PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO: A0221045

PROTOCOL TITLE: A 24-Week, Multicentre Trial, Comprising a 12-Week, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Phase Followed by a 12-Week Open-Label Phase, to Evaluate the Efficacy and Safety of a Fesoterodine Flexible Dose Regimen in Elderly Patients With Overactive Bladder

Study Centers: A total of 60 centers took part in the study and randomized subjects: 1 each in Austria and Switzerland; 4 each in Belgium and Norway; 2 each in Denmark and Italy; 6 each in Germany, Portugal and Sweden; 3 each in Israel and Turkey; 5 each in Slovakia, Finland and Spain; and 7 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 26 June 2008 to 08 September 2010

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To compare the efficacy, in terms of a reduction of urgency episodes, of 12-weeks flexible dose fesoterodine relative to placebo in elderly subjects with overactive bladder (OAB).

Secondary Objectives:

- To compare the effect of 12-week, flexible dose regimens of fesoterodine relative to placebo on other patient-reported outcomes (PRO) in elderly subjects with OAB.
- To assess the safety and tolerability of 12-week, flexible dose regimens of fesoterodine relative to placebo in elderly subjects with OAB.
- To assess the safety, tolerability, and efficacy of an open-label (OL) flexible dose regimen of fesoterodine in elderly subjects with OAB for a further 12 weeks of treatment following the double-blind (DB), placebo-controlled phase.
- To compare the efficacy and tolerability of morning versus (vs) evening dosing of fesoterodine sustained release (SR).

METHODS:

Study Design: This was a 24-week (12 weeks DB and 12 weeks OL) randomized, placebo-controlled, parallel-group, multicenter study. The first part of the study consisted of a 2-week no-treatment Screening period and a 12-week DB treatment phase that required a total of 5 visits: Screening visit, Randomization/Baseline visit, Week 4 visit, Week 8 visit, and an end of DB treatment visit at Week 12. The second part of the study consisted of a 12-week OL treatment phase that required a total of 3 visits (Week 16, Week 20, and an end of treatment visit at Week 24) and a follow-up telephone call at Week 26.

During the Screening period any current pharmacological treatments for OAB were to be stopped, and the subjects were to complete 3-day micturition diaries prior to the Baseline visit. In the 12-week DB treatment phase, enrolled subjects who met all entry criteria were eligible to be randomized to receive fesoterodine SR 4 mg or equivalent placebo once daily (QD), and were randomized to receive instructions to take the study medication either in the evening or in the morning. The randomization was stratified by age (>75 years, ≤75 years) so that there was a 1:1 ratio for fesoterodine to placebo within each stratum.

The DB treatment phase was followed by a 12-week OL phase to ensure all eligible subjects received fesoterodine SR treatment. At the Week 24 visit, all subjects ended their treatment; all subjects were then to be followed up by telephone at Week 26. Throughout the 24-week study, subjects were permitted only 1 dose increase to fesoterodine 8 mg. Likewise, subjects who increased their dose from 4 mg to 8 mg at any time during the 24-week study were allowed to decrease back to the 4 mg dose; that decrease was the final dose adjustment allowed.

Study procedures are detailed in Table 1.

Table 1. Schedule of Activities

Activities to be Completed	Double-Blind Placebo-Control Phase					Open-Label Phase			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Screening Week -2[a] (±7 Days)	Rand/ Baseline, Week 0	End of Week 4 (±7 Days)	End of Week 8 (±7 Days)	End of DB Phase Week 12 (±7 Days)	End of Week 16[b] (±7 Days)	End of Week 20 (±7 Days)	End of Week 24 (±7 Days)	Follow up Week 26 (±7 Days)
Written informed consent	X								
Demographics and medical history	X								
Sitting blood pressure and pulse rate	X	X	X	X	X	X	X	X	
Physical examination	X								
Inclusion/exclusion criteria	X	X							
Blood draw (hematology and chemistry) and ECG[c]	X								
Urine dipstick test	X								
Dose assessment and adjustment			X	X		X[d]	X[d]		
Unblinding process					X				
PPBC		X	X	X	X			X	
PPUS		X	X	X	X			X	
OAB-q		X	X	X	X			X	
Dispense micturition bladder diary	X	X	X	X			X		
Evaluation of micturition bladder diary (3-day)		X	X	X	X			X	
KHQ (UK only)		X			X				
EQ-5D		X			X				
MMSE		X			X				
OAB-s[e]					X			X	
Patient Treatment Benefit Scale					X			X	
Adverse events		X	X	X	X	X	X	X	X
Concomitant medication and non-drug treatment	X	X	X	X	X	X	X	X	
Dispense trial medication		X[f]	X[f]	X[f]	X[g]	X[g]	X[g]		
Trial medication return/count			X	X	X	X	X	X	
Assess drug compliance			X	X	X	X	X	X	

Table 1. Schedule of Activities

DB = double-blind; ECG = electrocardiogram; EQ-5D = European Quality of Life 5-Dimension scale; KHQ = King's Health Questionnaire; MMSE = Mini-Mental State Examination; OAB-q = Overactive Bladder Questionnaire; OAB-s = Overactive Bladder Satisfaction Questionnaire; PPBC = Patient Perception of Bladder Condition; PPUS = Patient Perception of Urgency Scale; Rand = randomization; UK = United Kingdom.

a. Screening period may have been increased as required to either allow necessary washout of prior treatment with solifenacin (3 weeks) or to enable treatment and clearance of urinary tract infection.
b. Optional visit for subjects who received active treatment during the DB treatment period and did not increase to 8 mg at Visit 5.
c. All laboratory and urine dipstick tests and ECGs were required to be performed within 31 days preceding Visit 2.
d. Potential for increase of dose was assessed for subjects who received placebo in the DB phase.
e. OAB-s selected questions.
f. Blinded treatment.
g. Open label treatment.

Number of Subjects (Planned and Analyzed): Approximately 790 subjects were planned to be randomized in this study. A total of 1045 subjects were screened of which 794 were assigned to study treatment (50 in Austria, 11 in Belgium, 25 in Denmark, 97 in Finland, 64 in Germany, 25 in Israel, 29 in Italy, 65 in Norway, 65 in Portugal, 68 in Slovakia, 80 in Spain, 127 in Sweden, 15 in Switzerland, 14 in Turkey, and 59 in the UK): 398 subjects to fesoterodine and 396 subjects to placebo. Of the 794 subjects randomized, 785 subjects received study treatment (fesoterodine [392] and placebo [393]). All 785 treated subjects were analyzed for safety; 756 subjects were included in the Full Analysis Set (FAS) for efficacy.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥65 years old with OAB symptoms (subject-reported) for ≥3 months prior to Screening visit according to International Continence Society guidelines, mean urinary frequency of ≥8 micturitions per 24 hours as verified by the micturition diary prior to Randomization/Baseline visit, and mean number of urgency episodes per 24 hours as verified by the Screening micturition diary prior to Baseline (urgency episodes were defined as those with Urinary Sensation Scale [USS] rating ≥3).

Study Treatment: Fesoterodine SR was supplied as white 4 mg or 8 mg tablets dispensed from a blister pack. Placebo was provided as tablets with the same appearance as the fesoterodine SR tablets.

In the 12-week DB treatment phase, randomized subjects were started on a dose of fesoterodine SR 4 mg or equivalent placebo QD. After 4 weeks of treatment (at the Week 4 visit), subjects were permitted a one-time dose increase to 8 mg, if needed, in order to further optimize their treatment. If they remained on the 4 mg dose after 4 weeks of treatment, they were permitted to increase their dose to 8 mg after 8 weeks of treatment (at the Week 8 visit) if necessary. Any change in dose was to be made based on a clinical benefit vs tolerability assessment. The DB treatment phase was followed by a 12-week OL phase to ensure all eligible subjects received fesoterodine SR treatment. Subjects who received fesoterodine SR in the DB phase were to be maintained on the same dose during the OL phase. Subjects who received placebo during the DB phase were started on fesoterodine SR 4 mg with the option to increase their dose to 8 mg at the Week 16 or Week 20 visit. Throughout the 24-week study, subjects were permitted only 1 dose increase to fesoterodine 8 mg (and 1 decrease from 8 mg back to 4 mg, if necessary).

Subjects were instructed to swallow, without chewing, their 1 tablet of study drug with water QD with or without food. During the DB phase, subjects took study drug in the evening (within 4 hours of bedtime) or in the morning (within 2 hours of rising) according to randomization. During the OL phase, subjects were given the choice to take their study medication in the evening or in the morning.

Efficacy 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 USS rating of ≥3 marked for the corresponding micturition in the diary).

Secondary Endpoints:

Micturition Diary

- Percent change of micturition-related urgency episodes per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Change in mean number of severe micturition-related urgency episodes per 24 hours at Weeks 4, 8, and 12 relative to Baseline (severe urgency episodes were defined as those with the USS rating ≥4).
- Percent change of severe micturition-related urgency episodes per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Change in mean number of micturitions per 24 hours at Weeks 4, 8 and 12 relative to baseline (micturitions included episodes of voluntary micturition and episodes of urgency urinary incontinence (UUI).
- Percent change of micturitions per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Change in mean number of night-time micturitions per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Percent change of night-time micturitions per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Change in mean number of UUI episodes per 24 hours at Weeks 4, 8 and 12 relative to Baseline (UUI episodes were defined as those with the USS rating of 5 in the diary).
- Percent change of UUI episodes per 24 hours at Weeks 4, 8, and 12 relative to Baseline.
- Change in the daily sum rating in the USS at Weeks 4, 8, and 12 relative to Baseline.
- The percentage of subjects who were incontinent at Baseline (at least 1 UUI episode during the baseline period) and were dry (no UUI episodes) in the 3 days prior to Weeks 4, 8, 12 and 24.
- Change in number of urinary incontinence pads, barrier creams and powder (for skin protection) used by subjects with UUI.

All micturition diary related endpoints were also calculated at Week 24 for the OL phase analyses. Changes and percentage changes were calculated from Week 12 to Week 24 and from Baseline to Week 24.

Subject Questionnaires

- Patient Treatment Benefit Scale (PTBS) (1 question).
    - Proportion of subjects who reported their treatment has improved (1=greatly improved, 2=improved).
- Patient Perception of Bladder Condition (PPBC) (1 question).
    - Change in PPBC at Weeks 4, 8, 12 and 24 relative to Baseline.
- Patient Perception of Urgency Scale (PPUS) (1 question).
    - Change in PPUS at Weeks 4, 8, 12 and 24 relative to Baseline.
- Overactive Bladder Questionnaire (OAB-q) (33 questions).
    - Change in total score of OAB-q at Weeks 4, 8, 12 and 24 relative to Baseline.
    - Change in total score of each domain of OAB-q at Weeks 4, 8, 12 and 24 relative to Baseline.
- Overactive Bladder Satisfaction Questionnaire (OAB-s) (8 questions).
    - Change in scores from the selected items at Weeks 12 and 24.
- King's Health Questionnaire (KHQ) (21 questions; applicable to sites located in the UK only and used to compare the performance of the KHQ with the other quality of life instruments).
    - Change in total score of each domain of KHQ at Week 12 relative to Baseline.
- EQ-5D (6 questions).
    - Change in total score of EQ-5D at Week 12 relative to Baseline.
    - Change in total score of each dimension of EQ-5D at Week 12 relative to Baseline.
- Mini-Mental Status Examination (MMSE) (11 questions/instructions).
    - Change in total score of MMSE at Week 12 relative to Baseline.

Safety Evaluations: Included adverse events (AEs), concomitant drug and non-drug treatments, and vital signs measurements. MMSE was administered at Baseline and

Week 12. Laboratory safety tests, electrocardiograms (ECGs), and physical examinations were performed at Screening only.

Statistical Methods: The datasets analyzed included:

- FAS: consisted of all subjects who were randomized and took at least 1 dose of DB treatment and provided baseline and post-baseline efficacy data for at least 1 endpoint and at least 1 time point during the DB phase.

- Full Analysis OL Set: all subjects who took at least 1 dose of study medication and provided at least 1 post DB phase efficacy measurement during the OLphase of the study.

- Per Protocol (PP) Analysis Set: consisted of all subjects in the FAS who completed the DB treatment phase and did not deviate from or violate the protocol in such a way that could affect efficacy outcome.

- Safety Analysis Set: consisted of all subjects who took at least 1 dose of study medication during the DB phase.

- Safety OL Analysis Set: consisted of all subjects who received at least 1 dose of the study treatment during the OL phase of the study.

Analysis of Primary Endpoint: The primary analysis for the primary endpoint was based on the FAS. An analysis of covariance (ANCOVA) model was used to compare fesoterodine (4 mg and 8 mg pooled) against placebo. The primary model included terms for treatment, dosing time, age category, and study center as fixed factors and baseline value as a continuous covariate. Least squares (LS) means for each treatment group and associated standard errors were derived. Differences in LS means were calculated and associated 2-sided 95% confidence intervals (CIs) and p-values were provided. Summary statistics (N, mean, median, minimum, maximum, and standard deviations) were also provided for Baseline and Week 12, along with the change from Baseline to Week 12 for each treatment group. If the assumptions of any of the planned analyses were not met, then alternative appropriate statistical techniques were to be used.

Analysis of Secondary Endpoints During the DB Phase: All analyses compared fesoterodine (doses of 4 and 8 mg pooled) vs placebo. Numeric changes in frequencies for diary-derived endpoints were summarized and analyzed using ANCOVA in a similar way to the analysis of the primary endpoint. Those endpoints based on percentage changes were summarized similarly to the primary endpoint and analyzed using non-parametric methods. Binary data were analyzed using logistic regression models for endpoints based on diary data and questionnaires during the DB phase. The model included terms for study center, treatment group, dosing time, and age category. Odds ratios (using placebo as the reference group), corresponding 95% CIs, and p-values were presented along with the summary statistics. These analyses were also supported by simple summaries (number and percentage) at each visit without covariate adjustment as for categorical data. The percentages of subjects who had at least 1 UUI episode in the 3-day diary at Baseline and had no episodes in the 3-day

diary at later visits were analyzed using logistic regression. Frequency tables (counts and percentages) were presented for each treatment group. The Van Elteren Test was used to compare the continuous efficacy endpoints between the treatment groups based on percentage changes derived from the diary data. The stratification variable was a 4-level indicator (morning dosing, ≤75 years; morning dosing, >75 years; evening dosing, ≤75 years; evening dosing, >75 years). Summary statistics were provided for Baseline and Weeks 4, 8, and 12 for each treatment group. These summary statistics were also provided for numeric and percentage changes from Baseline to Weeks 4, 8, and 12.

The PPBC and PPUS were analyzed using logistic regression (major improvement [yes/no] from Baseline and minor improvement [yes/no] from Baseline). Frequency tables for Baseline and Weeks 4, 8, and 12 were presented for each treatment group. The change from Baseline categories were also presented for Weeks 4, 8, and 12. The PTBS was analyzed using logistic regression. Frequency tables (counts and percentages in each response category) for Week 12 were presented for each treatment group. The OAB-q total score, symptom bother score, and domains were summarized for Baseline and Weeks 4, 8, and 12 and the changes in total score, symptom bother score, and domains from Baseline were also summarized and analyzed using ANCOVA. The OAB-s items were analyzed using logistic regression ("satisfied"/"not satisfied" for Questions 9, 10 and 11, and "meets or exceeds expectations"/"does not meet expectations" for Question 5). Frequency tables were also presented for Week 12. For subjects in the UK, the KHQ domains for Baseline and Week 12 and the changes in KHQ domains from Baseline to Week 12 were summarized, and the changes were analyzed using ANCOVA. The EQ-5D total score at Baseline and Week 12 and change from Baseline to Week 12 were summarized, and the change was analyzed using ANCOVA.

Analysis of Endpoints at the end of the OL Phase: The secondary endpoints (based on diary data and questionnaires during the OL phase) were summarized as changes from Baseline to Week 24 and as changes from Weeks 12 to 24.

Safety data were summarized using descriptive statistics. Data from the DB and the OL phases were reported separately.

RESULTS:

Subject Disposition and Demography: Table 2 summarizes subject disposition in the DB phase. One subject in each of the treatment groups died. Forty-six (11.6%) subjects in the fesoterodine group and 22 (5.6%) subjects in the placebo group withdrew due to AEs (36 [9.2%] subjects in the fesoterodine group and 17 [4.3%] subjects in the placebo group withdrew due to AEs considered treatment-related).

The DB FAS comprised 756 subjects:

- A total of 374 subjects who received DB fesoterodine: 188 subjects who were randomized to receive study medication in the morning and 186 randomized to receive medication in the evening.

- A total of 382 subjects who received DB placebo: 191 subjects who were randomized to receive study medication in the morning and 191 randomized to receive medication in the evening.

Table 2. Subject Disposition (Double-Blind Phase)

No. (%) of Subjects		Fesoterodine	Placebo
Screened	1045		
Assigned to study treatment		398	396
Treated		392 (98.5)	393 (99.2)
Randomized but not treated		6 (1.5)	3 (0.8)
Completed		314 (78.9)	341 (86.1)
Discontinued		78 (19.6)	52 (13.1)
Related to study drug		36 (9.2)	17 (4.3)
Adverse event		36 (9.2)[a,b]	17 (4.3)[c]
Not related to study drug		10 (2.6)	5 (1.3)
Adverse event		10 (2.6)	5 (1.3)
Relation to study drug not defined		31 (7.9)	30 (7.6)
Does not meet entrance criteria		1 (0.3)	2 (0.5)
Insufficient clinical response		12 (3.1)	8 (2.0)
Lost to follow-up		0	1 (0.3)
No longer willing to participate in study		14 (3.6)	17 (4.3)[d]
Other		0	1 (0.3)
Protocol violation		4 (1.0)	1 (0.3)
Subject died		1 (0.3)[e]	0[d]

Denominator for computing percentages for all items was number assigned to study treatment in that arm.
AE = adverse event; No. = number.

a. Seven subjects were counted in Table 29 as discontinued due to treatment-related AEs that began during the double-blind phase; however, the subjects completed the double-blind phase and were not withdrawn until the open-label phase so they were not counted here but were included as discontinued for open-label phase in Table 3.
b. One subject withdrew from the study due to an AE of gastritis that was not considered treatment-emergent, so this subject was not counted as discontinued due to AE in Table 29.
c. Two subjects withdrew from the study due to AEs that began on Day 0 and were not considered treatment-emergent; therefore they were not counted in as discontinued due to AE.
d. One subject withdrew consent to participate in the study and later died. This subject was counted in as discontinued due to AE.
e. Subject was counted in as discontinued due to AE (sepsis).

Table 3 summarizes subject disposition in the OL phase by the subject's treatment group during the DB phase. Similar proportions of subjects completed the DB phase and the OL phase of the study. One subject in the DB fesoterodine group completed the DB phase but did not enter the OL phase. The proportion of subjects who discontinued was slightly higher in the DB placebo/OL fesoterodine group than the DB/OL fesoterodine group.

Table 3. Subject Disposition (Open-Label Phase by DB Treatment Group)

No. (%) of Subjects	DB Fesoterodine/ OL Fesoterodine	DB Placebo/ OL Fesoterodine
Treated	313	341
Completed	282 (90.1)	299 (87.7)
Discontinued	31 (9.9)	42 (12.3)
Related to study drug	8 (2.6)	31 (9.1)
Adverse event	8 (2.6)[a]	31 (9.1)[b]
Not Related to study drug	3 (1.0)	2 (0.6)
Adverse event	3 (1.0)[c]	2 (0.6)
Relation to study drug not defined	20 (6.4)	9 (2.6)
Insufficient clinical response	11 (3.5)	5 (1.5)
No longer willing to participate in study	7 (2.2)	2 (0.6)
Other	2 (0.6)	1 (0.3)
Protocol violation	0	1 (0.3)

AE = adverse event; DB = double-blind; OL = open-label; No. = number; SAE = serious adverse event.
a. Four subjects withdrew due to AEs that were not considered treatment-emergent, so they were not counted as discontinued due to AE (open-label phase AEs) but were counted as discontinued due to AE (double-blind phase AEs).
b.One subject was withdrawn due to a non-treatment-emergent SAE (dyspnea) and so was not counted as discontinued due to AE in Table 29.
c. One subject withdrew due to an SAE of brain neoplasm (meningioma); the SAE was not treatment-emergent, so the subject was not counted as discontinued due to AE in Table 29.

The 785 subjects who were treated in the DB phase were split roughly evenly by gender (female 418/785, 53.2%) and were predominantly White (782/785, 99.6%; Table 4).

Table 4. Demographic Characteristics (Double-Blind Phase)

	Fesoterodine			Placebo		
	Male N=179	Female N=213	Total N=392	Male N=188	Female N=205	Total N=393
Age (years) [n (%)]:						
Mean	72.0	73.1	72.6	72.9	72.7	72.8
SD	5.3	6.1	5.8	5.6	5.8	5.7
Median	71.0	72.0	72.0	72.0	73.0	72.0
Range	65-89	65-90	65-90	65-89	65-88	65-89
Race [n (%)]:						
White	179 (100.0)	211 (99.1)	390 (99.5)	188 (100.0)	204 (99.5)	392 (99.7)
Black	0	0	0	0	1 (0.5)	1 (0.3)
Other	0	2 (0.9)	2 (0.5)	0	0	0
Body Mass Index (kg/m^2)						
Mean	27.5	28.2	27.9	27.9	28.5	28.2
SD	4.3	4.8	4.6	4.0	5.1	4.6
Range	16.8-42.3	16.6-47.8	16.6-47.8	19.5-41.0	17.5-44.9	17.5-44.9
N	178 (99.4)	212 (99.5)	390 (99.5)	188 (100.0)	204 (99.5)	392 (99.7)

Body Mass Index computed as Weight / $(Height/100)^2$.
N = number of subjects; n = number of subjects in category; SD = standard deviation.

The demographic characteristics of subjects entering the OL phase are summarized in Table 5).

Table 5. Demographic Characteristics (Open-Label Phase by DB Treatment Group)

	DB/OL Fesoterodine			DB Placebo/ OL Fesoterodine		
	Male N=144	Female N=169	Total N=313	Male N=167	Female N=174	Total N=341
Age (years) [n %)]:						
Mean	72.0	72.6	72.3	72.7	72.6	72.7
Median	71.0	71.0	71.0	72.0	72.5	72.0
SD	5.6	5.8	5.7	5.5	5.8	5.6
Range	65-89	65-90	65-90	65-87	65-88	65-88
Race [n (%)]:						
White	144 (100.0)	168 (99.4)	312 (99.7)	167 (100.0)	173 (99.4)	340 (99.7)
Black	0	0	0	0	1 (0.6)	1 (0.3)
Other	0	1 (0.6)	1 (0.3)	0	0	0
Body Mass Index (kg/m^2):						
Mean	27.5	28.1	27.8	28.0	28.3	28.1
SD	4.4	4.7	4.6	4.1	5.1	4.6
Range	16.8-42.3	16.6-47.8	16.6-47.8	20.0-41.0	17.5-44.9	17.5-44.9
N	144 (100.0)	168 (99.4)	312 (99.7)	167 (100.0)	173 (99.4)	340 (99.7)

Body Mass Index computed as Weight / $(Height/100)^2$.
DB = double-blind; N = number of subjects; n = number of subjects in category; OL = open label; SD = standard deviation.

Efficacy Results:

Primary Endpoint Result: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value <0.0001) from Baseline in the mean number of micturition-related urgency episodes per 24 hours compared to placebo (Table 6): the difference in the LS means (fesoterodine – placebo) was -1.54; the 95% CI for the difference was (-2.12, -0.97).

Table 6. Statistical Analysis of Numeric Changes in Mean Number of Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Mean	LS Mean (SE)	95% CI	Difference From Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	365	-3.70	-3.47 (0.23)	(-3.92, -3.01)	-1.54 (0.29)	(-2.12, -0.97)	<0.0001
DB Placebo	373	-2.42	-1.92 (0.24)	(-2.39, -1.46)	NA	NA	NA

CI = confidence interval; DB = double-blind; Diff = difference; LS = least squares; NA = not applicable; N = number of subjects; SE = standard error.

Secondary Endpoint Results:

- Percent Changes From Baseline of Micturition-Related Urgency Episodes: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value <0.0001) from Baseline in the percent changes from Baseline in micturition-related urgency episodes per 24 hours compared to placebo: the median difference (fesoterodine – placebo) was -14.44%; the 95% CI for the median difference was (-14.67%, -14.25%) (Table 7).

Table 7. Statistical Analysis of Percent Changes in Mean Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Median	Treatment Difference		
			Median[a]	95% CI[b]	p-Value[c]
DB Fesoterodine	365	-48.72	-14.44	(-14.67, -14.25)	<0.0001
DB Placebo	372	-24.03	NA	NA	NA

CI = confidence interval; DB = double-blind; N = number of subjects; NA = not applicable.
a. Hodges-Lehman estimate of median treatment difference.
b. Hodges-Lehman confidence interval.
c. p-value based on 2-sided Van-Elteren's test.

- Changes From Baseline in Mean Number of Severe Micturition-Related Urgency Episodes: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value=0.0001) from Baseline in the mean number of severe micturition-related urgency episodes per 24 hours compared to placebo: the difference in the LS means (fesoterodine – placebo) was -0.85; the 95% CI for the difference was (-1.28, -0.42) (Table 8).

Table 8. Statistical Analysis of Numeric Changes in Mean Number of Severe Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	365	-2.29	-2.40 (0.17)	(-2.74, -2.06)	-0.85 (0.22)	(-1.28, -0.42)	0.0001
DB Placebo	373	-1.71	-1.55 (0.18)	(-1.90, -1.20)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Severe Urgency Episodes as covariates.
CI = confidence interval; DB = double-blind; Diff = difference; N = number of subjects; NA=not applicable; LS = least squares; SE = standard error.

- Percent Changes From Baseline in Mean Number of Severe Micturition-Related Urgency Episodes: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value=0.0005) in the percent changes from Baseline in severe micturition-related urgency episodes per 24 hours compared to placebo (Table 9).

Table 9. Statistical Analysis of Percent Changes in Mean Number of Severe Micturition-Related Urgency Episodes per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)[a]

	N	Median	Treatment Difference		
			Median[b]	95% CI[c]	p-Value[d]
DB Fesoterodine	317	-94.44	0.00	(0.00, 0.00)	0.0005
DB Placebo	336	-75.50	NA	NA	NA

CI = confidence interval; DB = double-blind; N = number of subjects, NA = not applicable.
a. Hodges-Lehman estimate and confidence interval and p-values based on 2-sided Van-Elteren's test.
b. Hodges-Lehman estimate of median treatment difference.
c. Hodges-Lehman confidence interval.
d. p-value based on 2-sided Wilcoxon test (with continuity correction).

- Changes From Baseline of Mean Number of Micturitions: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value <0.0001) from Baseline in the mean number of micturitions per 24 hours compared to placebo: the difference in the LS means (fesoterodine – placebo) was -0.98; the 95% CI for the difference was (-1.33, -0.64) (Table 10).

Table 10. Statistical Analysis of Numeric Changes in Mean Number of Micturitions per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	365	-2.01	-1.91 (0.14)	(-2.19, -1.64)	-0.98 (0.18)	(-1.33, -0.64)	<0.0001
DB Placebo	374	-1.11	-0.93 (0.14)	(-1.21, -0.65)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Number of Micturitions as covariates.
CI = confidence interval; DB = double-blind; Diff = difference; LS = least squares; N = number of subjects; NA = not applicable; SE = standard error.

- Percent Changes From Baseline of Micturitions: Treatment with fesoterodine for Weeks 4, 8 and 12 resulted in clinically and statistically significant improvement, results are summarized in Table 11.

Table 11. Statistical Analysis of Percent Change in Mean Micturitions Per 24 Hours at Week 12 Relative to Baseline[a]

	N	Median	Treatment Difference		
			Median[b]	95% CI[c]	p-Value[d]
DB Fesoterodine	365	-17.65	-7.31	(-7.40, -7.19)	<0.0001
DB Placebo	374	-9.38	NA	NA	NA

CI = confidence interval; DB = double-blind; N = number of subjects, NA = not applicable.
a. Hodges-Lehman estimate and confidence interval and p-values based on 2-sided Van-Elteren's test.
b. Hodges-Lehman estimate of median treatment difference.
c. Hodges-Lehman confidence interval.
d. p-value based on 2-sided Wilcoxon test (with continuity correction).

- Changes From Baseline of Mean Number of Night-Time Micturitions: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement

(p-value=0.0026) from Baseline in the mean number of night-time micturitions per 24 hours compared to placebo: the difference in the LS means (fesoterodine – placebo) was -0.24; the 95% CI for the difference was (-0.40, -0.09) (Table 12).

Table 12. Statistical Analysis of Numeric Changes in Mean Number of Night-Time Micturitions per 24 Hours at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	365	-0.53	-0.51 (0.06)	(-0.64, -0.38)	-0.24 (0.08)	(-0.40, -0.09)	0.0026
DB Placebo	374	-0.30	-0.27 (0.07)	(-0.40, -0.14)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Number of Micturitions as covariates.
CI = confidence interval; DB = double-blind; Diff = difference; LS = least squares; N = number of subjects; NA = not applicable; SE = standard error.

- Percent Changes From Baseline of Night-Time Micturitions: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement, results are summarized in Table 13.

Table 13. Statistical Analysis of Percent Change in Mean Number of Night-Time Micturitions Per 24 Hours at Week 12 Relative to Baseline[a]

	N	Median	Treatment Difference		
			Median[b]	95% CI[c]	p-Value[d]
DB Fesoterodine	362	-22.22	-9.52	(-9.52, -9.09)	0.0012
DB Placebo	371	-14.29	NA	NA	NA

CI = confidence interval; DB = double-blind; N = number of subjects, NA = not applicable.
a. Hodges-Lehman estimate and confidence interval and p-values based on 2-sided Van-Elteren's test.
b. Hodges-Lehman estimate of median treatment difference.
c. Hodges-Lehman confidence interval.
d. p-value based on 2-sided Wilcoxon test (with continuity correction).

- Changes From Baseline in Mean Number of UUI Episodes: There was no significant difference (p-value: 0.1005) in the change from Baseline in number of UUI episodes per 24 hours between treatments based on this analysis.

  Percent Changes From Baseline in UUI Episodes: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value=0.0218) from Baseline in the percent changes from Baseline in UUI episodes per 24 hours compared to placebo.

- Changes From Baseline in the Daily Sum Rating in the USS: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value <0.0001) from Baseline in the daily sum rating in the USS compared to placebo (Table 14).

Table 14. Statistical Analysis of Numeric Change in Daily Sum Rating in the Urinary Sensation Scale (USS) at Week 12 Relative to Baseline – Full Analysis Set

	N	Unadjusted Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	365	-11.16	-10.90 (0.65)	(-12.17,-9.63)	-4.70	(-6.30,-3.10)	<.0001
DB Placebo	373	-7.09	-6.20 (0.66)	(-7.51,-4.90)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Number of Micturitions as covariates.
CI = confidence interval; DB = double-blind; Diff = difference; LS = least squares; N = number of subjects; NA = not applicable; SE = standard error.

- Percentages of Subjects who had UUI Episode(s) at Baseline and no UUI Episodes at Later Visits per 3-Day Diary: While the proportion of subjects who were responders compared to Baseline with respect to incontinence status in the 3-day diary at Weeks 8 and 12 was greater in the fesoterodine group than the placebo group, the difference was not statistically significant (Table 15).

Table 15. Statistical Analysis of Percentages of Subjects With UUI Episode(s) at Baseline and No UUI Episodes Per 3-Day Diary at Weeks 8 and 12 – Full Analysis Set (Double-Blind Phase)

	Evaluable[a]	Responder[b]	Difference From Placebo		
	N	n (%)	Odds Ratio	95% CI for OR	p-Value
DB Fesoterodine	158	84 (53.2)	1.515	(0.909, 2.528)	0.1113
DB Placebo	160	72 (45.0)	NA	NA	NA

Statistical analysis was based on logistic model with:Ttreatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening) and Age Category (>75 years, ≤75 years) as covariates.
CI = confidence interval; DB = double-blind; N = number of subjects; n = number of subjects meeting criterion; NA = not applicable; OR = odds ratio; UUI= urinary urgency incontinence.
a. Evaluable subjects were subjects with at least 1 UUI episode in the 3-day diary before Baseline who also had provided 3 days of diary data preceding Weeks 8 and 12.
b. Responder: subjects with no UUI episodes in 3-day diary preceding both Weeks 8 and 12. Non-responder: Subjects with at least 1 UUI episode in 3-day diary preceding Week 8 and/or Week 12.

- Changes From Baseline in Number of Urinary Incontinence Pads, Barrier Creams, and Powders for Skin Protection Used by Subjects With UUI: Among all subjects in the FAS during the DB phase, treatment with fesoterodine for 12 weeks resulted in statistically significant improvement (ie, reduction) from Baseline in the number of incontinence pads used by subjects with UUI compared to placebo. Table 16 presents LS mean changes from Baseline in creams and powders during the DB phase for subjects with UUI.

Table 16. Statistical Analysis of Numeric Change in Number of Urinary Incontinence Pads, Barrier Creams and Powder for Skin Protection Used by Subjects With UUI in the 3 Days Prior to Week 12 Relative to Baseline

	Fesoterodine		Placebo		
LS Mean change from Baseline to Week 12 (SE)	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**p-Value**
Number of pads per 24 hours – Subjects with UUI at Baseline	359	-0.46 (0.09)	366	-0.20 (0.09)	0.0230
Number of creams per 24 hours – Subjects with UUI at Baseline	358	-0.04 (0.03)	366	0.01 (0.03)	0.0909
Number of powders per 24 hours – Subjects with UUI at Baseline	358	0.01 (0.02)	366	0.04 (0.02)	0.2039
Number of pads per 24 hours (subjects with UUI at Baseline) – Subjects using pads at Baseline	170	-1.17 (0.19)	163	-0.58 (0.20)	0.0141
Number of creams per 24 hours (subjects with UUI at Baseline) – Subjects using creams at Baseline[a]	32	-0.82 (0.29)	15	0.18 (0.45)	0.0855

Statistical analysis based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Parameter value as covariates.
LS Mean = least squares mean; N = number of subjects; SE = standard error; UUI = urgency urinary incontinence.
a. Output for number of powders per 24 hours for subjects with UUI at Baseline not reported due to small sample sizes.

- Percentages of Subjects Who Reported Their Treatment Improved: The odds of subjects responding on the PTBS at Week 12 in the fesoterodine group were statistically significantly higher (p-value <0.0001) than the odds of responding in the placebo group (Table 17); odds ratio (OR)=3.096 and 95% CI for OR = (2.181, 4.395).

Table 17. Statistical Analysis of Patient Treatment Benefit Scale (PTBS) – Responder Analysis at Week 12 – Full Analysis Set (Double-Blind Phase)

	Evaluable	Responder	Difference From Placebo		
	N	**n (%)**	**Odds Ratio**	**95% CI for OR**	**p-Value**
DB Fesoterodine	334	226 (67.7)	3.096	(2.181, 4.395)	<0.0001
DB Placebo	340	146 (42.9)	NA	NA	NA

Responder: Greatly Improved or Improved.
Statistical analysis was based on logistic model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening) and Age Category (>75 years, ≤75 years).
CI = confidence interval; DB = double-blind; N = number of subjects; n = number of subjects meeting criterion; NA = not applicable; OR = odds ratio.

- PPBC: Changes From Baseline (Double-Blind Phase): The odds of subjects responding (showing improvement) on the PPBC at Week 12 in the fesoterodine group were statistically significantly higher (p-value <0.0001) than the odds of responding in the placebo group; OR=2.506 and 95% CI for OR = (1.767, 3.556). (Table 18).

Table 18. Statistical Analysis of PPBC Improvement From Baseline at Week 12 – Full Analysis Set

	Evaluable	Improved		Difference From Placebo		
				Odds Ratio	95% CI	p-Value
	n	n	(%)			
DB Fesoterodine	373	262	(70.2%)	2.506	(1.767,3.556)	<.0001
DB Placebo	380	209	(55.0%)	NA	NA	NA

PPBC category: 1=no problems at all, 6=many severe problems. Improvement in PPBC was defined as negative change from baseline.
Statistical analysis was based on logistic model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75, <=75) and Baseline PBC Category as covariates.
CI = confidence interval; DB = double-blind; PPBC = Patient Perception of Bladder Condition; NA = not applicable; n = number of subjects.

- PPUS Changes From Baseline: The odds of subjects responding (showing improvement) on the PPUS at Week 12 in the fesoterodine group were statistically significantly higher (p-value=0.0009) than the odds of responding in the placebo group (Table 19); OR=1.916 and 95% CI for OR = (1.305, 2.811).

Table 19. Statistical Analyis of PPUS Improvement From Baseline at Week 12 – Full Analysis Set

	Evaluable	Improved		Difference From Placebo		
				Odds Ratio	95% CI	p-Value
	n	n	(%)			
DB Fesoterodine	374	136	(36.4%)	1.916	(1.305, 2.811)	0.0009
DB Placebo	380	114	(30.0%)	NA	NA	NA

PPUS Category: 0=not able to hold urine, 1=able to hold urine until reach a toilet, 2=able to finish what doing before going to the toilet.
Improvement in PPUS was defined increase of 1 or more points in difference of scores relative to baseline.
Statistical analysis was based on logistic model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75, ≤75) and Baseline PPUS Category as covariates.
CI = confidence interval; DB = double-blind; PPUS = Patient Perception of Urgency Scale; NA = not applicable; n = number of subjects.

- OAB-q: Changes From Baseline in Health-Related Quality of Life (HRQL) Total Score: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-value <0.0001) from Baseline in the OAB-q HRQL total score compared to placebo (FAS): the difference in the LS means (fesoterodine − placebo) in scores was 4.48; the 95% CI for the difference was (2.24, 6.73) (Table 20).

Table 20. Statistical Analysis of Changes From Baseline in OAB-q HRQL Total Score at Week 12 – Full Analysis Set

	N	Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	371	12.84	11.62 (0.90)	(9.85, 13.40)	4.48 (1.14)	(2.24, 6.73)	<0.0001
DB Placebo	377	9.44	7.14 (0.93)	(5.31, 8.97)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline HRQL Total Score as covariates.
Difference >0 favors fesoterodine.
CI = confidence interval; DB = double-blind; Diff = difference; HRQL = health-related quality of life; LS = least squares; OAB-q = Overactive Bladder Questionnaire; N = number of subjects; NA = not applicable; SE = standard error.

- OAB-q: Change From Baseline in HRQL Subscale Scores: Treatment with fesoterodine for 12 weeks resulted in clinically and statistically significant improvement (p-values <0.05) from Baseline in the OAB-q Symptom Bother and HRQL subscale scores compared to placebo (FAS) (Table 21).

Table 21. LS Mean Treatment Differences for Changes From Baseline in OAB-q Scores at Week 12 – Full Analysis Set (Double-Blind Phase)

	Difference from Placebo (Fesoterodine – Placebo)		
	Diff (SE)	95% CI	p-Value
Symptom Bother Score[a]	-7.12 (1.29)	(-9.65, -4.59)	<0.0001
HRQL Scale[b]			
Coping subscale score	5.39 (1.44)	(2.57, 8.22)	0.0002
Concern subscale score	5.39 (1.29)	(2.84, 7.93)	<0.0001
Sleep subscale score	4.09 (1.38)	(1.38, 6.81)	0.0032
Social interaction subscale score	2.51 (1.03)	(0.49, 4.53)	0.0152

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline OAB-q component score as covariates.
CI = confidence interval; Diff = difference; HRQL = health-related quality of life; LS = least squares; OAB-q = Overactive Bladder Questionnaire; SE = standard error.
a. Lower scores were better; difference <0 favors fesoterodine.
b. Higher scores were better; difference >0 favors fesoterodine.

- OAB-s: Changes From Baseline in Scores From the Selected Items: The odds of subjects responding on the OAB-s items at Week 12 in the fesoterodine group (FAS) were statistically significantly higher (p-value <0.0001) than the odds of responding in the placebo group (Table 22).

Table 22. Statistical Analysis of Percentage of Responders on OAB-s Items at Week 12 – Full Analysis Set (Double-Blind Phase)

	Evaluable N	Responder n (%)	Difference From Placebo		
			Odds Ratio	95% CI for OR	p-Value
Question 5 (Medication Expectation)[a]					
DB Fesoterodine	348	200 (57.5)	2.881	(2.045, 4.058)	<0.0001
DB Placebo	359	126 (35.1)	NA	NA	NA
Questions 9, 10, 11 (Satisfaction)[b]					
DB Fesoterodine	347	107 (30.8)	3.537	(2.281, 5.484)	<0.0001
DB Placebo	358	49 (13.7)	NA	NA	NA

Statistical analysis was based on logistic model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening) and Age Category (>75 years, ≤75 years).
CI = confidence interval; DB = double-blind; N = number of subjects; n = number of subjects meeting criterion; NA = not applicable; OR = odds ratio; OAB-s = Overactive Bladder Satisfaction Questionnaire.
a. Responder = response of met or exceeded expectation.
b. Responder = response of satisfied on all 7 questions.

- KHQ; Changes From Baseline in Total Score of Each Domain (UK Sites Only, DB Phase): While the number of subjects completing the KHQ was small, treatment with fesoterodine for 12 weeks resulted in noticeable improvements compared to placebo in the Personal Relationships and Severity of Urinary Symptoms scores (Table 23).

Table 23. LS Mean Treatment Differences in Domain Scores of KHQ at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase; UK Study Centers Only)

Scale	Fesoterodine N	Placebo N	Fesoterodine – Placebo	
			LS Mean Diff (SE)	95% CI for LS Mean Diff
General health perception score	29	21	4.18 (4.12)	(-4.13, 12.49)
Incontinence impact score	29	21	-6.29 (8.63)	(-23.70, 11.11)
Role limitations score	29	20	-5.85 (9.28)	(-24.58, 12.88)
Physical limitations score	29	20	-3.81 (8.39)	(-20.74, 13.12)
Social limitations score	29	20	3.26 (6.80)	(-10.47, 16.99)
Personal relationships score	14	11	-11.11 (8.38)	(-28.71, 6.49)
Emotions score	29	20	-6.07 (6.88)	(-19.96, 7.83)
Sleep/energy score	29	20	4.46 (6.82)	(-9.30, 18.23)
Severity of urinary symptoms score	29	20	-10.19 (5.12)	(-20.53, 0.15)

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Score as covariates.
KHQ Domain Scores: 0=Best; 100=Worst.
A higher score indicated worse quality of life; therefore, a negative change from Baseline indicated improvement.
CI = confidence interval; Diff = difference; KHQ = King's Health Questionnaire; LS = least squares; N = number of subjects; SE = standard error; UK = United Kingdom.

- EQ-5D: Changes From Baseline in Single Utility Score: Both treatment groups showed small LS mean improvements at Week 12 relative to Baseline in the EQ-5D single utility score, but there was no significant difference between the treatments (Table 24).

Table 24. Statistical Analysis of Changes in EQ-5D Single Utility Score at Week 12 Relative to Baseline – Full Analysis Set (Double-Blind Phase)

	N	Mean	LS Mean (SE)	95% CI	Difference from Placebo		
					Diff (SE)	95% CI	p-Value
DB Fesoterodine	346	0.0064	0.0044 (0.0100)	(-0.0152, 0.0239)	0.0016 (0.0125)	(-0.0229, 0.0262)	0.8959
DB Placebo	362	0.0230	0.0027 (0.0102)	(-0.0172, 0.0227)	NA	NA	NA

Statistical analysis was based on analysis of covariance (ANCOVA) model with: Treatment; Study Center (centers with <5 subjects were pooled); Dosing Time (morning or evening); Age Category (>75 years, ≤75 years) and Baseline Single Utility Score as covariates.
CI = confidence interval; DB = double-blind; diff = difference; EQ-5D = European Quality of Life 5-Dimension Scale; LS = least squares; NA = not applicable; N = number of subjects; SE =standard error.

- MMSE: Changes From Baseline in Total Score: MMSE was administered at Baseline and Week 12 (end of the DB phase)/end of the study; there were no clinically relevant treatment-related changes (Table 25).

Table 25. Baseline Scores and Mean and Median Changes From Baseline in MMSE Total Score – Full Analysis Set (Double-Blind Phase)

	Fesoterodine N=374	Placebo N=382	Total N=756
Baseline			
N	374	382	756
Mean (SD)	28.20 (1.94)	28.09 (1.98)	28.14 (1.96)
Median	29.0	29.0	29.0
Min, Max	(20.0, 30.0)	(20.0, 30.0)	(20.0, 30.0)
Change to Week 12			
N	341	356	697
Mean (SD)	0.24 (1.76)	0.23 (1.82)	0.24 (1.79)
Median	0.0	0.0	0.0
Min, Max	(-5.0, 7.0)	(-9.0, 8.0)	(-9.0, 8.0)

Min = minimum; Max = maximum; MMSE = Mini-Mental State Exam; N = number of subjects; SD = standard deviation.
Range of possible scores=0 to 30; higher scores indicated better functioning.

Changes in bladder diary endpoints (OL phase) from Baseline to Week 24 and Week 12 to Week 24 are summarized in Table 26 and Table 27, respectively. Table 28 includes summary of PRO at Week 24 (OL phase).

Table 26. Summary of Bladder Diary Endpoints Changes From Baseline to Week 24 – Open-Label Full Analysis Set (Open-Label Phase by DB Treatment Group)

	DB Fesoterodine/ OL Fesoterodine		DB Placebo/ OL Fesoterodine	
Mean Change From Baseline to Week 24 (SD)	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Micturition-related urgency (episodes per 24 hours)	305	-4.07 (4.23)	332	-4.24 (4.62)
Severe micturition-related urgency (episodes per 24 hours)	305	-2.41 (3.30)	332	-2.57 (4.37)
Micturitions (episodes per 24 hours)	305	-2.36 (2.57)	332	-2.28 (2.89)
Night-time micturitions (episodes per 24 hours)	305	-0.67 (1.18)	332	-0.60 (1.24)
Daily sum rating of USS	305	-12.69 (11.72)	332	-12.87 (14.41)
Number of pads per 24 hours – subjects with UUI at Baseline	300	-0.42 (1.50)	325	-0.50 (2.20)
Number of creams per 24 hours – subjects with UUI at Baseline	299	-0.05 (0.42)	325	-0.02 (0.41)
Number of powders per 24 hours – subjects with UUI at Baseline	299	-0.02 (0.24)	325	0.01 (0.18)
Number of pads per 24 hours (subjects with UUI at Baseline) – subjects using pads at Baseline	148	-0.93 (1.99)	143	-1.18 (3.18)
Median Change From Baseline to Week 24	**N**	**Median**	**N**	**Median**
UUI (episodes per 24 hours) – all subjects	305	0.0	332	0.0
Median Percent Change From Baseline to Week 24	**N**	**Median Percent**	**N**	**Median Percent**
Micturition-related urgency[a] (episodes per 24 hours)	305	-52.8	331	-53.1
Severe micturition-related urgency[b] (episodes per 24 hours)	268	-100.0	302	-100.0
Micturitions (episodes per 24 hours)	305	-20.7	332	-20.0
Night-time micturitions[c] (episodes per 24 hours)	302	-25.0	330	-25.0
UUI[d] (episodes per 24 hours) – all subjects	147	-100.0	154	-100.0

DB = double-blind; N = number of subjects; OL = open-label; SD = standard deviation; UUI = urgency urinary incontinence; USS = Urinary Sensation Scale.

a. Subjects with 0 urgency episodes at Baseline were excluded from the table.
b. Subjects with 0 severe urgency episodes at Baseline were excluded from the table.
c. Subjects with 0 night-time micturitions at Baseline were excluded from the table.
d. Subjects with 0 UUI episodes at Baseline were excluded from the table.

Table 27 Summary of Bladder Diary Endpoints Changes From Week 12 to Week 24-Open-Label Full Analysis Set (Open-Label Phase by DB Treatment Group)

	DB Fesoterodine/ OL Fesoterodine		DB Placebo/ OL Fesoterodine	
Mean Change From Week 12 to Week 24 (SD)	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Micturition related urgency (episodes per 24 hours)	305	-0.11 (2.67)	333	-1.84 (3.64)
Severe micturition-related urgency (episodes per 24 hours)	305	0.12 (1.73)	332	-0.77 (3.02)
Micturitions (episodes per 24 hours)	305	-0.18 (1.70)	332	-1.16 (2.08)
Night-time micturitions (episodes per 24 hours)	305	-0.07 (0.92)	332	-0.27 (0.95)
Daily sum rating of USS	305	-0.52 (6.74)	332	-5.73 (10.83)
Number of pads per 24 hours – subjects with UUI at Baseline	302	0.06 (0.70)	328	-0.36 (1.33)
Number of creams per 24 hours – subjects with UUI at Baseline	302	-0.03 (0.43)	327	-0.06 (0.35)
Number of powders per 24 hours – subjects with UUI at Baseline	302	0.00 (0.07)	327	-0.02 (0.48)
Number of pads per 24 hours (subjects with UUI at Baseline) – subjects using pads at Baseline	148	0.09 (0.96)	143	-0.73 (1.89)
Median Change From Week 12 to Week 24	**N**	**Median**	**N**	**Median**
UUI (episodes per 24 hours) – all subjects	305	0.0	332	0.0
Median Percent Change From Week 12 to Week 24	**N**	**Median Percent**	**N**	**Median Percent**
Micturition related urgency[a](episodes per 24 hours)	262	0.0	304	-26.6
Severe micturition-related urgency[b](episodes per 24 hours)	140	0.0	189	-50.0
Micturitions (episodes per 24 hours)	305	0.0	332	-8.7
Night-time micturitions[c](episodes per 24 hours)	291	0.0	326	-3.1
UUI[d](episodes per 24 hours) – all subjects	51	0.0	81	-75.0

DB = double-blind; N = number of subjects; OL = open-label; SD = standard deviation; UUI = urgency urinary incontinence; USS = Urinary Sensation Scale.

a. Subjects with 0 urgency episodes at Week 12 were excluded from the table.
b. Subjects with 0 severe urgency episodes at Week 12 were excluded from the table.
c. Subjects with 0 night-time micturitions at Week 12 were excluded from the table.
d. Subjects with 0 UUI episodes at Week 12 were excluded from the table.

Table 28. Summary of Patient-Reported Outcomes at Week 24 – Open-Label Full Analysis Set (Open-Label Phase by DB Treatment Group)

	DB Fesoterodine/ OL Fesoterodine		DB Placebo/ OL Fesoterodine	
Percent of Subjects at Week 24	**N**	**Percent**	**N**	**Percent**
PTBS – % of subjects with improvement (responders)	299	78.3%	323	77.7%
PPBC – % of subjects with improvement compared to Week 12	305	31.8%	332	51.5%
PPUS – % of subjects with improvement compared to Week 12	304	19.1%	331	33.2%
OAB-s Question 5 % Responders (Medication Expectation)	305	65.6%	333	62.5%
OAB-s Question 9, 10a-10d, 11a-11b % Responders (Satisfaction with OAB Control)	305	43.0%	333	42.9%
Mean Change From Week 12 to Week 24 (SD)	**N**	**Mean (SD)**	**N**	**Mean (SD)**
OAB-q Symptom Bother score[a]	305	-2.05 (18.22)	333	-10.51 (19.42)
OAB-q HRQL Total Score[b]	305	2.67 (14.35)	333	7.44 (16.15)
OAB-q HRQL subscale scores[b]:				
Coping subscale score	305	3.82 (16.82)	333	9.02 (19.47)
Concern subscale score	305	1.68 (15.82)	333	7.81 (18.86)
Sleep subscale score	305	3.26 (17.28)	333	7.25 (19.54)
Social interaction subscale score	305	1.61 (14.19)	333	4.30 (15.77)

DB = double-blind; HRQL = health-related quality of life; N = number of subjects; OAB = overactive bladder; OL = open-label; OAB-q = Overactive Bladder Questionnaire; OAB-s = Overactive Bladder Satisfaction Questionnaire; PTBS = Patient Treatment Benefit Scale; PPBC = Patient Perception of Bladder Condition; PPUS = Patient Perception of Urgency Scale; SD = standard deviation.

a. Lower scores (negative change from Baseline) = improvement.
b. Higher scores (positive change from Baseline) = improvement.

Safety Results: An overall summary of treatment-emergent AEs (TEAEs) that occurred during the DB and OL phases is provided in Table 29. During the DB phase, the fesoterodine treatment group had a greater proportion of subjects in every category than the placebo group. However, the rate of serious adverse events (SAEs) was less than 5% for both treatment groups, and only 1 of these (urinary retention in a subject receiving DB fesoterodine) was considered treatment-related by the investigator.

During the OL phase, greater proportions of subjects who received placebo during the DB phase reported TEAEs, had dose reductions or temporary discontinuations due to TEAEs, and discontinued from the study due to TEAEs compared to those who received fesoterodine during the DB phase.

Table 29. Overview of Treatment-Emergent Adverse Events (Double-Blind and Open-Label Phases)

No. (%) of Subjects	Double-Blind Phase		Open-Label Phase	
	Fesoterodine	Placebo	DB Fesoterodine/ OL Fesoterodine	DB Placebo/ OL Fesoterodine
Subjects evaluable for AEs	392	393	313	341
Subjects with adverse event				
All causalities	244 (62.2)	142 (36.1)	96 (30.7)	164 (48.1)
Treatment-related	199 (50.8)	75 (19.1)	42 (13.4)	138 (40.5)
Subjects with serious adverse event				
All causalities	14 (3.6)[a]	9 (2.3)[b]	11 (3.5)	7 (2.1)[c]
Treatment-related	1 (0.3)	0	0	3 (0.9)
Subjects with severe adverse event				
All causalities	27 (6.9)	9 (2.3)	13 (4.2)	14 (4.1)
Treatment-related	17 (4.3)	2 (0.5)	4 (1.3)	12 (3.5)
Subjects discontinued due to adverse events				
All causalities	53 (13.5)	20 (5.1)	6 (1.9)	32 (9.4)
Treatment-related	42 (10.7)	15 (3.8)	4 (1.3)	31 (9.1)
Subjects with dose reduced or temporary discontinuation due to adverse events				
All causalities	21 (5.4)	7 (1.8)	9 (2.9)	18 (5.3)
Treatment-related	16 (4.1)	4 (1.0)	6 (1.9)	17 (5.0)

AEs = adverse events; DB = double-blind; No. = number; OL = open-label; SAE = serious adverse event.

a. Subjects with brain neoplasm [meningioma] and rectal adenoma had SAEs that began before Day 1 of treatment and were not considered treatment-emergent; therefore these events are not counted here.
b. One subject had an SAE of colon cancer metastatic that began after the subject withdrew consent to participate in the study, so it was considered non-treatment-emergent and does not appear here.
c. One subject had an SAE of dyspnea that began after withdrawal from the study, so it was not considered treatment-emergent and does not appear here.

During the DB phase, the TEAEs (all causalities) most frequently reported in the fesoterodine group were dry mouth, constipation, and dizziness. All of the cases of dry mouth in both treatment groups and all of the cases of constipation in both treatment groups except for 1 in the placebo group were considered treatment-related (Table 30).

Table 30. Most Frequently Reported (Occurring in at Least 2% of Subjects in Either Treatment Group) Treatment-Emergent Non-Serious Adverse Events (Double-Blind Phase)

No. (%) of Subjects	Fesoterodine N=392		Placebo N=393	
MedDRA System Organ Class/ Preferred Term	All Causalities	Treatment Related	All Causalities	Treatment Related
Gastrointestinal disorders				
Dry mouth	133 (33.9)	133 (33.9)	21 (5.3)	21 (5.3)
Constipation	35 (8.9)	35 (8.9)	10 (2.5)	9 (2.3)
Diarrhea	10 (2.6)	6 (1.5)	5 (1.3)	3 (0.8)
Nausea	9 (2.3)	7 (1.8)	4 (1.0)	3 (0.8)
Dyspepsia	9 (2.3)	9 (2.3)	2 (0.5)	2 (0.5)
Nervous system disorders				
Dizziness	14 (3.6)	10 (2.6)	4 (1.0)	3 (0.8)
Headache	11 (2.8)	11 (2.8)	5 (1.3)	4 (1.0)
Infections and infestations				
Nasopharyngitis	12 (3.1)	0	9 (2.3)	0
Urinary tract infection	10 (2.6)	1 (0.3)	7 (1.8)	2 (0.5)
General disorders and administration site conditions				
Fatigue	9 (2.3)	7 (1.8)	10 (2.5)	8 (2.0)
Vascular disorders				
Hypertension	7 (1.8)	2 (0.5)	8 (2.0)	3 (0.8)
Musculoskeletal and connective tissue disorders				
Back pain	2 (0.5)	0	8 (2.0)	0

MedDRA version 13.0 dictionary used.
Included data up to 7 days after last dose of study drug in phase.
MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = number of subjects.

The most frequent TEAEs (all causalities) in the DB/OL fesoterodine group during the OL phase by MedDRA System Organ Class (SOC) were infections and infestations and gastrointestinal disorders (Table 31).

Table 31. Most Frequently Reported (Occurring in at Least 2% of Subjects in Either Treatment Group) Treatment-Emergent Non-Serious Adverse Events (Open-Label Phase)

	DB Fesoterodine/ OL Fesoterodine	DB Placebo/ OL Fesoterodine
	n (%)	n (%)
Number (%) of subjects:		
Evaluable for adverse events	313	341
With adverse events	38 (12.1)	114 (33.4)
System Organ Class		
MedDRA (v13.0) preferred term		
Gastrointestinal disorders	26 (8.3)	105 (30.8)
Constipation	5 (1.6)	21 (6.2)
Dry mouth	21 (6.7)	95 (27.9)
Infections and infestations	14 (4.5)	4 (1.2)
Urinary tract infection	14 (4.5)	4 (1.2)
Nervous system disorders	0	7 (2.1)
Headache	0	7 (2.1)
Vascular disorders	2 (0.6)	7 (2.1)
Hypertension	2 (0.6)	7 (2.1)

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA version 13.0 dictionary used.
MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = number of subjects; v = version.

The most frequent treatment-related TEAEs (Table 32) in the DB/OL fesoterodine group by System Organ Class were gastrointestinal disorders (28 [8.9%] subjects). These AEs occurred in 112 (32.8%) subjects in the DB placebo/OL fesoterodine group.

Table 32. Incidence of Treatment-Emergent Adverse Event (Treatment Related) - Safety Analysis Set (Open-Label Phase by Treatment Received in the DB Phase)

No. (%) of Subjects	DB Fesoterodine/OL Fesoterodine N=313 n (%)	DB Placebo/OL Fesoterodine N=341 n (%)
MedDRA System Organ Class		
Preferred term		
Cardiac disorders	2 (0.6)	2 (0.6)
Palpitations	1 (0.3)	1 (0.3)
Tachyarrhythmia	1 (0.3)	0
Ventricular extrasystoles	0	1 (0.3)
Eye disorders	1 (0.3)	6 (1.8)
Dry eye	1 (0.3)	4 (1.2)
Eye inflammation	0	1 (0.3)
Glaucoma	0	1 (0.3)
Gastrointestinal disorders	28 (8.9)	112 (32.8)
Abdominal distension	0	2 (06)
Abdominal pain upper	1 (0.3)	1 (0.3)
Constipation	5 (1.6)	21 (6.2)
Diarrhoea	0	2 (0.6)
Dry mouth	21 (6.7)	94 (27.6)
Dyspepsia	2 (0.6)	4 (1.2)
Faeces hard	0	1 (0.3)
Flatulence	0	2 (0.6)
Gastritis	0	1 (0.3)
Haemorrhoids	1 (0.3)	0
Nausea	0	1 (0.3)
Reflux oesophagitis	0	1 (0.3)
Vomiting	0	2 (0.6)
General disorders and administration site conditions	0	6 (1.8)
Fatigue	0	3 (0.9)
Oedema peripheral	0	3 (0.9)
Hepatobiliary disorders	1 (0.3)	1 (0.3)
Biliary colic	0	1 (0.3)
Gallbladder disorder	1 (0.3)	0
Infections and infestations	4 (1.3)	4 (1.2)
Bronchitis	0	1 (0.3)
Cystitis	1 (0.3)	0
Oral candidiasis	2 (0.6)	0
Urinary tract infection	1 (0.3)	3 (0.9)
Injury, poisoning and procedural complications	2 (0.6)	0
Fall	1 (0.3)	0
Head injury	1 (0.3)	0
Ligament injury	1 (0.3)	0
Investigations	1 (0.3)	1 (0.3)
Blood pressure increased	1 (0.3)	0
Weight increased	0	1 (0.3)
Musculoskeletal and connective tissue disorders	0	1 (0.3)
Back pain	0	1 (0.3)
Nervous system disorders	3 (1)	15 (4.4)
Balance disorder	0	1 (0.3)
Dizziness	1 (0.3)	6 (1.8)
Dizziness postural	0	1 (0.3)
Headache	0	6 (1.8)
Restless legs syndrome	1 (0.3)	0
Somnolence	0	1 (0.3)
Transient ischaemic attack	0	1 (0.3)
Tremor	1 (0.3)	0

Table 32. Incidence of Treatment-Emergent Adverse Event (Treatment Related) - Safety Analysis Set (Open-Label Phase by Treatment Received in the DB Phase)

No. (%) of Subjects	DB Fesoterodine/OL Fesoterodine N=313 n (%)	DB Placebo/OL Fesoterodine N=341 n (%)
Psychiatric disorders	3 (1)	2 (0.6)
Abnormal dreams	1 (0.3)	0
Anxiety	1 (0.3)	0
Insomnia	1 (0.3)	1 (0.3)
Sleep disorder	0	1 (0.3)
Renal and urinary disorders	3 (1)	18 (5.3)
Dysuria	1 (0.3)	3 (0.9)
Hypertonic bladder	0	3 (0.9)
Pollakiuria	1 (0.3)	0
Urinary hesitation	0	5 (1.5)
Urinary retention	1 (0.3)	4 (1.2)
Urinary tract obstruction	0	1 (0.3)
Urine flow decreased	0	4 (1.2)
Reproductive system and breast disorders	0	1 (0.3)
Sexual dysfunction	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	7 (2.1)
Cough	0	2 (0.6)
Dysphonia	1 (0.3)	2 (0.6)
Dyspnoea exertional	0	1 (0.3)
Epistaxis	0	1 (0.3)
Nasal dryness	0	1 (0.3)
Oropharyngeal pain	0	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	3 (0.9)
Erythema	0	1 (0.3)
Hypertrichosis	0	1 (0.3)
Rash	1 (0.3)	1 (0.3)
Vascular disorders	1 (0.3)	6 (1.8)
Hypertension	1 (0.3)	4 (1.2)
Hypotension	0	1 (0.3)
Peripheral coldness	0	1 (0.3)

The AEs/SAEs are not separated out ie, table includes both non-serious and serious AEs.
MedDRA version 13.0 dictionary used.
Included data up to 7 days after last dose of study drug in phase.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = number of subjects; SAEs = serious adverse events.

Treatment-emergent SAEs (TESAEs) during the DB phase were reported by 14 (3.6%) and 9 (2.3%) subjects in the fesoterodine and placebo groups, respectively (Table 33). One TESAE of urinary retention of severe intensity in the fesoterodine group that resulted in the subject's discontinuation was considered treatment-related.

Table 33. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities) – (Double-Blind Phase)

MedDRA System Organ Class Preferred Term	DB Fesoterodine n (%)	DB Placebo n (%)
Number (%) of subjects:		
Evaluable for adverse events	392	393
With adverse events	14 (3.6)	9 (2.3)
Cardiac disorders	0	1 (0.3)
Atrial fibrillation	0	1 (0.3)
Eye disorders	2 (0.5)	0
Optic nerve infarction	1 (0.3)	0
Retinal detachment	1 (0.3)	0
Visual acuity reduced	1 (0.3)	0
Gastrointestinal disorders	3 (0.8)	1 (0.3)
Large intestinal haemorrhage	0	1 (0.3)
Pancreatitis	1 (0.3)	0
Peritonitis	1 (0.3)	0
Vomiting	1 (0.3)	0
General disorders and administration site conditions	1 (0.3)	0
Chest pain	1 (0.3)	0
Infections and infestations	2 (0.5)	2 (0.5)
Abscess	1 (0.3)	0
Appendicitis perforated	1 (0.3)	0
Diverticulitis	1 (0.3)	0
Erysipelas	0	1 (0.3)
Gastroenteritis	0	1 (0.3)
Sepsis	1 (0.3)	0
Injury, poisoning and procedural complications	0	2 (0.5)
Fall	0	1 (0.3)
Hip fracture	0	1 (0.3)
Joint injury	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1 (0.3)
Malignant melanoma	1 (0.3)	0
Prostate cancer	0	1 (0.3)
Nervous system disorders	2 (0.5)	0
Amnesia	1 (0.3)	0
Cerebral artery occlusion	1 (0.3)	0
Psychiatric disorders	1 (0.3)	0
Depression	1 (0.3)	0
Renal and urinary disorders	1 (0.3)	2 (0.5)
Haematuria	0	1 (0.3)
Urethral polyp	0	1 (0.3)
Urinary retention	1 (0.3)	0
Reproductive system and breast disorders	1 (0.3)	0
Benign prostatic hyperplasia	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0
Pulmonary embolism	1 (0.3)	0
Vascular disorders	1 (0.3)	0
Aneurysm ruptured	1 (0.3)	0

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA version 13.0 dictionary used.
MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = number of subjects.

TESAEs (all causalities) reported during the OL phase are summarized in Table 34. None of the TESAEs reported in subjects in the DB/OL fesoterodine group were considered treatment-related.

Table 34. Treatment-Emergent Serious Adverse Events (All Causality) – (Open Label Phase)

	DB Fesoterodine/ OL Fesoterodine	DB Placebo/ OL Fesoterodine
	n (%)	n (%)
Number (%) of subjects:		
Evaluable for adverse events	313	341
With adverse events	11 (3.5)	7 (2.1)
System Organ Class		
MedDRA Preferred Term		
Cardiac disorders	0	1 (0.3)
Adams-Stokes syndrome	0	1 (0.3)
Eye disorders	1 (0.3)	0
Cataract	1 (0.3)	0
Gastrointestinal disorders	1 (0.3)	0
Pancreatitis acute	1 (0.3)	0
General disorders and administration site conditions	0	1 (0.3)
Chest pain	0	1 (0.3)
Infections and infestations	2 (0.6)	1 (0.3)
Diverticulitis	1 (0.3)	1 (0.3)
Erysipelas	1 (0.3)	0
Injury, poisoning and procedural complications	2 (0.6)	1 (0.3)
Fall	2 (0.6)	1 (0.3)
Lumbar vertebral fracture	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.3)	0
Bladder transitional cell carcinoma	1 (0.3)	0
Metastases to bone	1 (0.3)	0
Ovarian fibroma	1 (0.3)	0
Prostate cancer	1 (0.3)	0
Nervous system disorders	2 (0.6)	2 (0.6)
Amnesia	1 (0.3)	0
Cognitive disorder	1 (0.3)	0
Transient ischaemic attack	0	2 (0.6)
Renal and urinary disorders	0	1 (0.3)
Urinary retention	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (0.3)
Rash	0	1 (0.3)

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA version 13.0 dictionary used.
MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = number of subjects.

Permanent Discontinuations: During the DB phase, the most frequent AEs resulting in discontinuation overall were dry mouth and urinary retention (Table 35).

Table 35. Treatment-Emergent Adverse Events (Occurring in 2 or More Subjects in Either Treatment Group) That Led to Permanent Discontinuation – Safety Analysis Set (Double-Blind Phase)

MedDRA System Organ Class Preferred Term No. (%) of Subjects	Fesoterodine		Placebo	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
No. of Subjects evaluable	392	392	393	393
Gastrointestinal disorders				
Dry mouth	11 (2.8)	11 (2.8)	1 (0.3)	1 (0.3)
Diarrhea	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Constipation	2 (0.5)	2 (0.5)	0	0
Abdominal pain	0	0	3 (0.8)	3 (0.8)
Renal and urinary disorders				
Urinary retention	4 (1.0)[a,b,c]	3 (0.8)[a,b]	1 (0.3)[d]	1 (0.3)
Dysuria	2 (0.5)	2 (0.5)	0	0
Nervous system disorders				
Headache	3 (0.8)	3 (0.8)	0	0
Dizziness	2 (0.5)	1 (0.3)	1 (0.3)	0
Ear and labyrinth disorders				
Vertigo	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)

MedDRA version 13.0 dictionary used.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; SAE = serious adverse event.
a. Subject was catheterized due to this severe SAE.
b. Subject was catheterized due to AEs of urinary retention and urinary hesitation. Both AEs were considered related to treatment; only urinary retention (considered severe) was considered the reason for study discontinuation.
c. Subject was catheterized due to this AE.
d. Subject was catheterized due to this AE.

During the OL phase, the most frequent AE resulting in discontinuation overall was dry mouth (Table 36).

Table 36. Treatment-Emergent Adverse Events (Occurring in 2 or More Subjects in Either Treatment Group) That Led to Permanent Discontinuation – Safety Analysis Set (Open-Label Phase by DB Treatment Group)

MedDRA System Organ Class Preferred Term No. (%) of Subjects	DB Fesoterodine/ OL Fesoterodine		DB Placebo/ OL Fesoterodine	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
No. of Subjects evaluable	313	313	341	341
Gastrointestinal disorders				
Dry mouth	3 (1.0)	3 (1.0)	7 (2.1)	7 (2.1)
Constipation	0	0	3 (0.9)	3 (0.9)
Renal and urinary disorders				
Urinary retention	0	0	3 (0.9)	3 (0.9)
Urine flow decreased	0	0	3 (0.9)	3 (0.9)
Urinary hesitation	0	0	2 (0.6)	2 (0.6)

MedDRA version 13.0 dictionary used.
Adverse events listed in decreasing frequency in the DB Placebo/OL Fesoterodine group and then in the DB Fesoterodine/OL Fesoterodine group
DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities, No. = number; OL = open label.

During the DB phase, the most frequent AEs resulting in dose reduction or temporary discontinuation overall were dry mouth and constipation. Fourteen (3.6%) and 1 (0.3%)

subjects in the fesoterodine and placebo groups, respectively, had AEs of dry mouth resulting in dose reduction or temporary discontinuation.

During the OL phase, the most frequent AEs resulting in dose reduction or temporary discontinuation overall were dry mouth and hypertonic bladder. A larger proportion of subjects in the DB placebo/OL fesoterodine group (3.5%) had AEs of dry mouth resulting in dose reduction or temporary discontinuation during the OL phase compared to the DB/OL fesoterodine group (0.6%).

Deaths: There were 2 deaths reported (one each in DB fesoterodine group and DB placebo group). One subject in the DB fesoterodine group, died approximately 2 weeks after ending treatment. The SAEs leading to death, all considered severe, were listed as abscess, appendicitis perforated, peritonitis, and sepsis; none was considered treatment-related. One subject in the DB placebo group, died of metastatic colon cancer that had not been apparent at Screening approximately 6 weeks after ending treatment; the event was not considered treatment-related.

There were no clinically meaningful changes from Baseline in vital signs during the DB or OL phases of the study.

CONCLUSIONS:

- Treatment of aged OAB subjects 65 years old and above with flexible-dose fesoterodine (4 mg or 8 mg QD) resulted in clinically relevant and statistically significant improvements compared to placebo in the primary efficacy endpoint (changes from Baseline in the number of micturition-related urgency episodes per 24 hours) at Week 12 (end of the DB phase).

- Treatment with flexible-dose fesoterodine (4 mg or 8 mg QD) resulted in clinically relevant and statistically significant improvements compared to placebo in most secondary diary and PRO endpoints in an elderly population at Week 12.

- The additional efficacy achieved with fesoterodine treatment compared to placebo in the primary endpoint and OAB-s items for the subgroups of subjects >75 years old (32% of the overall population) and those ≤75 years old was comparable to the results seen in the elderly study population as a whole.

- The additional efficacy achieved with fesoterodine treatment compared to placebo in bladder diary and PRO endpoints seen after 12 weeks of treatment was maintained through 24 weeks of treatment.

- Subjects advancing from placebo (12 weeks of treatment in the DB phase) to fesoterodine (12 weeks of treatment in the OL phase) had efficacy results (for bladder diary and PRO endpoints) at Week 24 (end of the OL phase) that were similar to those achieved at Week 24 by those receiving fesoterodine for 24 weeks during the DB and OL phases.

- The overall AE and safety profiles were consistent with known effects of fesoterodine.

- There were no new safety signals (including falls) in this medically complex elderly population.

- Fesoterodine was generally well tolerated in elderly subjects with OAB syndrome for up to 24 weeks.