relative to Baseline: The OAB-q symptom bother Score ranged from 0-100. For the symptom bother scale, an increase in score indicated greater symptom bother, whereas a decrease in score represented improvement. The change from baseline to Week 12 in the mean number of OAB-q symptom bother score was statistically significantly greater in the fesoterodine group, showing greater improvement compared to placebo (p-value=0.0001). Results are presented in Table 11.

Table 11. Change From Baseline in OAB-q Symptom Bother Score at Week 12-Full Analysis Set

	Fesoterodine	Placebo
N	286	267
Baseline		
Mean (SD)	66.67 (20.28)	64.74 (19.69)
Median (min, max)	70.00 (15.00, 100.00)	65.00 (15.00, 100.00)
Week 12		
Mean (SD)	42.06 (25.23)	48.75 (23.70)
Median (min, max)	40.00 (0.00, 100.00)	45.00 (2.50, 100.00)
Numerical change from Baseline to Week 12		
Mean (SD)	-24.61 (25.57)	-15.99 (24.53)
Median (min, max)	-22.50 (-90.00, 62.50)	-15.00 (-85.00, 65.00)
LS mean (SE)	-25.45 (1.68)	-18.11 (1.72)
95% CI for mean	(-27.58, -21.63)	(-18.95, -13.04)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	-7.34 (1.91)	
95% CI	(-11.10, -3.58)	
p-value	0.0001	

* The p-value was based on paired t-test comparing baseline with post-baseline values.
† Based on an ANCOVA model with terms for treatment and country with centered baseline value as a covariate.
Symptom bother score ranges from 0-100. Higher score values are indicative of greater symptom bother. Negative change in symptom bother score indicates improvement.
Half-scale rule was used: If >50% of individual items missing, the domain was missing.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; max = maximum; min = minimum; N = number of non-missing values for change from baseline to Week 12; OAB-q = overactive bladder questionnaire; SD = standard deviation; SE = standard error.

- Change in Score of Each HRQL Domain of OAB-q and Total Score at Week 12 - Full Analysis Set: High scores on the HRQL scale were indicative of better HRQL, and an increase in score was indicative of improvement. The scores of the HRQL Scale domains (and total score) showed statistically significant increases, from baseline to Week 12, in both the fesoterodine and the placebo treatment groups. The improvement in each domain of the HRQL Scale was statistically significantly greater in the fesoterodine group compared with placebo (all: p-values <0.05). Results are presented in Table 12.

Table 12. Change From Baseline in Score of Each HRQL Domain of OAB-q and HRQL Total Score at Week 12

	Fesoterodine	Placebo
Concern subscale score		
N	286	267
Baseline		
Mean (SD)	43.63 (26.00)	44.25 (25.58)
Median (min, max)	42.86 (0.00, 100.00)	45.71 (0.00, 100.00)
Week 12		
Mean (SD)	66.74 (27.13)	58.08 (26.40)
Median (min, max)	71.43 (0.00, 100.00)	60.00 (0.00, 100.00)
Numerical change from baseline to Week 12		
Mean (SD)	23.11 (27.77)	13.83 (25.03)
Median (min, max)	17.14 (-65.71, 100.00)	11.43 (-80.00, 85.71)
LS mean (SE)	24.11 (1.75)	15.10 (1.78)
95% CI for mean	(19.88, 26.35)	(10.81, 16.85)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	9.01 (1.98)	
95% CI	(5.12, 12.91)	
p-value	<0.0001	
Coping subscale score		
N	286	267
Baseline		
Mean (SD)	38.74 (26.24)	41.15 (26.04)
Median (min, max)	35.00 (0.00, 100.00)	40.00 (0.00, 100.00)
Week 12		
Mean (SD)	62.44 (28.59)	56.23 (26.87)
Median (min, max)	67.50 (0.00, 100.00)	57.50 (0.00, 100.00)
Numerical change from baseline to Week 12		
Mean (SD)	23.70 (26.69)	15.07 (24.20)
Median (min, max)	20.00 (-50.00, 97.50)	12.50 (-72.50, 92.50)
LS mean (SE)	23.73 (1.74)	15.98 (1.77)
95% CI for mean	(20.59, 26.80	(12.16, 17.99)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	7.75 (1.97)	
95% CI	(3.87, 11.62)	
p-value	<0.0001	
Sleep subscale score		
N	286	267
Baseline		
Mean (SD)	41.38 (25.66)	40.69 (26.28)
Median (min, max)	40.00 (0.00, 100.00)	36.00 (0.00, 100.00)
Week 12		
Mean (SD)	62.24 (27.12)	55.48 (26.83)
Median (min, max)	64.00 (0.00, 100.00)	56.00 (0.00, 100.00)
Numerical change from baseline to Week 12		
Mean (SD)	20.85 (27.42)	14.79 (25.74)
Median (min, max)	16.00 (-56.00, 92.00)	12.00 (-92.00, 96.00)
LS mean (SE)	22.07 (1.77)	15.55 (1.80)
95% CI for mean	(17.66, 24.04)	(11.68, 17.89)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	6.52 (2.00)	
95% CI	(2.60, 10.45)	
p-value	0.0012	
Social interaction subscale score		
N	286	267
Baseline		

Table 12. Change From Baseline in Score of Each HRQL Domain of OAB-q and HRQL Total Score at Week 12

	Fesoterodine	Placebo
Mean (SD)	65.03 (28.34)	68.40 (26.29)
Median (min, max)	68.00 (0.00, 100.00)	72.00 (0.00, 100.00)
Week 12		
Mean (SD)	79.51 (24.85)	77.26 (23.76)
Median (min, max)	88.00 (0.00, 100.00)	84.00 (0.00, 100.00)
Numerical change from baseline to Week 12		
Mean (SD)	14.47 (24.26)	8.85 (21.12)
Median (min, max)	8.00 (-52.00, 96.00)	8.00 (-80.00, 76.00)
LS mean (SE)	14.27 (1.44)	10.14 (1.47)
95% CI for mean	(11.65, 17.30)	(6.31, 11.40)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	4.13 (1.64)	
95% CI	(0.90, 7.36)	
p-value	0.0123	
Total HRQL score		
N	286	267
Baseline		
Mean (SD)	45.90 (23.72)	47.38 (22.70)
Median (min, max)	44.40 (0.80, 96.00)	48.00 (0.00, 96.80)
Week 12		
Mean (SD)	67.02 (25.04)	60.80 (23.21)
Median (min, max)	70.80 (1.60, 100.00)	63.20 (0.80, 99.20)
Numerical change from baseline to Week 12		
Mean (SD)	21.12 (24.62)	13.42 (21.92)
Median (min, max)	16.80 (-38.40, 93.60)	10.40 (-80.00, 84.00)
LS mean (SE)	21.55 (1.55)	14.46 (1.59)
95% CI for mean	(18.26, 23.98)	(10.78, 16.07)
p-value*	<0.0001	<0.0001
Treatment difference versus placebo†		
LS mean difference (SE)	7.10 (1.77)	
95% CI	(3.63, 10.57)	
p-value	<0.0001	

* P-value was based on paired t-test comparing baseline with post-baseline values.
† Based on an ANCOVA model with terms for treatment and country with centered baseline value as a covariate.
HRQL total score ranges from 0-100 and is a combination of four individual domains scores (Coping, Concern, Sleep, and Social Interaction).
Higher scores values are indicative of better HRQL.
Half-scale rule was used: If >50% of individual items missing, the domain was missing.
ANCOVA = analysis of covariance; CI = confidence interval; HRQL = health related quality of life; LS = least squares; max = maximum; min = minimum; N = number of non-missing values for change from baseline to Week 12; OAB-q = overactive bladder questionnaire; SD = standard deviation; SE = standard error.

Safety Results: The randomized, double-blind fesoterodine treatment group had a higher number of subjects reporting treatment-emergent AEs (TEAEs) compared to the randomized, double-blind placebo group (110 [35.7%] subjects, and 75 [24.9%] subjects, respectively) as summarized in Table 13. The incidence of treatment-related AEs was higher in the fesoterodine group, as compared to placebo and tolterodine (22.1%, 10.0% and 8.5%, respectively).

Table 13. Treatment-Emergent Adverse Events

	Tolterodine[a]		Fesoterodine		Placebo	
	All Causality	Treatment-Related	All Causality	Treatment-Related	All Causality	Treatment-Related
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects evaluable for adverse events	990	990	308	308	301	301
Number of adverse events	196	114	162	97	117	41
Subjects with adverse events	134 (13.5)	84 (8.5)	110 (35.7)	68 (22.1)	75 (24.9)	30 (10.0)
Subjects with serious adverse events	3 (0.3)	0	5 (1.6)	0	7 (2.3)	0
Subjects with severe adverse events	8 (0.8)	2 (0.2)	10 (3.2)	7 (2.3)	9 (3.0)	2 (0.7)
Subjects discontinued due to adverse events	12 (1.2)	7 (0.7)	11 (3.6)	7 (2.3)	12 (4.0)	6 (2.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	4 (1.3)	3 (1.0)	1 (0.3)	0

Included data up to 7 days after last dose of study drug.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.
a. The tolterodine group refers to subjects in the 2-week, open-label tolterodine run-in period, prior to the randomized, double-blind, fesoterodine versus placebo period.

Non-Serious Treatment-Emergent Adverse Events: Summary of non-serious treatment-emergent AEs for events having frequency rate ≥1 are summarized in Table 14 and incidence of treatment-emergent AEs (treatment-related) in ≥1% subjects are summarized in Table 15.

Table 14. Summary of Non-Serious Treatment-Emergent Adverse Events For Events Having Frequency Rate ≥1%

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v15.0) Preferred Term	Tolterodine (N=990)	Fesoterodine (N=308)	Placebo (N=301)
		n (%)	
Any AE	90 (9.1)	76 (24.7)	48 (15.9)
Eye disorders	1 (0.1)	3 (1.0)	0
Vision blurred	1 (0.1)	3 (1.0)	0
Gastrointestinal disorders	74 (7.5)	62 (20.1)	23 (7.6)
Constipation	11 (1.1)	12 (3.9)	4 (1.3)
Diarrhoea	4 (0.4)	2 (0.6)	4 (1.3)
Dry mouth	61 (6.2)	51 (16.6)	12 (4.0)
Dyspepsia	2 (0.2)	6 (1.9)	0
Nausea	7 (0.7)	1 (0.3)	3 (1.0)
Infections and infestations	12 (1.2)	10 (3.2)	18 (6.0)
Bronchitis	0	0	4 (1.3)
Influenza	0	1 (0.3)	3 (1.0)
Nasopharyngitis	6 (0.6)	3 (1.0)	4 (1.3)
Upper respiratory tract infection	3 (0.3)	2 (0.6)	3 (1.0)
Urinary tract infection	3 (0.3)	4 (1.3)	4 (1.3)
Musculoskeletal and connective tissue disorders	3 (0.3)	1 (0.3)	3 (1.0)
Back pain	3 (0.3)	1 (0.3)	3 (1.0)
Nervous system disorders	5 (0.5)	4 (1.3)	8 (2.7)
Dizziness	1 (0.1)	1 (0.3)	4 (1.3)
Headache	4 (0.4)	3 (1.0)	4 (1.3)

Subjects were only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects per treatment group; n = number of subjects with observation.

Table 15. Incidence of Treatment-Emergent Adverse Events (Treatment-Related) in ≥1% Subjects in Any Treatment Arm

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v15.0) Preferred Term	Tolterodine[a] (N=990)	Fesoterodine (N=308)	Placebo (N=301)
Eye disorders	5 (0.5)	4 (1.3)	1 (0.3)
Vision blurred	1 (0.1)	3 (1.0)	0
Gastrointestinal disorders	70 (7.1)	64 (20.8)	20 (6.6)
Constipation	10 (1.0)	11 (3.6)	3 (1.0)
Diarrhoea	3 (0.3)	1 (0.3)	3 (1.0)
Dry mouth	56 (5.7)	51 (16.6)	12 (4.0)
Dyspepsia	2 (0.2)	5 (1.6)	0
Nervous system disorders	4 (0.4)	2 (0.6)	9 (3.0)
Dizziness	1 (0.1)	0	3 (1.0)
Headache	1 (0.1)	1 (0.3)	4 (1.3)

If the same subject in a given treatment had >1 occurrence in the same preferred term event category, only the most severe occurrence was taken.
Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities had been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild.
Includes data up to 7 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with observation; N = total number of subjects in respective treatment group; TESS = treatment-emergent signs and symptoms.
a.The tolterodine group refers to subjects in the 2-week, open-label tolterodine run-in period, prior to the randomized, double-blind, fesoterodine versus placebo period

Serious Adverse Events (SAEs): Three subjects experienced a total of 4 SAEs during pre-randomization, before the open-label tolterodine run-in period, of which 1 event had a fatal outcome.

Five subjects experienced 5 SAEs in the randomized, double-blind fesoterodine group and 7 subjects experienced 10 SAEs in the randomized, double-blind placebo group (of which 1 had a fatal outcome). None of the SAEs in the fesoterodine or placebo groups was thought to be related to either the randomized treatment, or to the preceding tolterodine treatment during the run-in period. None of the SAEs was considered by the sponsor to be related to any study medication. In addition, 3 subjects experienced 3 SAEs in the open-label tolterodine run-in period; none were considered related to the study drug. A summary of all SAEs is provided in Table 16.

Deaths: A total of 2 subjects died during the study. One subject died before the run-in period (ie, before treatment with any study drug), due to respiratory failure and urosepsis. One subject in the randomized, double-blind placebo group died on study Day 104 due to gastric cancer.

Table 16. Serious Adverse Events

Serial Number	Preferred Term	Therapy Stop Day[a]	Event Onset Day[b]/Stop Day[c]	Event Onset Period Day[d]	Action Taken (Drug Level)	Causality	Outcome	Seriousness
Prior to Tolterodine Run-in Period and Randomization[e]								
1	Neuropathy peripheral	N/A	N/A	N/A	N/A	N/A	Recovered/ Resolved	Hospitalization
2	Acute myocardial infarction	N/A	N/A	N/A	N/A	N/A	Recovered/ Resolved with sequelae	Hospitalization
3	Urosepsis	N/A	N/A	N/A	N/A	N/A	Fatal	Fatal
	Respiratory failure	N/A	N/A	N/A	N/A	N/A	Fatal	Fatal
Open-label Tolterodine Run-in Period[e]								
4	Chest pain	12	12/16	12	Permanently withdrawn	Unrelated	Recovered/ Resolved	Hospitalization
5	Chest pain	10	9/13	9	Permanently withdrawn	Unrelated	Recovered/ Resolved	Hospitalization
6	Arterial occlusive disease	2	2/16	2	Permanently withdrawn	Unrelated	Recovered/ Resolved	Hospitalization
Randomized, Double-Blind Fesoterodine Group (8 mg) e								
7	Chronic obstructive pulmonary disease	103	99/101	84	Dose not changed	Unrelated	Recovered/ Resolved	Hospitalization
8	Hypertension	102	93/107	79	Dose not changed	Unrelated	Recovered/ Resolved	Hospitalization
9	Angina pectoris	99	57/73	43	Dose not changed	Unrelated	Recovered/ Resolved	Hospitalization
10	Prostate cancer	99	88/N/A	74	Dose not changed	Unrelated	Recovered/ Resolved	Important medical event
11	Myocardial infarction	22	24/54	10	Permanently withdrawn	Unrelated	Recovered/ Resolved	Hospitalization
Randomized, Double-Blind Placebo Group								
12	Cholecystitis acute	98	47/51	33	Temporarily withdrawn	Unrelated	Recovered/ Resolved	Hospitalization
13	Gastric cancer	60	60/ N/A	46	Permanently withdrawn	Unrelated	Fatal	Fatal
14	Uterine haemorrhage	82	82/85	63	Permanently withdrawn	Unrelated	Recovered/ Resolved with sequelae	Hospitalization
15	Adjustment disorder	65	58/ N/A	50	Permanently withdrawn	Unrelated	Not recovered/ Not resolved	Hospitalization

Table 16. Serious Adverse Events

Serial Number	Preferred Term	Therapy Stop Day[a]	Event Onset Day[b]/Stop Day[c]	Event Onset Period Day[d]	Action Taken (Drug Level)	Causality	Outcome	Seriousness
16	Cervical spinal stenosis	55	29/64	15	Permanently withdrawn	Unrelated	Recovered/ Resolved with sequelae	Hospitalization
	Dysphagia	55	58/N/A	44	Permanently withdrawn	Unrelated	Recovering/ Resolving	Hospitalization
	Pneumonia aspiration	55	58/N/A	44	Permanently withdrawn	Unrelated	Recovering/ Resolving	Hospitalization
17	Femur fracture	99	62/147	47	Dose not changed	Unrelated	Recovered/ Resolved	Hospitalization
	Atrial fibrillation	99	64/64	49	Dose not changed	Unrelated	Recovered/ Resolved	Important medical event
18	Hiatus hernia	41	33/N/A	18	Permanently withdrawn	Unrelated	Not recovered/ Not resolved	Hospitalization

MedDRA version 15.0 coding dictionary applied.
ID = identification; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not available or not applicable; OC = oracle clinical; PIMS = phase 1 Management System; SAE = serious adverse event; SDW = safety data warehouse.

a. Therapy stop day was calculated as OC last active therapy date minus OC first active therapy date plus 1.
b. Onset study day was calculated as SDW onset date minus OC first active therapy date plus 1.
c. Event stop day was calculated as SDW SAE stop date minus OC first active therapy date plus 1.
d. Onset period day was calculated as SDW onset date minus OC treatment period start date plus 1.
e. Source of actual treatment group or sequence was OC or PIMS.

Permanent Discontinuations Due to Adverse Events: Eleven (3.6%) subjects in the fesoterodine group, 12 (4.0%) subjects in the placebo group and 12 (1.2%) subjects in the tolterodine group discontinued due to all causality TEAEs as summarized in Table 17.

Table 17. Permanent Discontinuations Due to Adverse Events

	Tolterodine[a] N=990	Fesoterodine N=308	Placebo N=301
System Organ Class MedDRA (v15.0) Preferred Term	**n (%)**	**n (%)**	**n (%)**
Cardiac disorders	0	1 (0.3)	1 (0.3)
Myocardial infarction	0	1 (0.3)	0
Palpitations	0	0	1 (0.3)
Eye disorders	1 (0.1)	0	0
Dry eye	1 (0.1)	0	0
Vision blurred	1 (0.1)	0	0
Gastrointestinal disorders	2 (0.2)	6 (1.9)	2 (0.7)
Abdominal distension	0	1 (0.3)	0
Constipation	0	3 (1.0)	0
Diarrhoea	1 (0.1)	0	0
Dry mouth	1 (0.1)	4 (1.3)	1 (0.3)
Dyspepsia	0	2 (0.6)	0
Hiatus hernia	0	0	1 (0.3)
General disorders and administration site conditions	4 (0.4)	1 (0.3)	1 (0.3)
Chest pain	1 (0.1)	0	0
Fatigue	2 (0.2)	0	0
Non-cardiac chest pain	1 (0.1)	0	0
Oedema peripheral	0	1 (0.3)	1 (0.3)
Infections and infestations	2 (0.2)	0	0
Bacteriuria	1 (0.1)	0	0
Urinary tract infection	1 (0.1)	0	0
Injury, poisoning and procedural complications	0	0	1 (0.3)
Muscle strain	0	0	1 (0.3)
Investigations	0	1 (0.3)	0
Weight increased	0	1 (0.3)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0	3 (1.0)
Back pain	0	0	1 (0.3)
Cervical spinal stenosis	0	0	1 (0.3)
Intervertebral disc protrusion	0	0	1 (0.3)
Joint swelling	1 (0.1)	0	0
Muscle spasms	1 (0.1)	0	0
Myofascial pain syndrome	0	0	1 (0.3)
Pain in extremity	0	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.3)
Gastric cancer	0	0	1 (0.3)
Nervous system disorders	1 (0.1)	0	1 (0.3)
Headache	0	0	1 (0.3)
Migraine	1 (0.1)	0	0
Psychiatric disorders	0	2 (0.6)	1 (0.3)
Adjustment disorder	0	0	1 (0.3)
Insomnia	0	2 (0.6)	0
Renal and urinary disorders	0	4 (1.3)	1 (0.3)
Bladder prolapsed	0	1 (0.3)	0
Micturition urgency	0	1 (0.3)	0
Pollakiuria	0	0	1 (0.3)
Urinary hesitation	0	2 (0.6)	0
Reproductive system and breast disorders	0	0	1 (0.3)

Table 17. Permanent Discontinuations Due to Adverse Events

	Tolterodine[a] N=990	Fesoterodine N=308	Placebo N=301
System Organ Class **MedDRA (v15.0) Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Uterine haemorrhage	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	0	0
Dry throat	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.3)
Rash	0	0	1 (0.3)
Vascular disorders	1 (0.1)	0	0
Arterial occlusive disease	1 (0.1)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with observation; N = total number of subjects in respective treatment group
The tolterodine group refers to subjects in the 2-week, open-label tolterodine run-in period, prior to the randomized, double-blind, fesoterodine versus placebo period.

Dose Reductions or Temporary Discontinuations Due to Adverse Events: There were no dose reductions due to AEs in any treatment group. There were no temporary discontinuations due to AEs in the open-label tolterodine run-in period. In the randomized, double-blind fesoterodine group, 4 subjects reported a total of 6 AEs for which the study drug was stopped temporarily; none of these AEs was considered serious by the Investigators. In the randomized, double-blind placebo group, 1 subject reported 1 AE for which study drug was stopped temporarily; considered as serious by the Investigator (Table 18).

Table 18. Temporary Discontinuations Due to Adverse Events

Serial Number	System Organ Class Preferred Term	Treatment[a]/ Treatment Phase	Study Start Day/ Stop Day[b]	Period Start Day/ Stop day[c]	Study Day Treatment Stopped	Severity	Outcome	Causality	SAE Yes/No
1	Hepatobiliary disorders Cholecystitis acute	Placebo/ Active	47/51	33/37	98	Severe	Resolved	Other illness - acute cholecystitis	Yes
2	Gastrointestinal disorders Dry mouth	Fesoterodine/ Active	41/82	23/47	58	Moderate	Resolved	Study drug	No
	Gastrointestinal disorders Dry mouth	Fesoterodine/ Active	53/57	35/39	58	Mild	Resolved	Study drug	No
	Gastrointestinal disorders Dry mouth	-/ Post	41/82	1/17	58	Moderate	Resolved	Study drug	No
3	Surgical and medical procedures Bone lesion excision	Fesoterodine/ Active	23/23	9/9	58	Moderate	Resolved	Other - bone spur removal	No
4	Gastrointestinal disorders Constipation	Fesoterodine/ Active	86/90	72/76	99	Moderate	Resolved	Study drug	No
5	General disorders and administration site conditions Oedema peripheral	Fesoterodine/ Active	22/28	6/12	95	Moderate	Resolved	Study drug	No

Subjects randomized to the double blind fesoterodine group were scheduled to receive 4 mg during Week 1, then 8 mg for the remainder of the study.
SAEs (according to Investigators assessment).
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

a. Study treatment at time of adverse event.
b. Day relative to start of tolterodine study treatment. First day of tolterodine treatment = Day 1.
c. Day relative to first day of each treatment period. First day of each treatment period = Day 1.

Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety: No significant changes in mean or median, BP or heart rate were observed in any treatment group.

CONCLUSIONS:

- The primary aim of this study was achieved which demonstrated the efficacy of 8 mg fesoterodine on UUI reduction in OAB subjects with suboptimal response to tolterodine LA. The study demonstrated statistical significance in UUI reduction from baseline (end of the tolterodine run-in period) to Week 12 for fesoterodine 8 mg (within-group mean change) and in comparison to placebo.

- The fesoterodine group also showed statistically significant improvements for change from baseline to Week 12 in the mean number of micturition-related urgency episodes.

- The fesoterodine group showed a statistically significant improvement in diary dry rate at Week 4 compared to placebo. The improvement was not statistically significant at Week 12.

- Statistically significant improvements in change from baseline to Week 12 in PPBC, UPS, OAB-q symptom bother scores, total HRQL and each domain of the HRQL Scale were observed in the fesoterodine group compared to the placebo group.

- The safety and tolerability profiles of fesoterodine and tolterodine were consistent with previous studies. No safety concern was identified and the most common AEs were dry mouth and constipation.