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

PROTOCOL NO.: A0221009

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Fesoterodine as an "Add-On" Therapy in Men With Persistent Overactive Bladder Symptoms Under Monotherapy of Alpha Blocker for Lower Urinary Tract Symptoms

Study Centers: A total of 121 centers took part in the study and randomized subjects; 48 in the United States (US), 8 each in Canada and Germany, 6 each in Philippines and Poland, 5 each in Brazil, Slovakia and Sweden, 4 each in India and Korea, 3 each in Belgium, Columbia, Greece, and the Netherlands, and 2 each in Malaysia, Norway, Singapore, Spain, and Thailand.

Study Initiation Date and Final Completion Date: 06 December 2007 to 03 February 2009

Phase of Development: Phase 3b

Study Objectives:

Primary Objective: To evaluate the effect of fesoterodine on overactive bladder (OAB) symptom improvement, versus placebo, as an "add-on" therapy, in men with persistent OAB symptoms of urinary frequency and urgency with/without urgency incontinence who had been receiving alpha-blocker monotherapy for lower urinary tract symptoms (LUTS) at a stable dose for at least 6 weeks.

Secondary Objectives:

- To evaluate the effect of "add-on" fesoterodine on International Prostate Symptom Scale (IPSS) versus placebo.
- To evaluate the effect of "add-on" fesoterodine on patient reported outcomes (PRO) versus placebo.
- To evaluate the safety and tolerability of "add-on" fesoterodine.

METHODS: This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, multi-national and multi-center study to evaluate the treatment effect of the addition of fesoterodine versus placebo, to ongoing alpha-blocker therapy, in men with

persistent OAB symptoms who had been taking a stable dose of an alpha-blocker for LUTS for a minimum of 6 weeks.

The study consisted of a 1-week screening period and a 12-week double-blind treatment period, requiring a total of 5 scheduled in-clinic visits: screening visit (Week 1), baseline visit (Week 0), Week 4 visit, Week 8 visit, and end-of-study visit (Week 12 or early termination).

At the baseline visit, eligible subjects were randomized in a 1:1 ratio to receive either fesoterodine or matching placebo, in addition to continuing on a stable dose of their currently prescribed alpha-blocker medication, for 12 weeks of treatment.

The 3-day bladder diary was collected at baseline, and at the Week 4 and 12 visits. Multiple PRO measurements, including Patient Perception of Bladder Condition (PPBC), Urgency Perception Scale (UPS) Questionnaire (formerly known as Patient Perception of Urgency Scale [PPUS]), and OAB Questionnaire (OAB-q), were also administered at baseline and at the Week 4 and 12 visits to assess the effect of "add-on" fesoterodine on OAB symptoms. The IPSS questionnaire was administered at baseline and at the Week 4 and 12 visits to assess the effect of "add-on" fesoterodine on IPSS.

Safety and tolerability were assessed at every visit. Post-void residual (PVR) urine volume at the baseline and all subsequent visits, and maximum urinary flow rate (Q_{max}) were recorded at baseline and the Week 12 visit. Prostate size and prostate-specific antigen (PSA) data were collected at baseline visit.

A schedule of activities is presented in Table 1.

Table 1. Schedule of Study Activities

Activities & Forms to Be Completed	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening Week –1 (±2 Days)	Randomization/ Baseline, Week 0	Week 4 (±7 Days)	Week 8 (±7 Days)	End-of-Study Week 12 (±7 Days) or Early Termination
Written informed consent	X				
Demographics & medical history	X				
Blood pressure & heart rate[a]	X	X	X	X	X
Physical examination & 12-lead ECG	X				
Inclusion/exclusion criteria	X	X			
Blood draw (hematology and chemistry, PSA)	X				
Urine dipstick test	X				
Prostate size		X			
PVR		X	X	X	X
Q_{max}		X			X
IPSS		X	X		X
Patient's perception of bladder condition		X	X		X
Urgency perception scale		X	X		X
Overactive bladder questionnaire		X	X		X
Dispense bladder diary (3-day)	X	X		X	
Evaluation of bladder diary (3-day)		X	X		X
Adverse events[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	X
Dose adjustment[d]			X	X	
Dispense study medication		X	X	X	
Study medication return/count			X	X	X
Assess drug compliance			X	X	X

ECG = electrocardiogram; IPSS = International Prostate Symptom Scale; PSA = prostate-specific antigen; PVR = post-void residual; Q_{max} = maximum urinary flow rate.

a. At the screening visit, supine and standing blood pressure and heart rate were measured; at other visits, only sitting blood pressure and heart rate were measured.

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

c. Impala is a centralized randomization system used to obtain the single subject identification number, randomization number, and randomization assignment. It also functions to predict and trigger drug re-supply for a site.

d. Based upon a discussion between the subjects and the Investigators of efficacy and tolerability reported by the subjects, the dose of the study drug could be adjusted at Week 4 and Week 8. At Week 4, the Investigators could increase the dose to 8 mg (fesoterodine or matching placebo) for the subjects who desired greater symptom improvement and reported good tolerability and continue the rest of the subjects on 4 mg. At Week 8, dose could be adjusted only for the subjects on 8 mg dose. For those who could not tolerate 8 mg, the dose could be reduced to 4 mg or the subject could be discontinued from study as appropriate. Subjects on 4 mg did not have dose adjustment at Week 8.

Number of Subjects (Planned and Analyzed): A total of 900 randomized subjects (450 subjects in each arm) was the planned enrollment for the study. A total of 947 male subjects were randomized: 473 to placebo add-on therapy and 474 to fesoterodine add-on therapy. A total of 472 subjects and 471 subjects were treated with placebo add-on therapy and fesoterodine add-on therapy, respectively.

Of the 947 subjects; 348 were randomized in the US, 103 in Poland, 89 in Germany, 82 in the Republic of Korea, 73 in Slovakia, 38 in Sweden, 35 in Canada, 30 in Spain, 28 in Brazil, 26 in Norway, 24 in the Netherlands, 13 each in Colombia and Philippines, 12 in Belgium, 11 in India, 7 in Singapore, and 5 each in Greece, Malaysia, and Thailand.

Diagnosis and Main Criteria for Inclusion: Male subjects aged 40 years and older, who were diagnosed with persistent symptoms of OAB with urinary frequency ≥8 times/24 hours and micturition-related urgency episodes ≥3 episode/24 hours and who were on a stable and well-tolerated dose of an alpha-blocker prescribed for LUTS for at least 6 weeks prior to screening (Visit 1), were eligible to be enrolled in the study.

Study Treatment: Study medication (fesoterodine and placebo) was supplied in blister cards: 4 mg card and 8 mg card containing 35 fesoterodine 4 mg and 8 mg tablets or their matching placebos sufficient for 4 weeks of treatment.

Each randomized subject was allocated specific blister cards for the 12-week double-blind treatment period. Subjects were instructed to take 1 tablet of study drug orally with water every day around the same time with or without food. All randomized subjects were initially to be treated with 4 mg of fesoterodine or placebo once daily for 4 weeks. At the Week 4 visit, the dose of study drug was adjusted through collaborative decision by the Investigator and the subject. For subjects who desired greater symptom improvement and reported acceptable safety and tolerability, the fesoterodine dose was to be increased to 8 mg in a blinded fashion; ie, the matching placebo for fesoterodine 8 mg tablets were provided to subjects in the placebo group who chose the dose increase. For the rest of the subjects, the dose was to be maintained at 4 mg of fesoterodine or matching placebo. For subjects receiving the 8 mg dose, the dose could be reduced again at the Week 8 visit through a similar collaborative decision by the Investigator and the subject.

Subjects were required to continue their prescribed alpha-blocker treatment for the duration of the study. They were not permitted to alter/adjust the dose of their current alpha-blocker or replace their current alpha-blocker treatment with another alpha-blocker during the study.

Efficacy and Safety Endpoints:

Primary Endpoint:

- Numeric change of micturition-related urgency episodes per 24 hours at Week 12 relative to baseline (micturition-related urgency episodes were defined as those with Urinary Sensation Scale (USS) rating of ≥3 marked for the corresponding micturition in the diary).

Secondary Endpoints:

Bladder Diary:

- Numeric change of micturition-related urgency episodes per 24 hours at Week 4 and percentage change of micturition-related urgency episodes per 24 hours at Weeks 4 and 12 relative to baseline;

- Numeric change and percentage change of micturitions per 24 hours at Weeks 4 and 12 relative to baseline;

- Numeric change and percentage change of nocturnal micturitions per 24 hours at Weeks 4 and 12 relative to baseline (nocturnal micturitions were defined as micturitions that occurred between the time the subject went to bed and the time he arose to start the next day);

- Numeric change and percentage change of urgency urinary incontinence (UUI) episodes per 24 hours at Weeks 4 and 12 relative to baseline (UUI episodes were defined as those with USS rating of 5 in the diary) in subjects with UUI at baseline;

- Numeric change and percentage change of severe micturition-related urgency episodes per 24 hours at Weeks 4 and 12 relative to baseline (severe micturition-related urgency episodes were defined as those with USS rating ≥4 marked for the corresponding micturition in the diary);

- Numeric change and percentage change of nocturnal micturition-related urgency episodes per 24 hours at Weeks 4 and 12 relative to baseline (nocturnal micturition-related urgency episodes were defined as micturition-related urgency episodes that occurred between the time the subject went to bed and the time he arose to start the next day);

- Change in USS sum rating per 24 hours at Weeks 4 and 12 relative to baseline (USS sum rating was defined as the total of USS ratings recorded for all micturitions over the course of a day in the diary).

International Prostate Symptom Score (IPSS):

- Change in IPSS total score (Sum Question 1 [Q1] to Q7) at Weeks 4 and 12 relative to baseline;

- Change in IPSS storage domain (Sum of Q2, Q4, and Q7) at Weeks 4 and 12 relative to baseline;

- Change in IPSS voiding domain (Sum of Q1, Q3, Q5, and Q6) at Weeks 4 and 12 relative to baseline;

- Change in IPSS quality of life (QoL) score (Q8) at Weeks 4 and 12 relative to baseline;

- Change in IPSS individual item scores (Q1, Q2, Q3, Q4, Q5, Q6, and Q7) at Weeks 4 and 12 relative to baseline.

Patient Perception of Bladder Condition (PPBC):

- Change in PPBC at Weeks 4 and 12 relative to baseline.

Urgency Perception Scale (formerly known as Patient Perception of Urgency Scale):

- Change in UPS at Weeks 4 and 12 relative to baseline.

OAB Questionnaire:

- Change in OAB-q symptom bother score at Weeks 4 and 12 relative to baseline;

- Change in score of each health related quality of life (HRQL) domain of OAB-q at Weeks 4 and 12 relative to baseline.

Safety Endpoints:

- Change of PVR urine volume at Weeks 4, 8 and 12 relative to baseline.

- Change of Q_{max} at Week 12 relative to baseline.

- Incidence of acute urinary retention requiring catheterization.

- Incidences of adverse events (AEs) related to increased voiding difficulty.

Safety Evaluations: Safety evaluations included AE monitoring, blood pressure (BP) and heart rate, physical examinations, electrocardiograms (ECG), laboratory testing, PVR volume measurements, and Q_{max} measurements.

Statistical Methods: Safety analyses were based on the safety analysis set defined as all subjects who took at least 1 dose of study drug. Efficacy analyses were based on the full analysis set (FAS) defined as all subjects who took at least 1 dose of assigned study drug and had at least 1 baseline or post-baseline efficacy assessment.

All tests were 2-sided. An alpha level of 0.05 was used for all statistical tests for treatment difference. An alpha level of 0.10 was used to determine the statistical significance of interaction terms in the analysis of covariance (ANCOVA) model.

To compare baseline with post-baseline measurements, a paired t-test was performed and p-values were reported.

ANCOVA model was used to compare treatments with respect to the primary endpoint. The ANCOVA model included treatment, country, and the baseline value as a covariate.

Secondary endpoints including numeric change of micturitions per 24 hours, nocturnal micturitions per 24 hours, nocturnal micturition-related urgency episodes per 24 hours, and change in Frequency-Urgency Sum (synonymous with USS sum rating) per 24 hours were analyzed using the ANCOVA model.

The numeric change of UUI episodes per 24 hours and severe micturition-related urgency episodes per 24 hours were analyzed using the van Elteren test (a stratified Wilcoxon-Mann-Whitney test) with baseline quartiles as strata because these data were found to violate the assumptions of normality.

The percent change from baseline for the bladder diary endpoints was analyzed using a ranked ANCOVA model. The ranked ANCOVA model used ranked percent change as the response and included the terms of treatment and country, and had ranked baseline value as a covariate.

IPSS and OAB-q endpoints were analyzed using the ANCOVA model and paired t-test. PPBC and UPS endpoints were analyzed using Cochran-Mantel-Haenszel test for ordinal data.

For the efficacy analysis, the last observation carried forward (LOCF) method was used to impute Week 12 missing data. Missing Week 4 data were not imputed and baseline data were not carried forward. For analyses involving change from baseline, only observations with both non-missing baseline and post-baseline data were included and counted in the total number (N) in the analysis. If data were missing for 1 day, the mean of the remaining 2 days was used to impute the missing day. Diary data with more than 1 missing day were considered missing for that visit.

Descriptive statistics were reported by treatment for screening/baseline prostate size and prostate specific antigen (PSA).

The van Elteren test was used to analyze PVR and Q_{max} safety endpoints, since these data were found to violate the assumptions of normality. For PVR, the LOCF method was used to impute Weeks 8 and 12 missing data. Missing Week 4 data were not imputed and baseline data were not carried forward.

RESULTS:

Subject Disposition and Demography: Subject disposition is summarized in Table 2. A total of 1336 subjects were screened for inclusion in this study; of these, 473 were randomized to treatment with placebo add-on therapy and 474 to fesoterodine add-on therapy. A total of 4 subjects were randomized but not treated (1 subject assigned to placebo add-on therapy and 3 subjects to fesoterodine add-on therapy). Of the 472 subjects treated with placebo add-on therapy, 89.8% completed the study. Similarly, 85.1% of the 471 subjects treated with fesoterodine add-on therapy completed the study.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Placebo Add-on N=472	Fesoterodine Add-on N=471
Screened =1336		
Assigned to study treatment	473	474
Treated	472	471
Completed	424 (89.8)	401 (85.1)
Discontinued	48 (10.2)	70 (14.9)
Related to study drug	17 (3.6)	40 (8.5)
Adverse event	12 (2.5)	35 (7.4)
Lack of efficacy	5 (1.1)	5 (1.1)
Not related to study drug	31 (6.6)	30 (6.4)
Adverse event	8 (1.7)	11 (2.3)
Lost to follow-up	2 (0.4)	2 (0.4)
Other[a]	12 (2.5)	10 (2.1)
Subject no longer willing to participate in study	9 (1.9)	7 (1.5)
Analyzed for efficacy		
Full analysis set[b]	472	471
Analyzed for safety		
Adverse events	472	471

Discontinuations that occurred outside the lag period were attributed to the last study treatment received.
N = number of subjects in each treatment group.

a. Subjects summarized in this table as "other" are subjects who discontinued due to "other," "protocol violation," and "does not meet entrance criteria."
b. The full analysis set included all subjects who took at least 1 dose of assigned study drug and had at least 1 baseline or post-baseline efficacy assessment.

A summary of demographic and baseline characteristics is presented in Table 3. Demographic characteristics were comparable among subjects in both treatment groups. All subjects were male and 81.3% were white. The mean age was approximately 66 years in both treatment groups, with 56% of subjects ≥65 years old. The subjects had a mean OAB duration of approximately 5 years with 80% having a diagnosis of benign prostate hyperplasia. Two subjects (1 in each treatment group) did not have concomitant alpha blocker treatment. The median study treatment duration was 84 days in both treatment groups with compliance ranging from 97% to 98%.

Table 3. Demographic Characteristics - Safety Analysis Set

	Placebo Add-on (N=472)	Fesoterodine Add-on (N=471)	Total (N=943)
Age (years)			
18-44 (n, [%])	9 (1.9)	7 (1.5)	16 (1.7)
45-64 (n, [%])	189 (40.0)	211 (44.8)	400 (42.4)
≥65 (n, [%])	274 (58.1)	253 (53.7)	527 (55.9)
Mean (SD)	65.5 (9.1)	65.7 (9.1)	65.6 (9.1)
Range	40.0-88.0	41.0-93.0	40.0-93.0
Race			
n	472	471	943
White	388 (82.2)	379 (80.5)	767 (81.3)
Black	15 (3.2)	11 (2.3)	26 (2.8)
Asian	60 (12.7)	67 (14.2)	127 (13.5)
Other	9 (1.9)	14 (3.0)	23 (2.4)
Weight (kg)			
n	471 (99.8)	471 (100.0)	942 (99.9)
Mean (SD)	85.3 (16.8)	86.8 (18.6)	86.0 (17.8)
Range	48.2-181.9	48.0-172.3	48.0-181.9
Body mass index (kg/m^2)			
n	470 (99.6)	471 (100.0)	941 (99.8)
Mean (SD)	28.0 (4.6)	28.5 (5.4)	28.3 (5.0)
Range	16.5-52.8	16.6-61.1	16.5-61.1

N = number of subjects in each treatment group; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results: Fesoterodine add-on therapy did not show superior efficacy over placebo add-on therapy in the primary endpoint (ie, mean change in micturition-related urgency episodes per 24 hours at Week 12 relative to baseline). The treatment difference was not statistically significant (p-value = 0.1959) (Table 4).

In the secondary endpoints of mean change in micturitions per 24 hours, fesoterodine add-on therapy showed statistically significantly greater reductions in the number of micturitions per 24 hours from baseline versus placebo add-on therapy at both Week 4 and Week 12 (p-value = 0.0056 and p-value = 0.009, respectively). The percent change from baseline in the number of micturitions per 24 hours, was also statistically significant at both Weeks 4 and 12 (p-value = 0.0012 and p-value = 0.0027) in favor of fesoterodine add-on therapy (Table 6).

There were statistically significant differences in the reduction of severe micturition-related urgency episodes and frequency-urgency sum at Week 4 (p-value = 0.0062 and p-value = 0.0051, respectively) both in favor of fesoterodine add-on therapy, but not at Week 12 (Table 9, Table 11). For all other diary endpoints, there were no statistically significant treatment differences at both Week 4 and Week 12 (Table 5, Table 7, Table 8, and Table 10).

There were no statistically significant treatment differences in the majority of the IPSS parameters (ie, total score, domain scores, QoL score, and the individual item scores) at Weeks 4 and 12 (Table 12, Table 13, Table 14, and Table 15).

There were no statistically significant treatment differences for the endpoints on PPBC and UPS improvement at Weeks 4 and 12 (Table 16, Table 17).

In the OAB-q, there were statistically significant treatment differences in favor of fesoterodine add-on therapy in the improvement of the symptom bother score at both Week 4 and Week 12 (p-value = 0.004 and p-value = 0.0068, respectively). However, treatment differences in all other domains were not statistically significant, except for the HRQL total score at Week 4 (p-value = 0.0412) in favor of fesoterodine add-on therapy (Table 19).

Primary Endpoint Results:

Numeric Change of Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Baseline:

Table 4 presents a summary of change from baseline in mean number of micturition-related urgency episodes per 24 hours at Week 12.

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

	Placebo Add-on	Fesoterodine Add-on
N[a]	451	446
Baseline		
Mean (SD)	8.3 (3.8)	8.1 (4.2)
Median (range)	8.0 (1.0 to 24.3)	7.7 (1.0 to 29.3)
Week 12		
Mean (SD)	5.4 (4.4)	4.9 (4.5)
Median (range)	4.7 (0.0 to 23.3)	3.7 (0.0 to 22.3)
Numerical change from baseline to Week 12		
Mean (SD)	-2.9 (4.5)	-3.2 (4.7)
Median (range)	-2.7 (-23.3 to 20.0)	-3.0 (-29.3 to 13.3)
LS mean (SE)	-2.9 (0.2)	-3.2 (0.2)
95% CI for mean (p-value)[b]	-3.4, -2.5 (<0.0001)	-3.6, -2.8 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.4 (0.3)
95% CI		-0.9, 0.2
p-value		0.1959

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with baseline urgency episodes >0 per 24 hours (placebo: 470, fesoterodine: 471) and non-missing change from baseline to Week 12 (LOCF).

b. P-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Secondary Endpoints Results:

Bladder Diary Endpoints:

Numeric Change of Micturition-Related Urgency Episodes per 24 Hours at Week 4 and Percentage Change of Micturition-Related Urgency Episodes per 24 hours at Weeks 4 and 12 Relative to Baseline:

The change from baseline in mean number of micturition-related urgency episodes per 24 hours at Week 4 is presented in Table 5. The results for percent change from baseline to Weeks 4 and 12 are presented in Table 5. The p-value for treatment difference based on

percent change was not calculated because the treatment difference based on numerical change was not statistically significant.

Table 5. Change From Baseline in Mean Number and Percentage Change of Micturition-Related Urgency Episodes per 24 Hours at Week 4 and Week 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	450	445
Baseline		
Mean (SD)	8.3 (3.8)	8.1 (4.2)
Median (range)	8.0 (1.0 to 24.3)	7.7 (1.0 to 29.3)
Week 4		
Mean (SD)	6.5 (4.3)	5.8 (4.7)
Median (range)	6.3 (0.0 to 23.3)	4.7 (0.0 to 28.7)
Numerical change from baseline to Week 4		
Mean (SD)	-1.9 (3.8)	-2.3 (4.2)
Median (range)	-1.7 (-15.0 to 10.3)	-2.0 (-28.0 to 13.3)
LS mean (SE)	-1.9 (0.2)	-2.3 (0.2)
95% CI for mean (p-value)[b]	-2.2, -1.5 (<0.0001)	-2.7, -1.9 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.5 (0.2)
95% CI		-1.0, 0.0
p-value		0.0621
Percent change from baseline to Week 4		
Mean (SD)	-20.0 (49.1)	-25.6 (56.9)
Median (range)	-20.7 (-100.0 to 158.8)	-30.8 (-100.0 to 363.6)
N[a]	451	446
Baseline		
Mean (SD)	8.3 (3.8)	8.1 (4.2)
Median (range)	8.0 (1.0 to 24.3)	7.7 (1.0 to 29.3)
Week 12		
Mean (SD)	5.4 (4.4)	4.9 (4.5)
Median (range)	4.7 (0.0 to 23.3)	3.7 (0.0 to 22.3)
Percent change from baseline to Week 12		
Mean (SD)	-32.9 (58.0)	-35.7 (60.8)
Median (range)	-35.7 (-100.0 to 600.0)	-43.8 (-100.0 to 363.6)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with baseline urgency episodes >0 per 24 hours (placebo: 470, fesoterodine: 471) and non-missing change from baseline to Week 4 and 12 (LOCF).

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

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Numeric Change and Percentage Change of Micturitions per 24 Hours at Weeks 4 and 12 Relative to Baseline:

A summary of numerical and percent change from baseline in mean number of micturitions per 24 hours at Weeks 4 and 12 is provided in Table 6.

Table 6. Change From Baseline in Mean Number and Percentage Change of Micturitions Per 24 Hours at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	451	445
Baseline		
Mean (SD)	12.3 (3.3)	12.4 (3.4)
Median (range)	11.7 (8.0 to 27.3)	12.0 (7.0 to 29.3)
Week 4		
Mean (SD)	11.3 (3.4)	11.0 (3.5)
Median (range)	10.7 (4.3 to 28.7)	10.3 (4.3 to 29.3)
Numerical change from baseline to Week 4		
Mean (SD)	-0.9 (2.4)	-1.4 (2.6)
Median (range)	-1.0 (-9.7 to 8.0)	-1.3 (-21.0 to 8.3)
LS mean (SE)	-0.8 (0.1)	-1.3 (0.1)
95% CI for mean (p-value)[b]	-1.2, -0.7 (< 0.0001)	-1.7, -1.2 (< 0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.4 (0.2)
95% CI		-0.8, -0.1
p-value		0.0056
Percent change from baseline to Week 4		
Mean (SD)	-6.6 (18.9)	-10.5 (18.8)
Median (range)	-7.3 (-53.7 to 66.7)	-12.0 (-71.6 to 96.2)
Treatment difference in percentage change		
p-value[d]		0.0012
N[a]	452	446
Baseline		
Mean (SD)	12.2 (3.3)	12.4 (3.4)
Median (range)	11.7 (8.0 to 27.3)	12.0 (7.0 to 29.3)
Week 12		
Mean (SD)	10.7 (3.2)	10.4 (3.3)
Median (range)	10.3 (3.3 to 28.0)	9.7 (3.3 to 24.0)
Numerical change from baseline to Week 12		
Mean (SD)	-1.5 (2.6)	-2.0 (2.8)
Median (range)	-1.3 (-10.3 to 6.3)	-1.7 (-24.0 to 8.3)
LS mean (SE)	-1.5 (0.1)	-1.9 (0.1)
95% CI for mean (p-value)[b]	-1.7, -1.3 (< 0.0001)	-2.2, -1.7 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.4 (0.2)
95% CI		-0.7, -0.1
p-value		0.0090
Percent change from baseline to Week 12		
Mean (SD)	-11.0 (19.2)	-14.8 (19.3)
Median (range)	-12.5 (-58.3 to 51.4)	-14.9 (-81.8 to 96.2)
Treatment difference in percentage change		
p-value[d]		0.0027

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. For numerical change from baseline, this was the number of subjects with non-missing numerical change from baseline to Week 4 or Week 12 (LOCF). For percent change from baseline, this was the number of subjects with baseline micturitions >0 per 24 hours (placebo: 471, fesoterodine: 471) and non-missing change from baseline to Week 4 and Week 12 (LOCF).

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

d. p-value for median based on a ranked ANCOVA model with terms for country, treatment, and ranked baseline value as a covariate.

Numeric Change and Percentage Change of Nocturnal Micturitions per 24 Hours at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in the mean number of nocturnal micturitions per 24 hours at Weeks 4 and 12 is presented in Table 7.

Table 7. Change From Baseline in Mean Number and Percent Change of Nocturnal Micturitions per 24 Hours at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	441	438
Baseline		
Mean (SD)	2.8 (1.4)	2.8 (1.4)
Median (range)	2.7 (0.3 to 9.0)	2.7 (0.3 to 10.7)
Week 4		
Mean (SD)	2.4 (1.4)	2.3 (1.4)
Median (range)	2.3 (0.0 to 9.0)	2.0 (0.0 to 10.7)
Numerical change from baseline to Week 4		
Mean (SD)	-0.3 (1.0)	-0.4 (1.0)
Median (range)	-0.3 (-5.3 to 4.0)	-0.3 (-3.7 to 3.3)
LS mean (SE)	-0.3 (0.1)	-0.4 (0.1)
95% CI for mean (p-value)[b]	-0.4, -0.2 (<0.0001)	-0.5, -0.3 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.1 (0.1)
95% CI		-0.2, 0.0
p-value		0.1112
Percent change from baseline to Week 4		
Mean (SD)	-6.7 (44.8)	-9.9 (60.4)
Median (range)	-11.1 (-100.0 to 300.0)	-16.7 (-100.0 to 700.0)
N[a]	442	439
Baseline		
Mean (SD)	2.8 (1.4)	2.8 (1.4)
Median (range)	2.7 (0.3 to 9.0)	2.7 (0.3 to 10.7)
Week 12		
Mean (SD)	2.3 (1.4)	2.2 (1.5)
Median (range)	2.0 (0.0 to 8.3)	2.0 (0.0 to 8.0)
Numerical change from baseline to Week 12		
Mean (SD)	-0.5 (1.1)	-0.6 (1.1)
Median (range)	-0.3 (-5.3 to 4.0)	-0.7 (-4.0 to 4.0)
LS mean (SE)	-0.5 (0.1)	-0.6 (0.1)
95% CI for mean (p-value)[b]	-0.6, -0.4 (<0.0001)	-0.7, -0.5 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.1 (0.1)
95% CI		-0.3, 0.0
p-value		0.0855
Percent change from baseline to Week 12		
Mean (SD)	-11.3 (58.2)	-15.3 (66.1)
Median (range)	-16.7 (-100.0 to 700.0)	-25.0 (-100.0 to 600.0)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with baseline nocturnal micturitions >0 per 24 hours (placebo: 460, fesoterodine: 463) and non-missing change from baseline to Week 4 and Week 12 (LOCF).

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Numeric Change and Percentage Change of UUI Episodes per 24 Hours at Weeks 4 and 12 Relative to Baseline in Subjects with UUI at Baseline:

A summary of the change from baseline in the mean number of UUI episodes per 24 hours at Weeks 4 and 12 is provided in Table 8.

Table 8. Change From Baseline in Mean Number and Percent Change of Urgency Urinary Incontinence Episodes per 24 Hours at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	104	103
Baseline		
Mean (SD)	1.2 (1.2)	1.5 (2.7)
Median (range)	1.0 (0.3 to 7.0)	0.7 (0.3 to 23.3)
Week 4		
Mean (SD)	0.6 (1.4)	0.7 (1.8)
Median (range)	0.0 (0.0 to 10.7)	0.0 (0.0 to 14.0)
Numerical change from baseline to Week 4		
Mean (SD)	-0.6 (1.7)	-0.8 (1.9)
Median (range)	-0.7 (-6.7 to 9.7)	-0.3 (-11.3 to 5.7)
Treatment difference in numerical change		
Difference[b]		0.00
p-value[c]		0.3847
Percent change from baseline to Week 4		
Mean (SD)	-43.5 (136.7)	-61.6 (85.3)
Median (range)	-100.0 (-100.0 to 966.7)	-100.0 (-100.0 to 425.0)
N[a]	104	103
Baseline		
Mean (SD)	1.2 (1.2)	1.5 (2.7)
Median (range)	1.0 (0.3 to 7.0)	0.7 (0.3 to 23.3)
Week 12		
Mean (SD)	0.3 (0.8)	0.4 (1.2)
Median (range)	0.0 (0.0 to 5.3)	0.0 (0.0 to 7.0)
Numerical change from baseline to Week 12		
Mean (SD)	-0.9 (1.4)	-1.0 (2.3)
Median (range)	-0.7 (-6.7 to 4.0)	-0.7 (-16.7 to 5.7)
Treatment difference in numerical change		
Difference[b]		0.00
p-value[c]		0.4449
Percent change from baseline to Week 12		
Mean (SD)	-66.4 (79.0)	-72.5 (77.2)
Median (range)	-100.0 (-100.0 to 300.0)	-100.0 (-100.0 to 425.0)

LOCF = last observation carried forward; N = number of subjects in each group; SD = standard deviation.

a. Number of subjects with baseline urgency urinary incontinence episodes >0 per 24 hours (placebo: 108, fesoterodine: 110) and non-missing change from baseline to Week 4 and Week 12 (LOCF).

b. Hodges-Lehmann estimate of the location shift between the 2 groups, which was calculated as the median of all pairwise differences in numerical change between the 2 groups.

c. Based on Van Elteren's test adjusted by baseline quartiles.

Numeric Change and Percentage Change of Severe Micturition-Related Urgency Episodes per 24 Hours at Weeks 4 and 12 Relative to Baseline:

A summary of change from baseline in mean number of severe micturition-related urgency episodes per 24 hours at Weeks 4 and 12 is provided in Table 9.

Table 9. Change From Baseline in Mean Number and Percent Change of Severe Micturition-Related Urgency Episodes per 24 Hours at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	339	310
Baseline		
Mean (SD)	3.1 (2.8)	3.3 (3.5)
Median (range)	2.3 (0.3 to 16.7)	2.3 (0.3 to 25.7)
Week 4		
Mean (SD)	2.0 (2.9)	1.7 (2.8)
Median (range)	0.7 (0.0 to 18.7)	0.3 (0.0 to 18.3)
Numerical change from baseline to Week 4		
Mean (SD)	-1.1 (2.6)	-1.6 (2.7)
Median (range)	-1.0 (-11.0 to -13.7)	-1.0 (-13.0 to 10.7)
Treatment difference in numerical change		
Difference[b]		-0.33
p-value[c]		0.0062
Percent change from baseline to Week 4		
Mean (SD)	-23.6 (130.7)	-49.3 (79.4)
Median (range)	-60.0 (-100.0 to 1366.7)	-78.6 (-100.0 to 500.0)
Treatment difference		
p-value[d]		0.0025
N[a]	340	311
Baseline		
Mean (SD)	3.1 (2.8)	3.3 (3.5)
Median (range)	2.2 (0.3 to 16.7)	2.3 (0.3 to 25.7)
Week 12		
Mean (SD)	1.4 (2.3)	1.4 (2.7)
Median (range)	0.3 (0.0 to 16.0)	0.0 (0.0 to 18.3)
Numerical change from baseline to Week 12		
Mean (SD)	-1.7 (2.8)	-1.9 (3.1)
Median (range)	-1.0 (-16.7 to 9.0)	-1.3 (-18.0 to 10.7)
Treatment difference in numerical change		
Difference[b]		0.00
p-value[c]		0.0825
Percent change from baseline to Week 12		
Mean (SD)	-46.6 (90.1)	-50.8 (100.7)
Median (range)	-88.4 (-100.0 to 600.0)	-100.0 (-100.0 to 600.0)

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each treatment group; SD = standard deviation.

a. Number of subjects with baseline severe urgency episodes >0 per 24 hours (placebo: 353, fesoterodine: 328) and non-missing change from baseline to Week 4 and Week 12 LOCF.
b. Hodges-Lehmann estimate of the location shift between the 2 groups, which was calculated as the median of all pairwise differences in numerical change between the 2 groups.
c. p-value based on Van Elteren's test adjusted by baseline quartiles.
d. p-value for median based on a ranked ANCOVA model with terms for country, treatment, and ranked baseline value as a covariate.

Numeric Change and Percentage Change of Nocturnal Micturition-Related Urgency Episodes per 24 Hours at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in mean number of nocturnal micturition-related urgency episodes per 24 hours is provided in Table 10.

Table 10. Change From Baseline in Mean Number and Percentage Change of Nocturnal Micturition-Related Urgency Episodes per 24 Hours at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	433	424
Baseline		
Mean (SD)	2.2 (1.3)	2.2 (1.3)
Median (range)	2.0 (0.3 to 7.7)	2.0 (0.3 to 10.7)
Week 4		
Mean (SD)	1.7 (1.3)	1.5 (1.4)
Median (range)	1.3 (0.0 to 9.0)	1.3 (0.0 to 10.7)
Numerical change from baseline to Week 4		
Mean (SD)	-0.6 (1.2)	-0.7 (1.2)
Median (range)	-0.3 (-6.3 to 4.0)	-0.7 (-6.0 to 4.0)
LS mean (SE)	-0.6 (0.1)	-0.7 (0.1)
95% CI for mean (p-value)[b]	-0.7, -0.4 (< 0.0001)	-0.8, -0.6 (< 0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.1 (0.1)
95% CI		-0.3, 0.0
p-value		0.1748
Percent change from baseline to Week 4		
Mean (SD)	-17.3 (68.9)	-20.5 (87.1)
Median (range)	-25.0 (-100.0 to 400.0)	-33.3 (-100.0 to 800.0)
N[a]	434	425
Baseline		
Mean (SD)	2.2 (1.3)	2.2 (1.3)
Median (range)	2.0 (0.3 to 7.7)	2.0 (0.3 to 10.7)
Week 12		
Mean (SD)	1.3 (1.3)	1.3 (1.4)
Median (range)	1.0 (0.0 to 8.3)	1.0 (0.0 to 8.0)
Numerical change from baseline to Week 12		
Mean (SD)	-0.9 (1.4)	-0.9 (1.4)
Median (range)	-0.7 (-7.3 to 5.3)	-0.7 (-5.7 to 4.7)
LS mean (SE)	-0.9 (0.1)	-0.9 (0.1)
95% CI for mean (p-value)[b]	-1.0, -0.8 (<0.0001)	-1.0, -0.7 (< 0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		0.0 (0.1)
95% CI		-0.1, 0.2
p-value		0.6572
Percent change from baseline to Week 12		
Mean (SD)	-33.4 (70.4)	-25.9 (104.2)
Median (range)	-40.0 (-100.0 to 400.0)	-50.0 (-100.0 to 800.0)

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with baseline nocturnal urgency episodes >0 (placebo: 451, fesoterodine: 449) and non-missing change from baseline to Week 4 and Week 12 LOCF.
b. p-value was based on paired t-test comparing baseline with post-baseline values.
c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Change in USS Sum Rating per 24 Hours at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in Frequency-Urgency Sum (synonymous with USS sum) per 24 hours at Weeks 4 and 12 is provided in Table 11.

Table 11. Change From Baseline in Urinary Sensation Scale Sum Per 24 Hours at Week 4 and Week 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	451	445
Baseline		
Mean (SD)	34.8 (11.0)	34.7 (12.7)
Median (range)	33.0 (16.7 to 88.3)	32.3 (10.3 to 116.7)
Week 4		
Mean (SD)	30.0 (11.6)	28.2 (12.9)
Median (range)	28.3 (7.3 to 90.3)	25.3 (6.3 to 105.7)
Numerical change from baseline to Week 4		
Mean (SD)	-4.8 (9.5)	-6.5 (10.3)
Median (range)	-4.3 (-44.3 to 25.3)	-5.7 (-77.0 to 38.3)
LS mean (SE)	-4.7 (0.5)	-6.4 (0.5)
95% CI for mean (p-value)[b]	-5.7, -3.9 (<0.0001)	-7.5, -5.6 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-1.7 (0.6)
95% CI		-2.9, -0.5
p-value		0.0051
N[a]	452	446
Baseline		
Mean (SD)	34.7 (11.0)	34.7 (12.7)
Median (range)	33.0 (16.7 to 88.3)	32.3 (10.3 to 116.7)
Week 12		
Mean (SD)	26.9 (11.1)	25.7 (12.4)
Median (range)	26.0 (6.3 to 73.7)	23.3 (5.3 to 92.3)
Numerical change from baseline to Week 12		
Mean (SD)	-7.9 (10.8)	-8.9 (11.9)
Median (range)	-7.0 (-58.0 to 30.0)	-8.3 (-82.7 to 38.3)
LS mean (SE)	-7.8 (0.6)	-8.9 (0.6)
95% CI for mean (p-value)[b]	-8.9, -6.9 (<0.0001)	-10.1, -7.8 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-1.0 (0.7)
95% CI		-2.3, 0.3
p-value		0.1231

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 (LOCF).

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Endpoints Evaluated Through IPSS:

Change in IPSS Total Score (Sum Q1 to Q7) at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in IPSS total score at Weeks 4 and 12 is presented in Table 12.

Table 12. Change From Baseline in International Prostate Symptom Score (Total Score, Sum of Questions 1-7) at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	454	453
Baseline		
Mean (SD)	18.6 (6.5)	19.3 (6.6)
Median (range)	18.0 (4.0 to 34.0)	19.0 (3.0 to 34.0)
Week 4		
Mean (SD)	15.7 (6.5)	15.9 (7.3)
Median (range)	15.0 (3.0 to 34.0)	16.0 (2.0 to 35.0)
Numerical change from baseline to Week 4		
Mean (SD)	-2.8 (5.8)	-3.4 (5.7)
Median (range)	-3.0 (-26.0 to 13.0)	-3.0 (-22.0 to 10.0)
LS mean (SE)	-3.1 (0.3)	-3.4 (0.3)
95% CI for mean (p-value)[b]	-3.4, -2.3 (<0.0001)	-3.9,- 2.9 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.3 (0.4)
95% CI		-1.0, 0.4
p-value		0.3579
N[a]	456	454
Baseline		
Mean (SD)	18.6 (6.5)	19.3 (6.5)
Median (range)	18.0 (4.0 to 34.0)	19.5 (3.0 to 34.0)
Week 12		
Mean (SD)	14.3 (6.6)	14.6 (7.1)
Median (range)	14.0 (2.0 to 35.0)	14.0 (0.0 to 33.0)
Numerical change from baseline to Week 12		
Mean (SD)	-4.3 (6.4)	-4.7 (6.6)
Median (range)	-4.0 (-25.0 to 12.0)	-4.0 (-23.0 to 18.0)
LS mean (SE)	-4.4 (0.3)	-4.4 (0.3)
95% CI for mean (p-value)[b]	-4.9, -3.7 (<0.0001)	-5.3, -4.0 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.0 (0.4)
95% CI		-0.8, 0.7
p-value		0.9274

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 LOCF.

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Change in IPSS Storage Domain (Sum of Q2, Q4, and Q7) at Weeks 4 and 12 Relative to Baseline:

The treatment difference was statistically significant at Week 4 (p-value = 0.0223) but not at Week 12 (p-value = 0.1744) (Table 13).

Table 13. Change From Baseline in International Prostate Symptom Score Storage Domain (Sum of Questions 2, 4, and 7) at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	457	456
Baseline		
Mean (SD)	9.3 (2.8)	9.5 (2.8)
Median (range)	9.0 (3.0 to 15.0)	10.0 (2.0 to 15.0)
Week 4		
Mean (SD)	8.0 (3.0)	7.7 (3.1)
Median (range)	8.0 (1.0 to 15.0)	8.0 (1.0 to 15.0)
Numerical change from baseline to Week 4		
Mean (SD)	-1.3 (2.8)	-1.8 (2.8)
Median (range)	-1.0 (-11.0 to 7.0)	-2.0 (-12.0 to 5.0)
LS mean (SE)	-1.4 (0.1)	-1.8 (0.1)
95% CI for mean (p-value)[b]	-1.6, -1.0 (<0.0001)	-2.0, -1.5 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.4 (0.2)
95% CI		-0.7, -0.1
p-value		0.0223
N[a]	458	456
Baseline		
Mean (SD)	9.3 (2.8)	9.5 (2.8)
Median (range)	9.0 (3.0 to 15.0)	10.0 (2.0 to 15.0)
Week 12		
Mean (SD)	7.2 (3.0)	7.0 (3.2)
Median (range)	7.0 (1.0 to 15.0)	7.0 (0.0 to 15.0)
Numerical change from baseline to Week 12		
Mean (SD)	-2.1 (3.1)	-2.4 (3.3)
Median (range)	-2.0 (-12.0 to 6.0)	-2.0 (-13.0 to 7.0)
LS mean (SE)	-2.1 (0.2)	-2.4 (0.2)
95% CI for mean (p-value)[b]	-2.4, -1.8 (<0.0001)	-2.7, -2.1 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.3 (0.2)
95% CI		-0.6, 0.1
p-value		0.1744

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 LOCF.

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Change in IPSS Voiding Domain (Sum of Q1, Q3, Q5, and Q6) at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in IPSS voiding domain at Weeks 4 and 12 is provided in Table 14.

Table 14. Change From Baseline in International Prostate Symptom Score Voiding Domain (Sum of Questions 1, 3, 5, and 6) at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	455	454
Baseline		
Mean (SD)	9.3 (4.8)	9.8 (4.9)
Median (range)	9.0 (0.0 to 20.0)	10.0 (0.0 to 20.0)
Week 4		
Mean (SD)	7.7 (4.5)	8.2 (5.0)
Median (range)	4.0 (0.0 to 6.0)	4.0 (0.0 to 6.0)
Numerical change from baseline to Week 4		
Mean (SD)	-1.6 (3.9)	-1.6 (3.8)
Median (range)	-1.0 (-16.0 to 9.0)	-1.0 (-15.0 to 9.0)
LS mean (SE)	-1.7 (0.2)	-1.6 (0.2)
95% CI for mean (p-value)[b]	-1.9, -1.2 (<0.0001)	-2.0, -1.3 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		0.1 (0.2)
95% CI		-0.4, 0.5
p-value		0.7564
N[a]	457	455
Baseline		
Mean (SD)	9.3 (4.8)	9.8 (4.9)
Median (range)	9.0 (0.0 to 20.0)	10.0 (0.0 to 20.0)
Week 12		
Mean (SD)	7.1 (4.6)	7.6 (4.7)
Median (range)	6.0 (0.0 to 20.0)	7.0 (0.0 to 20.0)
Numerical change from baseline to Week 12		
Mean (SD)	-2.2 (4.1)	-2.2 (4.2)
Median (range)	-2.0 (-17.0 to 10.0)	-2.0 (-15.0 to 12.0)
LS mean (SE)	-2.3 (0.2)	-2.1 (0.2)
95% CI for mean (p-value)[b]	-2.6, -1.8 (<0.0001)	-2.6, -1.8 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		0.2 (0.2)
95% CI		-0.3, 0.7
p-value		0.4010

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 LOCF.

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Change in IPSS QoL Score (Q8) at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in IPSS QoL score at Weeks 4 and 12 is provided in Table 15.

Table 15. Change From Baseline in International Prostate Symptom Score Quality of Life Score (Question 8) at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	455	455
Baseline		
Mean (SD)	4.2 (1.1)	4.3 (1.1)
Median (range)	4.0 (0.0 to 6.0)	4.0 (1.0 to 6.0)
Week 4		
Mean (SD)	3.7 (1.3)	3.7 (1.4)
Median (range)		
Numerical change from baseline to Week 4		
Mean (SD)	-0.5 (1.2)	-0.6 (1.2)
Median (range)	0.0 (-5.0 to 5.0)	0.0 (-6.0 to 4.0)
LS mean (SE)	-0.5 (0.1)	-0.6 (0.1)
95% CI for mean (p-value)[b]	-0.6, -0.4 (<0.0001)	-0.7, -0.5 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.1 (0.1)
95% CI		-0.2, 0.0
p-value		0.1472
N[a]	457	455
Baseline		
Mean (SD)	4.2 (1.1)	4.3 (1.1)
Median (range)	4.0 (0.0 to 6.0)	4.0 (1.0 to 6.0)
Week 12		
Mean (SD)	3.3 (1.4)	3.3 (1.4)
Median (range)	3.0 (0.0 to 6.0)	3.0 (0.0 to 6.0)
Numerical change from baseline to Week 12		
Mean (SD)	-0.9 (1.3)	-1.0 (1.4)
Median (range)	-1.0 (-6.0 to 4.0)	-1.0 (-6.0 to 4.0)
LS mean (SE)	-1.0 (0.1)	-1.0 (0.1)
95% CI for mean (p-value)[b]	-1.0, -0.8 (<0.0001)	-1.1, -0.9 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-0.0 (0.1)
95% CI		-0.2, 0.1
p-value		0.5839

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 LOCF.

b. p-value was based on paired t-test comparing baseline with post-baseline values.

c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

<u>Change in IPSS Individual Item Scores (Q1, Q2, Q3, Q4, Q5, Q6, and Q7) at Weeks 4 and 12 Relative to Baseline</u>:

None of the IPPS individual item scores showed statistically significant treatment differences at any time point, with the exception of Question 2. For Question 2 ("Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?"), the treatment difference was statistically significant at Week 4 (p-value <0.0001), but not at Week 12 (p-value = 0.0614).

Patient Perception of Bladder Condition (PPBC):

Change in PPBC at Weeks 4 and 12 Relative to Baseline:

A summary of PPBC data is provided in Table 16.

Table 16. Change From Baseline in Patient Perception of Bladder Condition at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on		Fesoterodine Add-on	
	n	%	n	%
N[a]	457	100	459	100
Change from baseline to Week 4				
Major improvement	63	13.8	83	18.1
Minor improvement	160	35.0	171	37.3
No change	212	46.4	180	39.2
Deterioration	22	4.8	25	5.4
p-value CMH test[b]				0.1136
N[a]	459	100	459	100
Change from baseline to Week 12				
Major improvement	130	28.3	124	27.0
Minor improvement	138	30.1	166	36.2
No change	170	37.0	148	32.2
Deterioration	21	4.6	21	4.6
p-value CMH test[b]				0.5775

CMH = Cochran-Mantel-Haenszel; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. Number of subjects with non-missing baseline and Week 4 and Week 12 (last observation carried forward) values.

b. p-value was obtained from a CMH test with modified ridit scoring, stratified by pooled center.

Urgency Perception Scale (UPS, formerly Patient Perception of Urgency Scale):

Change in UPS at Weeks 4 and 12 Relative to Baseline:

A summary of the change from baseline in UPS at Weeks 4 and 12 is presented in Table 17.

Table 17. Change From Baseline in Urgency Perception Scale at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on		Fesoterodine Add-on	
	n	%	n	%
N[a]	458	100	458	100
Change from baseline to Week 4				
Improvement	98	21.4	111	24.2
No change	326	71.2	306	66.8
Deterioration	34	7.4	41	9.0
p-value CMH test[b]				0.7433
N[a]	459	100	459	100
Change from baseline to Week 12				
Improvement	129	28.1	132	28.8
No change	299	65.1	290	63.2
Deterioration	31	6.8	37	8.1
p-value CMH test[b]				0.9402

CMH = Cochran-Mantel-Haenszel; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. Number of subjects with non-missing baseline and Week 4 and Week 12 (last observation carried forward) values.

b. p-value was obtained from a CMH test with modified ridit scoring, stratified by pooled center.

Overactive Bladder Questionnaire (OAB-q):

Change in OAB-q Symptom Bother Score at Weeks 4 and 12 Relative to Baseline:

A summary of OAB-q symptom bother score data is provided in Table 18. Negative change and a lower score on the symptom bother domain were indicative of the improvement and less bother. Positive changes and higher scores on the total HRQL and individual domains were indicative of the improvement and less impact on the QoL.

The fesoterodine add-on therapy group had an LS mean change from baseline of -11.6 in OAB-q Symptom Bother Score compared to –8.9 for the placebo add-on therapy group at Week 4. At Week 12, the fesoterodine add-on therapy group had an LS mean change from baseline of –15.2 compared to –12.4 for the placebo add-on therapy group. The treatment difference was statistically significant at both time points (p-value = 0.0040 for Week 4 and p-value = 0.0068 for Week 12).

Table 18. Change From Baseline in Overactive Bladder Questionnaire Symptom Bother Score at Weeks 4 and 12 - Full Analysis Set

	Placebo Add-on	Fesoterodine Add-on
N[a]	458	459
Baseline		
Mean (SD)	46.3 (17.0)	47.9 (18.0)
Median (range)	45.0 (2.5 to 97.5)	45.0 (7.5 to 97.5)
Week 4		
Mean (SD)	38.2 (17.3)	36.4 (17.9)
Median (range)	35.0 (0.0 to 92.5)	35.0 (0.0 to 97.5)
Numerical change from baseline to Week 4		
Mean (SD)	-8.2 (15.6)	-11.5 (16.0)
Median (range)	-5.0 (-85.0 to 37.5)	-10.0 (-65.0 to 35.0)
LS mean (SE)	-8.9 (0.8)	-11.6 (0.8)
95% CI for mean (p-value)[b]	-9.6, -6.7 (<0.0001)	-12.9, -10.0 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-2.7 (0.9)
95% CI		-4.5, -0.9
p-value		0.0040
N[a]	459	459
Baseline		
Mean (SD)	46.3 (17.0)	47.9 (18.0)
Median (range)	45.0 (2.5 to 97.5)	45.0 (7.5 to 97.5)
Week 12		
Mean (SD)	34.3 (17.6)	32.2 (17.9)
Median (range)	32.5 (0.0 to 92.5)	30.0 (0.0 to 97.5)
Numerical change from baseline to Week 12		
Mean (SD)	-12.0 (17.5)	-15.7 (18.7)
Median (range)	-12.5 (-72.5 to 35.0)	-15.0 (-80.0 to 40.0)
LS mean (SE)	-12.4 (0.9)	-15.2 (0.9)
95% CI for mean (p-value)[b]	-13.6, -10.4 (<0.0001)	-17.4, -13.9 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		-2.8 (1.0)
95% CI		-4.8, -0.8
p-value		0.0068

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 (LOCF).
b. p-value was based on paired t-test comparing baseline with post-baseline values.
c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

A summary of HRQL total score and each individual domain of the OAB-q is presented in Table 19.

Table 19. Change From Baseline in Overactive Bladder Questionnaire Health-Related Quality of Life Domains at Weeks 4 and 12 - Full Analysis Set

Total Score	Placebo Add-on	Fesoterodine Add-on
N[a]	458	459
Baseline, mean (SD)	66.2 (19.3)	64.1 (20.6)
Median (range)	68.8 (3.2 to 99.2)	66.4 (2.4 to 100.0)
Week 4, mean (SD)	72.7 (18.3)	73.1 (19.6)
Median (range)	76.8 (12.8 to 99.2)	77.6 (7.2 to 100.0)
Numerical change from baseline to Week 4		
Mean (SD)	6.5 (15.4)	9.0 (15.6)
Median (range)	4.8 (-41.6 to 80.0)	6.4 (-37.6 to 76.0)
LS mean (SE)	6.9 (0.8)	8.7 (0.8)
95% CI for mean (p-value)[b]	5.1, 8.0 (<0.0001)	7.6, 10.4 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.9 (0.9)
95% CI		0.1, 3.6
p-value		0.0412
N[a]	459	459
Baseline, mean (SD)	66.1 (19.3)	64.1 (20.6)
Median (range)	68.8 (3.2 to 99.2)	66.4 (2.4 to 100.0)
Week 12, mean (SD)	76.3 (18.1)	76.7 (18.9)
Median (range)	81.6 (8.0 to 100.0)	81.6 (13.6 to 100.0)
Numerical change from baseline to Week 12		
Mean (SD)	10.2 (17.4)	12.6 (17.9)
Median (range)	7.2 (-53.6 to 70.4)	8.8 (-48.8 to 79.2)
LS mean (SE)	10.0 (0.9)	11.5 (0.8)
95% CI for mean (p-value)[b]	8.6, 11.7 (<0.0001)	11.0, 14.2 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.5 (1.0)
95% CI		-0.5, 3.4
p-value		0.1373
Concern Domain		
N[a]	458	459
Baseline, mean (SD)	65.6 (21.8)	63.7 (22.4)
Median (range)	68.6 (2.9 to 100.0)	65.7 (0.0 to 100.0)
Week 4, mean (SD)	73.0 (20.5)	73.4 (21.4)
Median (range)	77.1 (0.0 to 100.0)	77.1 (0.0 to 100.0)
Numerical change from baseline to Week 4		
Mean (SD)	7.4 (17.6)	9.7 (17.8)
Median (range)	5.7 (-54.3 to 94.3)	8.6 (-42.9 to 74.3)
LS mean (SE)	8.0 (0.9)	9.7 (0.9)
95% CI for mean (p-value)[b]	5.8, 9.0 (<0.0001)	8.1, 11.4 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.7 (1.0)
95% CI		-0.3, 3.8
p-value		0.0941
N[a]	459	459
Baseline, mean (SD)	65.6 (21.8)	63.7 (22.4)
Median (range)	68.6 (2.9 to 100.0)	65.7 (0.0 to 100.0)
Week 12, mean (SD)	76.7 (19.7)	77.0 (20.2)
Median (range)	82.9 (17.1 to 100.0)	82.9 (5.7 to 100.0)
Numerical change from baseline to Week 12		
Mean (SD)	11.1 (19.7)	13.3 (19.9)
Median (range)	8.6 (-57.1 to 80.0)	11.4 (-40.0 to 85.7)
LS mean (SE)	11.1 (0.9)	12.4 (0.9)
95% CI for mean (p-value)[b]	9.3, 12.9 (<0.0001)	11.5, 15.2 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.3 (1.1)
95% CI		-0.8, 3.4
p-value		0.2273

Table 19. Change From Baseline in Overactive Bladder Questionnaire Health-Related Quality of Life Domains at Weeks 4 and 12 - Full Analysis Set

Total Score	Placebo Add-on	Fesoterodine Add-on
Coping Domain		
N[a]	458	459
Baseline, mean (SD)	63.8 (23.1)	61.3 (24.9)
Median (range)	65.0 (0.0 to 100.0)	65.0 (0.0 to 100.0)
Week 4, mean (SD)	71.0 (22.0)	71.4 (23.5)
Median (range)	75.0 (2.5 to 100.0)	77.5 (0.0 to 100.0)
Numerical change from baseline to Week 4		
Mean (SD)	7.2 (17.9)	10.1 (18.8)
Median (range)	5.0 (-50.0 to 82.5)	7.5 (-52.5 to 85.0)
LS mean (SE)	7.5 (0.9)	9.6 (0.9)
95% CI for mean (p-value)[b]	5.6, 8.9 (<0.0001)	8.4, 11.8 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		2.1 (1.1)
95% CI		0.0, 4.3
p-value		0.0507
N[a]	459	459
Baseline, mean (SD)	63.8 (23.1)	61.3 (24.9)
Median (range)	65.0 (0.0 to 100.0)	65.0 (0.0 to 100.0)
Week 12, mean (SD)	74.6 (22.1)	75.1 (22.7)
Median (range)	80.0 (2.5 to 100.0)	80.0 (5.0 to 100.0)
Numerical change from baseline to Week 12		
Mean (SD)	10.8 (20.3)	13.8 (20.8)
Median (range)	7.5 (-57.5 to 85.0)	10.0 (-52.5 to 85.0)
LS mean (SE)	10.6 (1.0)	12.5 (1.0)
95% CI for mean (p-value)[b]	9.0, 12.7 (<0.0001)	11.9, 15.7 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.9 (1.2)
95% CI		-0.4, 4.1
p-value		0.1136
Sleep Domain		
N[a]	458	459
Baseline, mean (SD)	55.4 (22.8)	53.9 (24.3)
Median (range)	56.0 (0.0 to 100.0)	56.0 (0.0 to 100.0)
Week 4, mean (SD)	62.5 (22.2)	63.2 (23.9)
Median (range)	68.0 (0.0 to 100.0)	64.0 (0.0 to 100.0)
Numerical change from baseline to Week 4		
Mean (SD)	7.1 (19.2)	9.4 (18.8)
Median (range)	4.0 (-44.0 to 84.0)	8.0 (-60.0 to 72.0)
LS mean (SE)	7.6 (1.0)	9.6 (1.0)
95% CI for mean (p-value)[b]	5.4, 8.9 (<0.0001)	7.6, 11.1 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.9 (1.1)
95% CI		-0.3, 4.1
p-value		0.0845
N[a]	459	459
Baseline, mean (SD)	55.3 (22.8)	53.9 (24.3)
Median (range)	56.0 (0.0 to 100.0)	56.0 (0.0 to 100.0)
Week 12, mean (SD)	66.9 (22.1)	68.3 (23.6)
Median (range)	72.0 (0.0 to 100.0)	72.0 (0.0 to 100.0)
Numerical change from baseline to Week 12		
Mean (SD)	11.5 (21.0)	14.4 (21.3)
Median (range)	8.0 (-40.0 to 96.0)	12.0 (-68.0 to 76.0)
LS mean (SE)	11.5 (1.1)	13.8 (1.0)
95% CI for mean (p-value)[b]	9.6, 13.5 (<0.0001)	12.4, 16.3 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		2.2 (1.2)
95% CI		-0.2, 4.6

Table 19. Change From Baseline in Overactive Bladder Questionnaire Health-Related Quality of Life Domains at Weeks 4 and 12 - Full Analysis Set

Total Score	Placebo Add-on	Fesoterodine Add-on
p-value		0.0662
Social Interaction Domain		
N[a]	458	459
Baseline, mean (SD)	81.5 (19.2)	79.2 (21.5)
Median (range)	88.0 (8.0 to 100.0)	84.0 (0.0 to 100.0)
Week 4, mean (SD)	85.2 (17.8)	85.1 (18.9)
Median (range)	92.0 (16.0 to 100.0)	92.0 (16.0 to 100.0)
Numerical change from baseline to Week 4		
Mean (SD)	3.7 (15.7)	5.9 (15.7)
Median (range)	0.0 (-60.0 to 72.0)	4.0 (-56.0 to 80.0)
LS mean (SE)	3.7 (0.8)	5.2 (0.8)
95% CI for mean (p-value)[b]	2.2, 5.1 (<0.0001)	4.5, 7.3 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		1.4 (0.9)
95% CI		-0.3, 3.2
p-value		0.1085
N[a]	459	459
Baseline, mean (SD)	81.5 (19.2)	79.2 (21.5)
Median (range)	88.0 (8.0 to 100.0)	84.0 (0.0 to 100.0)
Week 12, mean (SD)	87.8 (16.7)	87.1 (17.9)
Median (range)	96.0 (0.0 to 100.0)	96.0 (0.0 to 100.0)
Numerical change from baseline to Week 12		
Mean (SD)	6.3 (17.5)	7.9 (18.3)
Median (range)	4.0 (-92.0 to 76.0)	4.0 (-56.0 to 80.0)
LS mean (SE)	6.0 (0.8)	6.3 (0.8)
95% CI for mean (p-value)[b]	4.7, 7.9 (<0.0001)	6.2, 9.5 (<0.0001)
Treatment difference in numerical change[c]		
LS mean difference (SE)		0.3 (0.9)
95% CI		-1.6, 2.1
p-value		0.7685

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; N = number of subjects in each treatment group; SD = standard deviation; SE = standard error.

a. Number of subjects with non-missing numerical change from baseline to Week 4 and Week 12 (LOCF).
b. p-value was based on paired t-test comparing baseline with post-baseline values.
c. Based on an ANCOVA model with terms for country, treatment, and baseline value as a covariate.

Safety Results:

Change of PVR Urine Volume at Weeks 4, 8, and 12 Relative to Baseline:

A summary of PVR change from baseline is presented in Table 20. The treatment difference in numerical change from baseline in PVR was significant at Week 4 (p-value = 0.0005), Week 8 (p-value <0.0001), and Week 12 (p-value = 0.0003). The Hodges-Lehmann estimate of the location shift, a measure of the difference in central tendency between the 2 groups, was 6, 7, and 9 mL at Weeks 4, 8, and 12, respectively, which indicated an increase of PVR from baseline in the fesoterodine add-on group compared to the placebo add-on group.

Table 20. Change From Baseline in Post-Void Residual Urine Volume at Weeks 4, 8, and 12 - Safety Analysis Set

Mean PVR Volume (mL) per 24 Hours	Placebo Add-on	Fesoterodine Add-on
Week 4		
N[a]	453	454
Baseline		
Median (range)	27.0 (0.0 to 373.0)	30.0 (0.0 to 187.0)
Numerical change from baseline to Week 4		
Median (range)[b]	0.0 (-251.0 to 193.0)	0.0 (-174.0 to 274.0)
Treatment difference in numerical change		Fesoterodine vs placebo
Difference[b]		6.00
p-value[c]		0.0005
Week 8		
N[a]	454	456
Baseline		
Median (range)	27.0 (0.0 to 373.0)	30.0 (0.0 to 187.0)
Numerical change from baseline to Week 8		
Median (range)[b]	0.0 (-180.0 to 255.0)	0.0 (-180.0 to 275.0)
Treatment difference in numerical change		Fesoterodine vs placebo
Difference[b]		7.00
p-value[c]		<0.0001
Week 12		
N[a]	454	456
Baseline		
Median (range)	27.0 (0.0 to 373.0)	30.0 (0.0 to 187.0)
Numerical change from baseline to Week 12		
Median (range)[b]	0.0 (-172.0 to 405.0)	3.5 (-156.0 to 392.0)
Treatment difference in numerical change		Fesoterodine vs placebo
Difference[b]		9.0
p-value[c]		0.0003

LOCF = last observation carried forward; N = number of subjects in each treatment group; PVR = post-void residual; vs = versus.

a. Number of subjects with non-missing numerical change from baseline to Week 4, Week 8 (LOCF), or Week 12 (LOCF).

b. Hodges-Lehmann estimate of the location shift between the 2 groups, which was calculated as the median of all pairwise differences in numerical change between the 2 groups.

c. p-value was based on Van Elteren's test adjusted by baseline quartiles.

In an ad-hoc analysis, subjects who had a PVR volume and/or change from baseline >200 mL at Week 4, Week 8, or Week 12 are summarized in Table 21. A total of 2.6% of subjects in the fesoterodine add-on group had a change in PVR from baseline >200 mL versus 0.7% of subjects in the placebo add-on group at Week 12. A total of 4.8% of subjects in the fesoterodine add-on group had a PVR volume >200 mL versus 1.5% of subjects in the placebo add-on group at Week 12.

Table 21. PVR Volume (mL) and Change From Baseline at Weeks 4, 8, and 12

Number (%) of Subjects	Placebo Add-on	Fesoterodine Add-on
PVR at baseline		
N	468	471
>200 mL	1 (0.2)	0
PVR at Week 4		
N	453	454
>200 mL	1 (0.2)	13 (2.9)
Change from baseline >200 mL	0	5 (1.1)
PVR at Week 8		
N	454	456
>200 mL	4 (0.9)	23 (5.0)
Change from baseline >200 mL	1 (0.2)	11 (2.4)
PVR at Week 12		
N	454	456
>200 mL	7 (1.5)	22 (4.8)
Change from baseline >200 mL	3 (0.7)	12 (2.6)

N = number of subjects with available PVR value at baseline and the corresponding visit; PVR = post-void residual.

Change of Q_{max} at Week 12 Relative to Baseline:

A summary of the change from baseline in Q_{max} is presented in Table 22. The treatment difference in numerical change from baseline in Q_{max} was not statistically significant at Week 12 (p-value = 0.2251).

Table 22. Change From Baseline in Maximum Urinary Flow Rate at Week 12 - Safety Analysis Set

Mean Q_{max} (mL/sec) per 24 Hours	Placebo Add-on	Fesoterodine Add-on
Week 12		
N[a]	427	425
Baseline		
Median (range)	11.0 (2.8 to 44.0)	11.2 (2.0 to 54.7)
Numerical change from baseline to Week 12		
Median (range)[b]	0.0 (-25.9 to 43.0)	0.0 (-46.9 to 47.4)
Treatment difference in numerical change		Fesoterodine versus placebo
Difference[b]		-0.40
p-value[c]		0.2251

N = number of subjects in each group; Qmax = maximum urinary flow rate.
a. Number of subjects with non-missing numerical change from baseline to Week 12.
b. Hodges-Lehmann estimate of the location shift between the 2 groups, which was calculated as the median of all pairwise differences in numerical change between the 2 groups.
c. p-value was based on Van Elteren's test adjusted by Baseline quartiles.

Incidence of Acute Urinary Retention Requiring Catheterization:

Urinary retention was reported by 2 (0.4%) and 11 (2.3%) subjects in the placebo add-on therapy and fesoterodine add-on therapy groups, respectively. One subject with urinary retention in each treatment group required catheterization (Table 23). All cases occurred before Week 8. None of the urinary retention events in the fesoterodine group was reported as serious AE (SAE). Dysuria was reported by 4 (0.8%) subjects in the placebo add-on therapy group and 16 (3.4%) of the fesoterodine add-on therapy group.

Table 23. Urinary Retention - Safety Analysis Set

	Placebo Add-on (N=472)	Fesoterodine Add-on (N=471)
Subjects reporting urinary retention	2 (0.4)	11 (2.3)
Urinary retention requiring catheterization	1 (0.2)	1 (0.2)
Urinary retention not requiring catheterization	1 (0.2)	10 (2.1)

N = number of subjects in each treatment group.

Incidences of AEs Related to Increased Voiding Difficulty:

Urinary AEs indicating increased difficulty in urination are identified in Table 24. Most of these AEs were considered treatment-related. None of the urinary retention events in the fesoterodine group was reported as SAE.

Table 24. Urinary Treatment-Emergent Adverse Events (All-Causalities and Treatment-Related) - Safety Analysis Set

Number (%) of Subjects	Placebo Add-on (N=472)		Fesoterodine Add-on (N=471)	
MedDRA Preferred Term	All-Causality	Treatment-Related	All-Causality	Treatment-Related
Dysuria	4 (0.8)	3 (0.6)	16 (3.4)	15 (3.2)
Urinary retention	2 (0.4)	2 (0.4)	11 (2.3)	11 (2.3)
Urine flow decreased	0	0	4 (0.8)	4 (0.8)
Residual urine volume	0	0	1 (0.2)	1 (0.2)
Residual urine volume increased	0	0	1 (0.2)	1 (0.2)
Residual urine	0	0	1 (0.2)	1 (0.2)
Urinary hesitation	2 (0.4)	2 (0.4)	0	0

If the same subject in a given treatment had more than 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. Includes data up to 7 days after the last dose of study drug.
Medical Dictionary for Regulatory Activities ([MedDRA], version 11.1) coding applied.
N = number of subjects in each treatment group.

AEs: An overview of treatment-emergent AEs (TEAEs, all causality and treatment-related) is presented in Table 25.

Table 25. Overview of Treatment-Emergent Adverse Events (All Causalities and Treatment-Related) - Safety Analysis Set

n (%)	Placebo Add-on	Fesoterodine Add-on
Subjects evaluable for AEs	472	471
All Causalities		
Number of AEs	243	418
Subjects with AEs	157 (33.3)	230 (48.8)
Subjects with SAEs	11 (2.3)	11 (2.3)
Subjects with severe AEs	13 (2.8)	20 (4.2)
Subjects who discontinued due to AEs	20 (4.2)	46 (9.8)
Subjects with dose reductions or temporary discontinuations due to AEs	12 (2.5)	27 (5.7)
Treatment-Related		
Number of AEs	110	271
Subjects with AEs	83 (17.6)	169 (35.9)
Subjects with SAEs	2 (0.4)	2 (0.4)
Subjects with severe AEs	4 (0.8)	11 (2.3)
Subjects who discontinued due to AEs	12 (2.5)	35 (7.4)
Subjects with dose reductions or temporary discontinuations due to AEs	7 (1.5)	23 (4.9)

AEs and SAEs are not separated out.
Includes data up to 7 days after the last dose of study drug. Except for the number of AEs, subjects were counted only once per treatment in each row. SAEs according to the Investigators assessment.
AE = adverse event; n = number of subjects with specified criteria; SAE = serious adverse event.

TEAEs (All Causality and Treatment-Related): Table 26 presents TEAEs (all causality and treatment related) reported in ≥1% of subjects.

The AEs most frequently reported in the fesoterodine add-on therapy group were dry mouth (21.2%) and constipation (6.6%). They were the most common AEs in the placebo add-on therapy group as well, with incidence rates of 6.1% and 2.1%, respectively.

The treatment-related TEAEs most frequently reported in the fesoterodine add-on therapy group were dry mouth (20.2%) and constipation (5.9%) which were reported by 5.7% and 1.9% subjects, respectively in placebo add-on therapy. All urinary retention cases were considered treatment-related in both treatment groups (2 subjects in the placebo add-on therapy group and 11 subjects in the fesoterodine add-on therapy group).

Table 26. Treatment-Emergent Adverse Events (All-Causalities and Treatment-Related) Reported in ≥1% of Any Treatment Group - Safety Analysis Set

System Organ Class MedDRA Preferred Term	Placebo Add-on (N=472)		Fesoterodine Add-on (N=471)	
	All-Causality n (%)	Treatment-Related n (%)	All-Causality n (%)	Treatment-Related n (%)
Gastrointestinal disorders	50 (10.6)	38 (8.1)	144 (30.6)	127 (27.0)
Abdominal pain	2 (0.4)	2 (0.4)	6 (1.3)	5 (1.1)
Constipation	10 (2.1)	9 (1.9)	31 (6.6)	28 (5.9)
Diarrhoea	7 (1.5)	5 (1.1)	9 (1.9)	3 (0.6)
Dry mouth	29 (6.1)	27 (5.7)	100 (21.2)	95 (20.2)
Dyspepsia	1 (0.2)	1 (0.2)	9 (1.9)	6 (1.3)
Gastritis	1 (0.2)	1 (0.2)	5 (1.1)	5 (1.1)
Nausea	4 (0.8)	2 (0.4)	6 (1.3)	5 (1.1)
Infections and infestations	28 (5.9)	5 (1.1)	32 (6.8)	5 (1.1)
Influenza	3 (0.6)	0	6 (1.3)	1 (0.2)
Nasopharyngitis	2 (0.4)	1 (0.2)	5 (1.1)	1 (0.2)
Sinusitis	2 (0.4)	0	5 (1.1)	0
Musculoskeletal and connective tissue disorders	18 (3.8)	4 (0.8)	19 (4.0)	7 (1.5)
Back pain	9 (1.9)	1 (0.2)	7 (1.5)	3 (0.6)
Nervous system disorders	18 (3.8)	8 (1.7)	30 (6.4)	15 (3.2)
Dizziness	8 (1.7)	4 (0.8)	6 (1.3)	4 (0.8)
Headache	8 (1.7)	2 (0.4)	15 (3.2)	8 (1.7)
Psychiatric disorders	9 (1.9)	6 (1.3)	12 (2.5)	8 (1.7)
Insomnia	5 (1.1)	4 (0.8)	9 (1.9)	6 (1.3)
Renal and urinary disorders	15 (3.2)	8 (1.7)	33 (7.0)	30 (6.4)
Dysuria	4 (0.8)	3 (0.6)	16 (3.4)	15 (3.2)
Urinary retention	2 (0.4)	2 (0.4)	11 (2.3)	11 (2.3)
Reproductive system and breast disorders	6 (1.3)	2 (0.4)	11 (2.3)	7 (1.5)
Erectile dysfunction	1 (0.2)	1 (0.2)	5 (1.1)	4 (0.8)

AEs and SAEs are not separated out, ie, table includes both non-serious and serious AEs.
If the same subject in a given treatment had more than 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.
Includes data up to 7 days after the last dose of study drug.
Medical Dictionary for Regulatory Activities (MedDRA, version 11.1) coding applied.
AE = adverse event; N = number of subjects in each treatment group; n = number of subjects with adverse event; SAE = serious adverse event.

Severity of AEs: The majority of TEAEs were mild to moderate in severity. Severe AEs were reported by 13 (2.8%) subjects with 20 events in the placebo add-on therapy group and by 20 (4.2%) subjects with 26 events in the fesoterodine add-on therapy group. Of these, 4 events were considered to be treatment-related in the placebo add-on therapy group, and 14 events were considered to be treatment-related in the fesoterodine add-on group.

SAEs: A total of 12 subjects in each treatment group reported at least 1 SAE. No SAE was reported by more than 1 subject in the fesoterodine add-on therapy group. In the placebo add-on therapy group, the only SAE reported by more than 1 subject was vomiting (2 subjects). Two SAEs in each treatment group were considered treatment-related (dysuria and urinary tract infection in the fesoterodine add-on therapy group; cellulitis and urinary retention in the placebo add-on therapy group) (Table 27).

Table 27. Serious Adverse Events

Serial Number	Serious Adverse Event (MedDRA Preferred Term)	Daily Dose at Onset (mg)	Day of Onset	Action Taken With Study Drug	Investigator Causality	Outcome
Fesoterodine Add-on						
1	Cellulitis staphylococcal	8	41	Permanently DC	Unrelated	Resolved
2	Orthostatic hypotension	8	54	None	Unrelated	Resolved
3	Lung neoplasm malignant	8	55	None	Unrelated	Not resolved
4	Transitional cell carcinoma	8	97	(Post-therapy)	Unrelated	Resolved
5	Colitis ulcerative	4	3	None	Unrelated	Resolved
6[a]	Inguinal hernia	4	X[b]	None	Unrelated	Resolved
7	Renal colic	4	36	None	Unrelated	Resolved
	Testicular torsion	4	50	None	Unrelated	Resolved
8	Atrial fibrillation	4	88	None	Unrelated	Resolved
9	Intervertebral disc protrusion	4	35	None	Unrelated	Resolved
10	Myocardial infarction	4	8	Temporarily DC	Unrelated	Resolved
11	Dysuria	4	3	Permanently DC	Related	Resolved
12	Urinary tract infection	4	80	None	Related	Recovering
Placebo Add-on						
13	Angina unstable	NA	10	Permanently DC	Unrelated	Resolved
14	Cellulitis	NA	24	Temporarily DC	Related	Resolved
	Lymphadenopathy	NA	24	Temporarily DC	Unrelated	Resolved
15[a]	Abortion spontaneous[c]	NA	121	(Post-therapy)	Unrelated	Resolved
16	Pneumonia	NA	19	Permanently DC	Unrelated	Not resolved
	Cardiac failure	NA	19	Permanently DC	Unrelated	Not resolved
17	Prostatitis	NA	56	None	Unrelated	Resolved
18	Hypertensive crisis	NA	21	None	Unrelated	Resolved
19	Urinary retention	NA	32	Permanently DC	Related	Resolved
20	Cerebrovascular insufficiency	NA	68	Permanently DC	Unrelated	Resolved
	Nausea	NA	68	Permanently DC	Unrelated	Resolved
	Vomiting	NA	68	Permanently DC	Unrelated	Resolved
21	Haematuria	NA	84	Temporarily DC	Unrelated	Resolved
22	Renal failure acute	NA	26	Permanently DC	Unrelated	Resolved[d]
	Vomiting	NA	15	Permanently DC	Unrelated	Resolved
	Diarrhoea	NA	15	Permanently DC	Unrelated	Resolved
23	Hypertension	NA	16	Temporarily DC	Unrelated	Resolved
	Hypokalemia	NA	17	Temporarily DC	Unrelated	Resolved
24	Atrial fibrillation	NA	61	Permanently DC	Unrelated	Resolved
Other (Pre-randomization)						
25	Not available	NA	NA	NA	NA	Fatal

DC = discontinued; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable.

a. The serious adverse events were not treatment emergent.
b. The onset date of this event predated the study but was not captured at screening.
c. This event was exposure in utero involving paternal exposure. The event was reported for the subject's wife and occurred post-therapy.
d. Resolved with sequelae.

Deaths: There was 1 death reported during the study. One subject, a 79-year-old male died of unknown causes prior to randomization. This subject did not receive any study drug.

Permanent Discontinuations due to AEs: A summary of the AEs leading to permanent discontinuation is provided in Table 28. The most common 5 AEs leading to permanent

discontinuation in the fesoterodine add-on therapy group were dysuria (7 subjects), urinary retention (6 subjects), dry mouth (4 subjects), constipation (3 subjects), and diarrhea (3 subjects). The only AE leading to permanent discontinuation in more than 1 subject the placebo add-on therapy group was diarrhea (2 subjects).

Table 28. Summary of Adverse Events (All Causality) Leading to Permanent Discontinuation

System Organ Class MedDRA Preferred Term	Placebo Add-on n	Fesoterodine Add-on n
Cardiac disorders		
Angina unstable	1	0
Atrial fibrillation	1	0
Ear and labyrinth disorders		
Tinnitus	0	1
Vertigo	0	1
Eye disorders		
Conjunctivitis	0	1
Gastrointestinal disorders		
Abdominal pain	0	1
Constipation	1	3
Diarrhoea	2	3
Dry mouth	0	4
Dyspepsia	1	2
Gastritis	0	1
Nausea	0	2
Infections and infestations		
Bronchitis	1	0
Cellulitis staphylococcal	0	1
Pneumonia	1	
Injury, poisoning, and procedural complications		
Ankle fracture	0	1
Musculoskeletal and connective tissue disorders		
Muscle spasms	1	0
Nervous system disorders		
Cerebrovascular insufficiency	1	0
Dizziness	1	0
Headache	0	1
Paraesthesia	0	1
Syncope	0	1
Transient ischemic attack	0	1
Psychiatric disorders		
Insomnia	1	2
Renal and urinary disorders		
Dysuria	1	7
Haematuria	1	0
Micturition urgency	1	0
Renal failure acute	1	0
Urinary retention	1	6
Reproductive system and breast disorders		
Erectile dysfunction	0	1
Respiratory, thoracic and mediastinal disorders		
Dry throat	0	1
Dyspnoea	1	
Productive cough	0	1
Skin and subcutaneous tissue disorders		
Dermatitis atopic	0	1
Drug eruption	1	0
Rash	1	1

MedDRA = Medical Dictionary for Regulatory Activities (version 11.1); n = number of subjects with adverse events.

Dose Reductions or Temporary Discontinuations Due to AEs: A summary of the AEs leading to a dose reduction or temporary discontinuation is provided in Table 29.

Table 29. Summary of Adverse Events (All Causality) Resulting in a Dose Reduction or Temporary Discontinuation

System Organ Class MedDRA Preferred Term	Placebo Add-on n	Fesoterodine Add-on n
Cardiac disorders		
Myocardial infarction	0	1
Gastrointestinal disorders		
Abdominal discomfort	1	1
Abdominal pain	0	1
Abdominal pain upper	0	1
Colitis	0	1
Constipation	1	5
Diarrhoea	0	3
Dry mouth	1	8
Vomiting	0	1
Infections and infestations		
Cellulitis	1	0
Nasopharyngitis	0	1
Upper respiratory tract infection	0	1
Investigations		
Heart rate irregular	1	0
Residual urine volume	0	1
Metabolism and nutrition disorders		
Hypokalemia	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	1	0
Back pain	0	1
Musculoskeletal pain	0	1
Musculoskeletal stiffness	1	0
Nervous system disorders		
Headache	0	2
Syncope	1	0
Psychiatric disorders		
Disorientation	1	0
Insomnia	0	1
Renal and urinary disorders		
Dysuria	0	3
Haematuria	1	0
Pollakiuria	1	0
Urinary retention	0	3
Urine flow decreased	0	1
Skin and subcutaneous tissue disorders		
Rash	1	0
Vascular disorders		
Hypertension	1	0
Hypotension	0	1

MedDRA = Medical Dictionary for Regulatory Activities (version 11.1); n = number of subjects with adverse events.

Other Safety Results: At baseline, sitting systolic and diastolic BP was similar across treatment groups. At Week 4 and Week 8, the fesoterodine add-on therapy group had changes from baseline in sitting systolic BP of -1.9 mm Hg and -2.2 mm Hg and the placebo add-on therapy group had changes from baseline of -0.2 mm Hg and -0.4 mm Hg. The mean change in sitting diastolic BP was the same for both treatment groups at Week 4 (-0.2 mm Hg) and -0.9 mm Hg for the placebo add-on therapy group and -0.3 mm Hg for the fesoterodine add-on therapy group at Week 8. At the end of treatment (Week 12), the change in systolic and diastolic BP was 0.2 mm Hg and -0.4 mm Hg for the placebo add-on therapy group and -0.5 mm Hg and 0.3 mm Hg for the fesoterodine add-on therapy group.

At baseline, mean heart rate was the same for both treatment groups (70.7 bpm). The fesoterodine add-on therapy group had mean changes from baseline in heart rate at Week 4 and Week 8 of 1.8 bpm and 2.6 bpm and the placebo add-on therapy group had mean changes of 0.6 bpm and 0.7 bpm, respectively. At the end of treatment (Week 12), mean change from baseline in heart rate was 1.1 bpm for the placebo add-on therapy group and 1.9 bpm for the fesoterodine add-on therapy group.

CONCLUSIONS:

In men who had persistent OAB symptoms while receiving alpha-blocker therapy, fesoterodine add-on therapy in a 12-week flexible dose regimen showed:

- No statistically significant treatment difference versus placebo add-on in the primary endpoint, ie, change of micturition-related urgency episodes per 24 hour from baseline to Week 12.

- No statistically significant treatment difference versus placebo add-on in the majority of bladder diary endpoints, IPSS endpoints, and OAB-specific PRO endpoints. A statistically significant treatment difference versus placebo add-on was observed in a few of the secondary endpoints which showed a reduction of micturitions per 24 hours from baseline to Weeks 4 and 12 and improvement in symptom bother domain of OAB-q from baseline to Weeks 4 and 12.

- For the pre-defined additional urinary safety endpoints, the following results were observed in this 12-week study:

    - Dysuria and urinary retention were reported by 3.4% and 2.3% of subjects in the fesoterodine add-on group, respectively, versus 0.8% and 0.4% of subjects in the placebo add-on group, respectively. One case of urinary retention required catheterization in each treatment group.

    - There was a small increase in PVR in the fesoterodine add-on group versus the placebo add-on group as characterized by median treatment difference in change from baseline (9 mL) and percentage of subjects with PVR change from baseline >200 mL (2.6% versus 0.7%) at Week 12.

    - Q_{max} measurements were similar in both groups.

- Fesoterodine was well-tolerated and generally safe in this 12-week study as an add-on treatment to ongoing alpha-blocker therapy.