**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.**: A0221095

**PROTOCOL TITLE**: A 12-Week, Phase 4, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Trial in Overactive Bladder Subjects to Confirm the Efficacy of 8 mg Fesoterodine Compared to 4 mg Fesoterodine

**Study Centers:** A total of 241 centers took part in the study and randomized subjects, 125 centers in the United States, 16 centers in Germany, 12 centers in Canada, 10 centers in Sweden, 9 centers in Slovakia, 7 centers each in Czech Republic and the United Kingdom, 6 centers each in the Republic of Korea and Ukraine, 4 centers each in Hungary and Norway, 3 centers each in Argentina, Lithuania, Russian Federation, South Africa, Poland and Taiwan, 2 centers each in Chile, Colombia, Denmark, Finland, France, Greece, and Italy, 1 center each in Egypt, and Mexico, Philippines.

**Study Initiation Date and Final Completion Date:** 23 May 2011 to 04 November 2012

**Phase of Development**: Phase 4

**Study Objectives:**

Primary Objective:

- To demonstrate the greater efficacy of 8 mg of fesoterodine compared to 4 mg fesoterodine and to placebo in reducing urgency urinary incontinence (UUI) in subjects with overactive bladder (OAB) after 12 weeks of treatment.

Secondary Objectives:

- To determine the efficacy of 8 mg fesoterodine and 4 mg fesoterodine on diary endpoints after 4 and 12 weeks of treatment and patient reported outcomes (PRO) after 12 weeks of treatment in subjects with OAB.

- To determine the efficacy of 8 mg fesoterodine and 4 mg fesoterodine compared to placebo on diary endpoints after 4 and 12 weeks of treatment and PRO after 12 weeks of treatment in subjects with OAB.

- To summarize safety and tolerability data for 12 weeks of treatment with fesoterodine 8 mg and 4 mg and placebo in subjects with OAB.

## METHODS

**Study Design:** This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Approximately 1990 subjects were planned to be randomized into this study. The study consisted of a 2-week single-blind placebo run-in period and a 12-week double-blind treatment period, including 3 clinic visits for Screening, Randomization, and End-of-treatment (EOT). Contact was maintained at intervals during the study and a final follow-up telephone contact 1 week after the EOT for subjects with ongoing adverse events (AEs) at EOT. Eligible subjects were randomized at Visit 2 in a 2:2:1 ratio to 1 of the 3 treatment arms of the study: 8 mg fesoterodine once daily (QD), 4 mg fesoterodine QD or placebo. The proportion of subjects in the study was controlled so that a maximum of approximately 65% had not previously used antimuscarinics.

All subjects assigned to the fesoterodine arms started at 4 mg daily, those assigned to the 8 mg arm were escalated to 8 mg daily after 1 week. No further dose adjustments were permitted for the remaining 11 weeks of the study. Schedule of activities are displayed in Table 1.

## Table 1. Schedule of Activities

| Protocol Activity | Visit 1[a] | Visit 2 | Efficacy Assessment Telephone Contact | Interim Telephone Contact | Visit[b] 3/ET |
|---|---|---|---|---|---|
| | Screening -2 Weeks | Baseline Week 0 Randomize (±7 Days) | Week 4 (±7 Days) | Week 8 (±7 Days) | Week 12 (-7+14 Days) |
| Written informed consent | X | | | | |
| Demographics and medical history | X | | | | |
| Sitting blood pressure & pulse rate | X | X | | | X |
| Physical examination | X | | | | |
| Inclusion/exclusion criteria | X | X | | | |
| Urinalysis (dipstick) | X[c] | X[c] | | | X[c] |
| Urine pregnancy test for women of child bearing potential | X | X | | | |
| Dispense 3-day bladder diary | X | X | | | |
| Evaluation of bladder diary (3-day) | | X | X[d] | | X |
| Patient Perception of Bladder Condition (PPBC) | X | X | | | X |
| Urgency Perception Scale (UPS) | | X | | | X |
| Overactive Bladder Questionnaire (OAB-q) | | X | | | X |
| Adverse events[e] | X | X | X | X | X |
| Concomitant medication and non-drug treatment | X | X | X | X | X |
| Dispense study medication | X | X | | | |
| Telephone call[f] | | X | X | X | X |
| Study medication return/count Compliance check | | X | X | X | X |

ET = early termination.

a. If subjects needed to discontinue medication to be eligible to participate, the informed consent could have been taken more than 2 weeks prior to Visit 1.
b. Adverse events ongoing at the end of treatment were followed-up, approximately 1 week post last dose, by telephone or other suitable means of contact.
c. A dipstick positive for leukocyte esterase and/or nitrites was sent for culture and sensitivity at the site's local laboratory. The subject was excluded if positive.
d. The subject was reminded to complete the diary and to return the diary to the site. If the diary was not received within 1 week, the subject was contacted to confirm status of diary.
e. Serious adverse events were reported once 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 or single-blind placebo.
f. A telephone call was scheduled approximately 7 days prior to each scheduled visit at which a 3-day bladder diary was completed, to remind the subject to complete the diary prior to the visit and return the diary. If the telephone contact was not successful/possible, the subject was followed-up by letter or other means as appropriate.

**Number of Subjects (Planned and Analyzed):** It was planned to screen up to 4980 subjects and randomize a total of 1990 subjects (795 to each fesoterodine group and 400 for the placebo group).

A total of 4326 subjects were actually screened and 2012 subjects were randomized to treatment following the 2 week placebo run-in period (804 to fesoterodine 8 mg, 806 subjects

to fesoterodine 4 mg, and 402 subjects to placebo). Subject enrollment by country and as per treatment group is presented in Table 2.

**Table 2. Subject Enrollment by Country**

| Country (Number of Centers) | Placebo N=386 n (%) | Fesoterodine 4 mg N=790 n (%) | Fesoterodine 8 mg N=779 n (%) |
|---|---|---|---|
| United States of America (125) | 185 (47.9) | 365 (46.2) | 346 (44.4) |
| Germany (16) | 63 (16.3) | 106 (13.4) | 121 (15.5) |
| Sweden (10) | 17 (4.4) | 28 (3.5) | 39 (5.0) |
| Ukraine (6) | 13 (3.4) | 33 (4.2) | 32 (4.1) |
| Slovakia (9) | 14 (3.6) | 36 (4.6) | 22 (2.8) |
| Korea (6) | 10 (2.6) | 26 (3.3) | 24 (3.1) |
| Canada (12) | 12 (3.1) | 23 (2.9) | 21 (2.7) |
| Poland (3) | 10 (2.6) | 20 (2.5) | 22 (2.8) |
| Czech Republic (7) | 10 (2.6) | 19 (2.4) | 17 (2.2) |
| Hungary (4) | 4 (1.0) | 22 (2.8) | 12 (1.5) |
| United Kingdom (7) | 3 (0.8) | 16 (2.0) | 16 (2.1) |
| South Africa (3) | 5 (1.3) | 15 (1.9) | 15 (1.9) |
| Lithuania (3) | 2 (0.5) | 13 (1.6) | 17 (2.2) |
| Norway (4) | 10 (2.6) | 12 (1.5) | 9 (1.2) |
| Taiwan (3) | 5 (1.3) | 6 (0.8) | 17 (2.2) |
| Chile (2) | 3 (0.8) | 10 (1.3) | 8 (1.0) |
| Russian Federation (3) | 4 (1.0) | 10 (1.3) | 7 (0.9) |
| Argentina (3) | 1 (0.3) | 5 (0.6) | 10 (1.3) |
| Denmark (2) | 4 (1.0) | 6 (0.8) | 6 (0.8) |
| Italy (2) | 4 (1.0) | 5 (0.6) | 6 (0.8) |
| France (2) | 1 (0.3) | 4 (0.5) | 5 (0.6) |
| Greece (2) | 1 (0.3) | 3 (0.4) | 4 (0.5) |
| Finland (2) | 1 (0.3) | 2 (0.3) | 2 (0.3) |
| Mexico (1) | 2 (0.5) | 2 (0.3) | 0 |
| Colombia (2) | 0 | 3 (0.4) | 0 |
| Egypt (1) | 2 (0.5) | 0 | 0 |
| Philippines (1) | 0 | 0 | 1 (0.1) |

n = number of subjects with an observation; N = total number of subjects.

**Diagnosis and Main Criteria for Inclusion:** Male and female subjects, aged 18 years and older, with 6 months or more OAB symptoms, a mean of between 2 or more and 15 or less UUI per 24 hours and a minimum of 8 micturitions per 24 hours and a rating of bladder condition as "Some Moderate Problems", Severe Problems" or "Many Severe Problems" on the Patient Perception of Bladder Condition (PPBC) questionnaire.

Exclusion Criteria: Any condition that would have contraindicated the use of fesoterodine; conditions or prior treatment that may have affected bladder function; clinically significant urinary tract infection (UTI); initiation of electostimulation, bladder training or pelvic floor muscle exercises within 4 weeks of visit 1; or subjects who had any medical or psychological condition or social circumstance that would have impaired their ability to participate reliably in the study protocol, interfered with the interpretation of study results, or increased risk to themselves or others by participating.

**Study Treatment:** The subjects received study medication (placebo QD) for the 2 week run-in period. The subjects took their first tablet of single-blind medication at Visit 1. Subjects took the double-blind study medication for 12 weeks QD starting with their first tablet of double-blind medication at Visit 2. Tablets were sustained-release 4 mg or 8 mg fesoterodine or matching placebo. One tablet was taken orally with a sufficient amount of water QD and swallowed whole. It was not to be chewed, divided, or crushed. The study drug was taken in the morning, with or without food.

**Efficacy Endpoints:**

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

Secondary Endpoints:

- Change in mean number of micturitions (frequency) per 24 hours at Weeks 4 and 12 relative to Baseline.
- Percent change of micturitions per 24 hours at Weeks 4 and 12 relative to Baseline.
- Change in mean number of UUI episodes per 24 hours at Week 4 relative to Baseline (UUI episodes are defined as those micturitions with Urinary Sensation Scale rating of 5 in the diary). Only subjects with non-zero UUI at Baseline were included in the analysis.
- Percent change of UUI episodes per 24 hours at Week 4 and 12 relative to Baseline (UUI episodes are defined as those micturitions with Urinary Sensation Scale rating of 5 in the diary). Only subjects with non-zero UUI at Baseline were included in the analysis.
- Change in mean number of micturition-related urgency episodes per 24 hours at Weeks 4 and 12 relative to Baseline (Micturition-related urgency episodes are defined as those micturitions with Urinary Sensation Scale (USS) rating of ≥3 in the diary).
- Percent change of micturition-related urgency episodes per 24 hours at Weeks 4 and 12 relative to Baseline (Micturition-related urgency episodes are defined as those micturitions with USS rating of ≥3 in the diary). Only subjects with non-zero micturition-related urgency episodes at Baseline were included in the analysis.
- Change in PPBC at Week 12 relative to Baseline.
- Change in Urgency Perception Scale (UPS) at Week 12 relative to Baseline.
- Change in Overactive Bladder Questionnaire (OAB-q) symptom bother score and change in the Total Health-Related Quality of Life (HRQL) score of the OAB-q and score of each HRQL domain of the OAB-q at Week 12 relative to Baseline.

- Diary dry rate at Weeks 4 and 12.

Safety Endpoints:

- Adverse events.
- Vital Signs.
- Urinalysis, urine culture and sensitivity.

**Safety Evaluations:** Assessment of AEs, vital signs, Blood pressure and pulse rate were recorded at all clinic visits. Physical examination was performed at the screening visit for assessment of study qualification, and urine microscopy, culture and sensitivity testing were performed in the event of symptoms throughout the study.

**Statistical Methods:** The Full Analysis Set (FAS) included all subjects who took at least 1 dose of assigned study drug and had at least 1 Baseline or post-baseline efficacy assessment. Efficacy analysis was based on the FAS. The safety analysis set included all subjects who took at least 1 dose of study drug. Safety analysis and Screening/Baseline assessments were based on the safety analysis set.

Primary Efficacy Analysis: Change in mean number of UUI episodes per 24 hours at Week 12 relative to Baseline.

The number of UUI episodes per 24 hours was calculated as the sum of all UUI episodes (micturitions with a USS=5) divided by the total number of days that diary data were collected at that visit. Only subjects with non-zero UUI, ie the subject demonstrated evidence of UUI, at Baseline were included in the analysis.

If statistical assumptions in regard to the adequacy of the fitted model were met, an analysis of covariance (ANCOVA) model was used to compare the fesoterodine 8 mg, fesoterodine 4 mg, and placebo arms with respect to numeric change from Baseline to Week 12 endpoints. The model included terms for “treatment”, “country”, and “Baseline value” as a covariate, in which centered Baseline (Baseline – mean Baseline) was used to ensure that the treatment effect was estimated at the mean covariate value. The primary comparison was fesoterodine 8 mg versus (vs) 4 mg, which was performed following a closed-testing procedure. The treatment effect of fesoterodine 8 mg vs placebo was tested first. The treatment difference of fesoterodine 8 mg vs fesoterodine 4 mg was only tested if a statistically significant difference between fesoterodine 8 mg and placebo was determined.

If normality assumption was violated, the appropriate variable transformations were attempted in order to normalize the data. If necessary, the non-parametric method, the Van Elteren's test was used. The appropriate point estimate was used, such as the Hodges-Lehman median or a Winsorized mean, to quantify the treatment effect.

“Baseline value” was used as a covariate in the analysis of the corresponding change from Baseline efficacy data in the ANCOVA model. "Ranked Baseline value" was used as a covariate for the ranked ANCOVA model. “Country” was also included in the ANCOVA or ranked ANCOVA model. The two interaction terms, “treatment by Baseline” and “treatment

by country", were assessed at the 10% level of significance. For analysis of the change in mean number of UUI episode per 24 hours, the ANCOVA model with Baseline, country, treatment, and country by treatment interaction showed that the interaction term was not significant ($p>0.1$). Thus, the country by treatment interaction was deleted from the model. The Baseline by treatment interaction was significant ($p<0.1$) in the ANCOVA model with terms for Baseline, country, treatment, and Baseline by treatment interaction, which was determined as the final model. The interaction was quantitative, indicating a larger treatment difference for subjects with larger Baseline values.

Secondary Analyses: For changes in micturitions and micturition-related urgency episodes, no interaction term was significant and the final ANCOVA model included terms for Baseline, country, and treatment.

For changes in the scores of OAB-q, the final ANCOVA model included terms for Baseline, country, treatment, and Baseline by treatment interaction, where the Baseline by treatment interaction was quantitative, as for UUI above.

Treatment comparisons were performed with a two-sided test at the 5% significance level. No adjustment of $\alpha$-levels was made for multiple comparisons.

Paired t-tests were used to compare Baseline with post-baseline measurements within each treatment group.

Numeric changes from Baseline of UUI episodes per 24 hours at Week 4, micturitions per 24 hours at Weeks 4 and 12, micturition-related urgency episodes per 24 hours at Weeks 4 and 12 were analyzed as described for the primary efficacy endpoint.

Percent change from Baseline was analyzed only if the corresponding numeric change from Baseline at the same visit was statistically significant. Percentage change from Baseline endpoints were analyzed using a ranked ANCOVA model for which the rank of percent change was the response variable. The ranked ANCOVA model included "treatment", "country", and "ranked Baseline value" as a covariate. Treatment comparisons were performed using the similar closed-testing procedure as that for numeric change from Baseline. This applied to percent changes from Baseline of UUI episodes per 24 hours at Weeks 4 and 12, micturitions per 24 hours at Weeks 4 and 12, micturition-related urgency episodes per 24 hours at Weeks 4 and 12.

Change in PPBC and UPS at Weeks 12 relative to Baseline were analyzed using a Cochran-Mantel-Haenszel test with modified ridit scoring stratified by country and applying a closed-testing procedure. Change in OAB-q symptom bother score, HRQL total score and in scores of each HRQL domain of OAB-q at Week 12 relative to Baseline was analyzed as described for the primary efficacy endpoint.

Descriptive statistics, including N, mean, standard deviation (SD), median, and range, were reported for Baseline and change from Baseline at Week 4 and 12 visits.

## RESULTS

**Subject Disposition and Demography:** From a total of 4326 subjects screened, 2012 subjects were randomized to treatment following the 2 week placebo run-in period (804 subjects to fesoterodine 8 mg, 806 subjects to fesoterodine 4 mg, and 402 subjects to placebo) and 1955 were treated with at least 1 dose of double-blind medication (779 subjects with fesoterodine 8 mg, 790 subjects with fesoterodine 4 mg, and 386 subjects with placebo). The study was completed by a total of 1745 subjects, 681 (87.4%) subjects in the fesoterodine 8 mg group, 712 (90.1%) subjects in the fesoterodine 4 mg group, and 352 (91.2%) subjects in the placebo group (Table 3).

**Table 3. Subject Disposition and Subjects Analyzed**

| Parameter | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Screened 4326 | | | |
| Assigned to study treatment | 402 | 806 | 804 |
| Treated | 386 | 790 | 779 |
| Completed n (%) | 352 (91.2) | 712 (90.1) | 681 (87.4) |
| Discontinued n (%)[a] | 34 (8.8) | 78 (9.9) | 98 (12.6) |
| Subject died | 0 | 0 | 1 (0.1%) |
| Relationship to study drug not defined | 20 (5.2) | 51 (6.5) | 52 (6.7) |
| Did not meet entrance criteria | 5 (1.3) | 9 (1.1) | 14 (1.8) |
| Insufficient clinical response | 4 (1.0) | 8 (1.0) | 2 (0.3) |
| Lost to follow-up | 4 (1.0) | 9 (1.1) | 15 (1.9) |
| No longer willing to participate in study | 6 (1.6) | 13 (1.6) | 10 (1.3) |
| Other | 1 (0.3) | 1 (0.1) | 3 (0.4) |
| Protocol violation | 0 | 11 (1.4) | 8 (1.0) |
| Related to study drug | 5 (1.3) | 16 (2.0) | 35 (4.5) |
| AE | 5 (1.3) | 16 (2.0) | 35 (4.5) |
| Not related to study drug | 9 (2.3) | 11 (1.4) | 10 (1.3) |
| AE | 9 (2.3) | 11 (1.4) | 10 (1.3) |
| Analyzed for efficacy | | | |
| Full analysis set | 386 (100) | 790 (100) | 779 (100) |
| Analyzed for safety | | | |
| Adverse events | 376 (97.4) | 774 (98.0) | 766 (98.3) |
| Laboratory data | 355 (92.0) | 728 (92.2) | 709 (91.0) |

AE = adverse event; n=number of subjects with an observation.

a. Discontinuations have been attributed to the last study treatment received.

Demographic characteristics of treated study subjects are summarized in Table 4.

## Table 4: Demographic Characteristics

| Demographic Characteristics | Placebo | | | Fesoterodine 4 mg | | | Fesoterodine 8 mg | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male N=70 | Female N=316 | Total N=386 | Male N=143 | Female N=647 | Total N=790 | Male N=152 | Female N=627 | Total N=779 |
| Age (years) | | | | | | | | | |
| 18 to 44, n (%) | 6 (8.6) | 43 (13.6) | 49 (12.7) | 15 (10.5) | 99 (15.3) | 114 (14.4) | 18 (11.8) | 81 (12.9) | 99 (12.7) |
| 45 to 64, n (%) | 32 (45.7) | 161 (50.9) | 193 (50.0) | 48 (33.6) | 332 (51.3) | 380 (48.1) | 59 (38.8) | 318 (50.7) | 377 (48.4) |
| ≥ 65, n (%) | 32 (45.7) | 112 (35.4) | 144 (37.3) | 80 (55.9) | 216 (33.4) | 296 (37.5) | 75 (49.3) | 228 (36.4) | 303 (38.9) |
| Mean (SD) | 62.1 (12.5) | 59.1 (12.6) | 59.6 (12.7) | 63.1 (13.3) | 57.8 (13.2) | 58.8 (13.3) | 61.9 (13.6) | 59.3 (12.6) | 59.8 (12.9) |
| Range | 23–83 | 19–85 | 19–85 | 26–87 | 18–89 | 18–89 | 23–94 | 21–89 | 21–94 |
| Hormonal status | | | | | | | | | |
| Premenopausal | – | 56 (17.7) | – | – | 141 (21.8) | – | – | 111 (17.7) | – |
| Postmenopausal | – | 240 (75.9) | – | – | 470 (72.6) | – | – | 482 (76.9) | – |
| Perimenopausal | – | 18 (5.7) | – | – | 34 (5.3) | – | – | 30 (4.8) | – |
| Childbearing potential | | | | | | | | | |
| Yes | – | 57 (18.0) | – | – | 132 (20.4) | – | – | 117 (18.7) | – |
| No | – | 259 (82.0) | – | – | 515 (79.6) | – | – | 509 (81.2) | – |
| BMI ($kg/m^2$) | | | | | | | | | |
| Mean (SD) | 30.1 (7.0) | 30.8 (7.8) | 30.7 (7.7) | 28.5 (5.4) | 31.0 (7.8) | 30.5 (7.5) | 28.2 (5.4) | 30.8 (7.1) | 30.3 (6.9) |
| Range | 18.8–53.5 | 17.9–61.3 | 17.9–61.3 | 17.9–51.2 | 16.9–65.8 | 16.9–65.8 | 17.9–46.1 | 17.1–60.8 | 17.1–60.8 |
| Race, n (%) | | | | | | | | | |
| White | 53 (75.7) | 255 (80.7) | 308 (79.8) | 114 (79.7) | 536 (82.8) | 650 (82.3) | 120 (78.9) | 515 (82.1) | 635 (81.5) |
| Black | 8 (11.4) | 44 (13.9) | 52 (13.5) | 17 (11.9) | 75 (11.6) | 92 (11.6) | 19 (12.5) | 69 (11.0) | 88 (11.3) |
| Asian | 8 (11.4) | 10 (3.2) | 18 (4.7) | 10 (7.0) | 24 (3.7) | 34 (4.3) | 11 (7.2) | 36 (5.7) | 47 (6.0) |
| Other | 1 (1.4) | 7 (2.2) | 8 (2.1) | 2 (1.4) | 12 (1.9) | 14 (1.8) | 2 (1.3) | 7 (1.1) | 9 (1.2) |

BMI = body mass index; N, n = number; SD = standard deviation.

**Efficacy Results:** The decrease in mean number of UUI episode per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group (p<0.0001; Table 5). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group (p=0.0109).

**Table 5. ANCOVA of Change From Baseline in Mean Number of UUI Episodes per 24 Hours at Week 12 – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| n[a] | 370 | 733 | 718 |
| Baseline | | | |
| Mean (SD) | 4.09 (2.42) | 3.87 (2.09) | 3.94 (2.28) |
| Median (min, max) | 3.33 (0.67, 14.67) | 3.00 (1.33, 14.33) | 3.33 (0.33, 22.67) |
| Week 12 | | | |
| Mean (SD) | 1.89 (2.88) | 1.15 (1.95) | 0.93 (1.84) |
| Median (min, max) | 0.67 (0.00, 16.33) | 0.33 (0.00, 14.33) | 0.00 (0.00, 17.00) |
| Numerical change from Baseline to Week 12 | | | - |
| Mean (SD) | -2.20 (2.97) | -2.72 (2.31) | -3.01 (2.55) |
| Median (min, max) | -2.33 (-14.67, 12.33) | -2.33 (-13.67, 11.67) | -2.67 (-22.67, 7.33) |
| LS Mean (SE) | -2.22 (0.12) | -2.85 (0.09) | -3.12 (0.09) |
| 95% CI for mean | (-2.45, -1.98) | (-3.03, -2.67) | (-3.30, -2.94) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | - |
| LS Mean difference (SE) | - | -0.64 (0.13) | -0.91 (0.13) |
| 95% CI | - | (-0.89, -0.39) | (-1.16, -0.66) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -0.27 (0.11) |
| 95% CI | - | - | (-0.48, -0.06) |
| p-value[c] | - | - | 0.0109 |

ANCOVA = Analysis of covariance; BL = baseline; CI = confidence interval; FAS = Full analysis set; LS = least squares; max = maximum; min = minimum; N/n = number; SD = standard deviation; SE = standard error; vs = versus.

a. Number of subjects with Baseline Urgency Urinary Incontinence greater than 0 per 24 hours and non-missing change from Baseline to Week 12.
b. p-value based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country, centered Baseline value and centered Baseline by treatment interaction.

Numeric Changes of UUI Episodes per 24 Hours (Week 4)

The decrease in mean number of UUI episode per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group compared with the placebo group ($p<0.0001$; Table 6). The comparison of the decreases in the fesoterodine 8 mg vs. 4 mg groups showed no statistically significant difference between these treatments ($p=0.0662$). The decrease in mean number of UUI episode per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p<0.0001$; Table 6).

Percent Changes of UUI Episodes per 24 Hours (Week 4 and Week 12):

The percent change in the mean number of UUI episode per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$; Table 6). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p=0.0006$).

The percent change in the mean number of UUI episode per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p=0.0001$).

For the comparison relative to Baseline at Week 4, the percent change in mean number of UUI episode per 24 hours was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The treatment difference between fesoterodine 8 mg vs. 4 mg by percent change in mean number of UUI episode per 24 hours at Week 4 was not analyzed because the corresponding numeric comparison showed no statistically significant difference (Table 6).

The percent change in the mean number of UUI episode per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p<0.0001$).

## Table 6. ANCOVA of Numeric and Percent Changes From Baseline of UUI Episodes per 24 Hours – FAS

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Change from Baseline in mean number of UUI episodes per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 704 |
| Baseline | | | |
| Mean (SD) | 4.07 (2.38) | 3.89 (2.09) | 3.95 (2.30) |
| Median (min, max) | 3.33 (0.67, 14.67) | 3.00 (1.33, 14.33) | 3.33 (0.33, 22.67) |
| Week 4 | | | |
| Mean (SD) | 2.25 (2.67) | 1.58 (2.29) | 1.42 (1.96) |
| Median (min, max) | 1.33 (0.00, 15.33) | 0.67 (0.00, 23.67) | 0.67 (0.00, 13.00) |
| Numerical change from Baseline to Week 4 | | | |
| Mean (SD) | -1.82 (2.54) | -2.30 (2.33) | -2.54 (2.62) |
| Median (min, max) | -2.00 (-14.17, 11.33) | -2.33 (-13.67, 9.67) | -2.33 (-22.67, 10.00) |
| LS Mean (SE) | -1.99 (0.12) | -2.55 (0.09) | -2.75 (0.09) |
| 95% CI for mean | (-2.23, -1.75) | (-2.74, -2.36) | (-2.94, -2.57) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | -0.56 (0.13) | -0.76 (0.13) |
| 95% CI | - | (-0.82, -0.30) | (-1.02, -0.50) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -0.20 (0.11) |
| 95% CI | - | - | (-0.41, 0.01) |
| p-value[c] | - | - | 0.0662 |
| Percent change from Baseline in mean number of UUI episodes per 24 Hours at Week 12 | | | |
| n[a] | 370 | 733 | 718 |
| Baseline | | | |
| Mean (SD) | 4.09 (2.42) | 3.87 (2.09) | 3.94 (2.28) |
| Median (min, max) | 3.33 (0.67, 14.67) | 3.00 (1.33, 14.33) | 3.33 (0.33, 22.67) |
| Week 12 | | | |
| Mean (SD) | 1.89 (2.88) | 1.15 (1.95) | 0.93 (1.84) |
| Median (min, max) | 0.67 (0.00, 16.33) | 0.33 (0.00, 14.33) | 0.00 (0.00, 17.00) |
| Percent change from Baseline to Week 12 | | | |
| Mean (SD) | -54.27 (67.96) | -69.86 (52.92) | -75.72 (45.62) |
| Median (min, max) | -78.89 (-100.00, 350.00) | -93.75 (-100.00, 437.50) | -100.00 (-100.00, 325.00) |
| vs. Placebo | | | |
| p-value[d] | - | 0.0001 | <0.0001 |
| vs. Fesoterodine 4 mg | | - | |
| p-value[d] | - | - | 0.0006 |
| Percent change from Baseline in mean number of UUI episodes per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 704 |
| Baseline | | | |
| Mean (SD) | 4.07 (2.38) | 3.89 (2.09) | 3.95 (2.30) |
| Median (min, max) | 3.33 (0.67, 14.67) | 3.00 (1.33, 14.33) | 3.33 (0.33, 22.67) |
| Week 4 | | | |
| Mean (SD) | 2.25 (2.67) | 1.58 (2.29) | 1.42 (1.96) |
| Median (min, max) | 1.33 (0.00, 15.33) | 0.67 (0.00, 23.67) | 0.67 (0.00, 13.00) |
| Percent change from Baseline to Week 4 | | | |
| Mean (SD) | -45.70 (58.26) | -59.58 (53.08) | -61.65 (52.99) |
| Median (min, max) | -60.50 (-100.00, 283.33) | -77.78 (-100.00, 244.44) | -82.48 (-100.00, 500.00) |
| vs. Placebo | | | |
| p-value[d] | - | <0.0001 | <0.0001 |
| vs. Fesoterodine 4 mg | | | |
| p-value[d] | - | - | NC |

**Table 6. ANCOVA of Numeric and Percent Changes From Baseline of UUI Episodes per 24 Hours – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|

ANCOVA = Analysis of covariance; CI = confidence interval; FAS = Full analysis set; LS = least squares; NC = not calculated; max = maximum; min = minimum; N/n = number; SD = standard deviation; SE = standard error; UUI = urgency urinary incontinence; vs = versus.

a. Number of subjects with Baseline UUI >0 per 24 hours and non-missing change from Baseline to Week 12.
b. p-value based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country, centered Baseline value and centered Baseline by treatment interaction.
d. Based on a RANKED ANCOVA model with terms for treatment and pooled country with ranked Baseline value as a covariate. Note that this p-value was not calculated (NC) when the treatment difference based on mean numeric change was not significant ($p \geq 0.05$).

Diary Dry Rate at Weeks 4 and 12: The numbers (proportions) of subjects with zero UUI episodes at Week 12 were 415 (57.8%) for the fesoterodine 8 mg group, 361 (49.2%) for the fesoterodine 4 mg group, and 146 (39.5%) for the placebo group (Table 7).

At Week 12, the Diary Dry Rate of the fesoterodine 8 mg group was statistically significantly higher than the rate of the placebo group ($p<0.0001$). There was also a statistically significantly higher Diary Dry Rate determined for the fesoterodine 8 mg vs. 4 mg group ($p=0.0006$) and for the fesoterodine 4 mg vs. placebo group ($p=0.0027$).

At Week 4, Diary Dry Rates across all treatments were lower compared with Week 12. The numbers (proportions) of subjects with zero UUI episodes at Week 4 were 255 (36.2%) for the fesoterodine 8 mg group, 254 (35.5%) for the fesoterodine 4 mg group, and 96 (26.4%) for the placebo group. The Diary Dry Rates of the fesoterodine 8 mg and the 4 mg groups were statistically significantly higher compared with the placebo group ($p=0.0016$ and $p=0.0015$). There was no statistically significant treatment effect on the Diary Dry Rate at Week 4 comparing fesoterodine 8 mg vs. 4 mg ($p=0.8121$; Table 7).

**Table 7. Number and Proportion of Subjects with Urgency Urinary Incontinence Episodes Equal to Zero at Weeks 4 and 12 - FAS**

| Value | Placebo | | Fesoterodine 4 mg | | Fesoterodine 8 mg | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Week 12 | | | | | | |
| N[a] | 370 | (100) | 733 | (100) | 718 | (100) |
| Subjects with zero UUI (Diary Dry rate[b]) | 146 | (39.5) | 361 | (49.2) | 415 | (57.8) |
| vs. placebo | | | | | | |
| p-value[c] | | - | | 0.0027 | | <0.0001 |
| vs. fesoterodine 4 mg | | | | | | |
| p-value[c] | | - | | - | | 0.0006 |
| Week 4 | | | | | | |
| N[a] | 364 | (100) | 715 | (100) | 704 | (100) |
| Subjects with zero UUI (Diary Dry rate[b]) | 96 | (26.4) | 254 | (35.5) | 255 | (36.2) |
| vs. placebo | | | | | | |
| p-value[c] | | - | | 0.0015 | | 0.0016 |
| vs. fesoterodine 4 mg | | | | | | |
| p-value[c] | | - | | - | | 0.8121 |

CMH = Cochran-Mantel-Haenszel; FAS = Full analysis set; N/n = number; UUI = Urgency urinary incontinence; vs = versus.

a. Number of subjects with Baseline UUI >0 per 24 hours and non-missing change from Baseline to Week 4/Week 12.
b. Diary Dry Rate (%) was defined as the proportion of subjects with no UUI episode for the 3 day diary, the numerator being the number of subjects with no UUI at a visit and the denominator the total number of subjects with UUI>0 at Baseline.
c. The p-value was obtained from a CMH general association test stratified by country.

Numeric Changes of Micturitions per 24 Hours: The decrease in the mean number of micturitions per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$; Table 8). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p=0.0006$). The decrease in mean number of micturitions per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg vs. the placebo group ($p<0.0001$).

For the comparison at Week 4, the decrease in the mean number of micturitions per 24 hours relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p=0.0082$; Table 8). The decrease in mean number of micturitions per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg vs. the placebo group ($p<0.0001$).

Percent Changes of Micturitions per 24 Hours: The percent change in the mean number of micturitions per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p<0.0001$). The percent change in mean number of micturitions per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p<0.0001$; Table 8).

For the comparison relative to Baseline at Week 4, the percent change in the mean number of micturitions per 24 hours was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The treatment difference in terms of a decrease of micturitions between fesoterodine 8 mg vs. 4 mg groups was also statistically significant ($p=0.0040$).

The decrease of the percent change in mean number of micturitions per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p<0.0001$).

**Table 8. ANCOVA of Numeric and Percent Changes From Baseline of Micturitions per 24 Hours – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Change from Baseline in mean number of micturitions per 24 hours at Week 12 | | | |
| n[a] | 370 | 733 | 719 |
| Baseline | | | |
| Mean (SD) | 12.82 (3.89) | 12.63 (3.65) | 12.70 (3.45) |
| Median (min, max) | 11.67 (5.67, 33.33) | 12.00 (5.00, 38.67) | 12.00 (5.67, 29.33) |
| Week 12 | | | |
| Mean (SD) | 11.18 (3.87) | 10.18 (3.53) | 9.75 (3.51) |
| Median (min, max) | 10.42 (4.00, 29.67) | 9.67 (4.33, 29.67) | 9.00 (3.33, 30.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | -1.64 (3.70) | -2.45 (3.27) | -2.95 (3.11) |
| Median (min, max) | -1.33 (-20.67, 9.50) | -2.33 (-18.00, 8.33) | -2.67 (-15.67, 12.33) |
| LS Mean (SE) | -1.58 (0.17) | -2.45 (0.13) | -2.97 (0.13) |
| 95% CI for mean | (-1.91, -1.24) | (-2.71, -2.19) | (-3.23, -2.71) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | -0.87 (0.19) | -1.40 (0.19) |
| 95% CI | - | (-1.23, -0.51) | (-1.76, -1.03) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. Fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -0.53 (0.15) |
| 95% CI | - | - | (-0.83, -0.23) |
| p-value[c] | - | - | 0.0006 |
| Change from Baseline in mean number of micturitions per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 705 |
| Baseline | | | |
| Mean (SD) | 12.84 (3.91) | 12.66 (3.67) | 12.74 (3.46) |
| Median (min, max) | 11.67 (5.67, 33.33) | 12.33 (5.00, 38.67) | 12.00 (5.67, 29.33) |
| Week 4 | | | |
| Mean (SD) | 11.66 (3.94) | 10.78 (3.60) | 10.48 (3.49) |
| Median (min, max) | 11.00 (4.33, 28.33) | 10.33 (4.00, 30.00) | 10.00 (3.67, 29.33) |
| Numerical change from Baseline to Week 4 | | | |
| Mean (SD) | -1.18 (3.28) | -1.88 (2.88) | -2.26 (2.96) |
| Median (min, max) | -1.00 (-18.00, 9.67) | -1.67 (-15.33, 10.33) | -2.00 (-14.33, 13.33) |
| LS Mean (SE) | -1.19 (0.16) | -1.95 (0.13) | -2.33 (0.13) |
| 95% CI for mean | (-1.51, -0.88) | (-2.19, -1.70) | (-2.57, -2.08) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | -0.75 (0.18) | -1.13 (0.18) |
| 95% CI | - | (-1.10, -0.41) | (-1.48, -0.79) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS Mean Difference (SE) | - | - | -0.38 (0.14) |
| 95% CI | - | - | (-0.67, -0.10) |
| p-value[c] | - | - | 0.0082 |
| Percent change from Baseline in mean number of micturitions per 24 hours at Week 12 | | | |
| n[a] | 370 | 733 | 719 |
| Baseline | | | |

**Table 8. ANCOVA of Numeric and Percent Changes From Baseline of Micturitions per 24 Hours – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Mean (SD) | 12.82 (3.89) | 12.63 (3.65) | 12.70 (3.45) |
| Median (min, max) | 11.67 (5.67, 33.33) | 12.00 (5.00, 38.67) | 12.00 (5.67, 29.33) |
| Week 12 | | | |
| Mean (SD) | 11.18 (3.87) | 10.18 (3.53) | 9.75 (3.51) |
| Median (min, max) | 10.42 (4.00, 29.67) | 9.67 (4.33, 29.67) | 9.00 (3.33, 30.00) |
| Percent change from Baseline to Week 12 | | | |
| Mean (SD) | -10.59 (24.90) | -17.70 (22.36) | -22.03 (21.54) |
| Median (min, max) | -12.16 (-64.04, 95.00) | -19.74 (-64.58, 92.59) | -24.14 (-76.74, 78.26) |
| vs. Placebo: p-value[d] | | <0.0001 | <0.0001 |
| vs. Fesoterodine 4 mg: p-value[d] | | | <0.0001 |
| Percent change from Baseline in mean number of micturitions per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 705 |
| Baseline | | | |
| Mean (SD) | 12.84 (3.91) | 12.66 (3.67) | 12.74 (3.46) |
| Median (min, max) | 11.67 (5.67, 33.33) | 12.33 (5.00, 38.67) | 12.00 (5.67, 29.33) |
| Week 4 | | | |
| Mean (SD) | 11.66 (3.94) | 10.78 (3.60) | 10.48 (3.49) |
| Median (min, max) | 11.00 (4.33, 28.33) | 10.33 (4.00, 30.00) | 10.00 (3.67, 29.33) |
| Percent change from Baseline to Week 4 | | | |
| Mean (SD) | -7.66 (22.57) | -13.47 (21.17) | -16.43 (21.43) |
| Median (min, max) | -9.01 (-60.94, 95.00) | -14.58 (-65.71, 96.30) | -17.24 (-70.91, 117.65) |
| vs. Placebo: p-value[d] | - | <0.0001 | <0.0001 |
| vs. Fesoterodine 4 mg: p-value[d] | - | - | 0.0040 |

ANCOVA = Analysis of covariance; CI = confidence interval; FAS = Full analysis set; LS = least squares; max = maximum; min = minimum; N, n = number; SD = standard deviation; SE = standard error; vs = versus.

a. Number of subjects with Baseline Micturition Frequency >0 per 24 hours and non-missing change from Baseline to Week 12.
b. p-value was based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country, and centered Baseline value.
d. Based on a RANKED ANCOVA model with terms for treatment and pooled country with ranked Baseline value as a covariate.

Numeric Changes of Micturition-Related Urgency Episodes per 24 Hours: The decrease in the mean number of micturition-related urgency episodes per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group (p<0.0001; Table 9). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group (p=0.0005). The decrease in mean number of micturition related UUI episodes per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg vs. the placebo group (p<0.0001; Table 9).

For the comparison at Week 4, the decrease in the mean number of micturition-related urgency episodes per 24 hours relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p=0.0121$). The decrease in mean number of micturition-related urgency episodes per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg vs. the placebo group ($p<0.0001$).

Percent Changes of Micturition-Related Urgency Episodes per 24 Hours: The percent change in the mean number of micturition-related urgency episodes per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$; Table 9). The decrease in the fesoterodine 8 mg group was also statistically significantly greater than in the fesoterodine 4 mg group ($p=0.0002$). The percent change in mean number of micturition-related urgency episodes per 24 hours at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p<0.0001$).

For the comparison relative to Baseline at Week 4, the percent change in the mean number of micturition-related urgency episodes per 24 hours was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The treatment difference in terms of a decrease of micturition-related urgency episodes between fesoterodine 8 mg vs. 4 mg groups was also statistically significant ($p=0.0348$).

The decrease of the percent change in the mean number of micturition-related urgency episodes per 24 hours at Week 4 relative to Baseline was statistically significantly greater in the fesoterodine 4 mg group than in the placebo group ($p=0.0003$; Table 9).

**Table 9. ANCOVA of Numeric and Percent Changes From Baseline of Micturition-Related Urgency Episodes per 24 Hours – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Change from Baseline in mean number of micturition-related urgency episodes per 24 hours at Week 12 | | | |
| n[a] | 370 | 733 | 719 |
| Baseline | | | |
| Mean (SD) | 11.24 (4.20) | 11.10 (3.89) | 10.96 (3.89) |
| Median (min, max) | 10.67 (2.00, 32.33) | 10.67 (2.33, 38.67) | 10.67 (2.00, 28.67) |
| Week 12 | | | |
| Mean (SD) | 8.27 (5.00) | 6.94 (4.64) | 6.14 (4.55) |
| Median (min, max) | 8.17 (0.00, 27.00) | 6.67 (0.00, 26.33) | 5.33 (0.00, 30.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | -2.97 (5.06) | -4.16 (4.62) | -4.83 (4.55) |
| Median (min, max) | -2.59 (-29.00, 14.33) | -3.67 (-26.67, 10.33) | -4.33 (-23.00, 12.00) |
| LS Mean (SE) | -2.99 (0.25) | -4.23 (0.19) | -5.01 (0.19) |
| 95% CI for mean | (-3.49, -2.50) | (-4.61, -3.85) | (-5.39, -4.63) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | -1.24 (0.27) | -2.02 (0.27) |
| 95% CI | - | (-1.77, -0.71) | (-2.55, -1.49) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. Fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -0.78 (0.22) |
| 95% CI | - | - | (-1.22, -0.34) |
| p-value[c] | - | - | 0.0005 |
| Change from Baseline in mean number of micturition-related urgency episodes per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 705 |
| Baseline | | | |
| Mean (SD) | 11.27 (4.22) | 11.14 (3.89) | 11.01 (3.91) |
| Median (min, max) | 10.67 (2.00, 32.33) | 10.67 (2.33, 38.67) | 10.67 (2.00, 28.67) |
| Week 4 | | | |
| Mean (SD) | 9.38 (4.88) | 8.29 (4.46) | 7.70 (4.52) |
| Median (min, max) | 9.00 (0.00, 27.00) | 8.33 (0.00, 30.00) | 7.67 (0.00, 28.33) |
| Numerical change from Baseline to Week 4 | | | |
| Mean (SD) | -1.89 (4.26) | -2.85 (3.96) | -3.31 (4.23) |
| Median (min, max) | -1.67 (-22.67, 14.33) | -2.67 (-26.67, 10.33) | -3.00 (-23.00, 10.00) |
| LS Mean (SE) | -1.85 (0.23) | -2.89 (0.18) | -3.40 (0.18) |
| 95% CI for mean | (-2.30, -1.40) | (-3.23, -2.54) | (-3.75, -3.05) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | -1.04 (0.25) | -1.55 (0.25) |
| 95% CI | - | (-1.52, -0.55) | (-2.04, -1.06) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. Fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -0.52 (0.21) |
| 95% CI | - | - | (-0.92, -0.11) |
| p-value[c] | - | - | 0.0121 |
| Percent change from Baseline in mean number of micturition-related urgency episodes per 24 hours at Week 12 | | | |
| n[a] | 370 | 733 | 719 |

**Table 9. ANCOVA of Numeric and Percent Changes From Baseline of Micturition-Related Urgency Episodes per 24 Hours – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Baseline | | | |
| Mean (SD) | 11.24 (4.20) | 11.10 (3.89) | 10.96 (3.89) |
| Median (min, max) | 10.67 (2.00, 32.33) | 10.67 (2.33, 38.67) | 10.67 (2.00, 28.67) |
| Week 12 | | | |
| Mean (SD) | 8.27 (5.00) | 6.94 (4.64) | 6.14 (4.55) |
| Median (min, max) | 8.17 (0.00, 27.00) | 6.67 (0.00, 26.33) | 5.33 (0.00, 30.00) |
| Percent change from Baseline to Week 12 | | | |
| Mean (SD) | -21.77 (59.04) | -35.01 (43.27) | -42.86 (39.19) |
| Median (min, max) | -22.73 (-100.00, 716.67) | -34.88 (-100.00, 310.00) | -44.29 (-100.00, 233.33) |
| vs. Placebo | | | |
| p-value[d] | - | <0.0001 | <0.0001 |
| vs. Fesoterodine 4 mg | | | |
| p-value[d] | - | - | 0.0002 |
| Percent change from Baseline in mean number of micturition-related urgency episodes per 24 hours at Week 4 | | | |
| n[a] | 364 | 715 | 705 |
| Baseline | | | |
| Mean (SD) | 11.27 (4.22) | 11.14 (3.89) | 11.01 (3.91) |
| Median (min, max) | 10.67 (2.00, 32.33) | 10.67 (2.33, 38.67) | 10.67 (2.00, 28.67) |
| Week 4 | | | |
| Mean (SD) | 9.38 (4.88) | 8.29 (4.46) | 7.70 (4.52) |
| Median (min, max) | 9.00 (0.00, 27.00) | 8.33 (0.00, 30.00) | 7.67 (0.00, 28.33) |
| Percent change from Baseline to Week 4 | | | |
| Mean (SD) | -12.55 (59.32) | -23.81 (38.70) | -28.33 (37.98) |
| Median (min, max) | -14.70 (-100.00, 716.67) | -23.26 (-100.00, 280.00) | -27.27 (-100.00, 150.00) |
| vs Placebo | | | |
| p-value[d] | - | 0.0003 | <0.0001 |
| vs fesoterodine 4 mg | | | |
| p-value[d] | - | - | 0.0348 |

ANCOVA = Analysis of covariance; CI = confidence interval; FAS = Full analysis set; LS = least squares; max = maximum; min = minimum; N/n = number; SD = standard deviation; SE = standard error; vs = versus.

a. Number of subjects with Baseline Urgency Episodes >0 per 24 hours and non-missing change from Baseline to Week 4/Week 12.
b. p-value was based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country, and centered Baseline value.
d. Based on a RANKED ANCOVA model with terms for treatment and pooled country with ranked Baseline value as a covariate.

PPBC: The change from Baseline to Week 12 in PPBC was statistically significantly different for the treatment comparison fesoterodine 8 mg vs. placebo (p<0.0001) based on a 4-category analysis (Table 10). A statistically significant difference in PPBC at Week 12 was also determined for the comparison fesoterodine 8 mg vs. 4 mg (p=0.0057). The proportion of subjects for whom treatment qualified as "major improvement" was higher in the fesoterodine treatment groups in comparison to placebo; 48.6% of subjects in the fesoterodine 8 mg group, 40.0% of subjects in the fesoterodine 4 mg group, and 27.6% of subjects in the placebo group. The change from Baseline to Week 12 in PPBC was also statistically significantly different for the treatment comparison fesoterodine 4 mg vs. placebo (p=0.0008; Table 10).

**Table 10. Change from Baseline in PPBC at Week 12 - FAS**

| PPBC "My bladder condition ..." | Placebo n | Placebo (%) | Fesoterodine 4 mg n | Fesoterodine 4 mg (%) | Fesoterodine 8 mg n | Fesoterodine 8 mg (%) |
|---|---|---|---|---|---|---|
| n[a] | 348 | (100) | 700 | (100) | 677 | (100) |
| Baseline: | | | | | | |
| Does not cause me any problems at all | 0 | (0.0) | 1 | (0.1) | 3 | (0.4) |
| Causes me some very minor problems | 3 | (0.9) | 0 | (0.0) | 3 | (0.4) |
| Causes me some minor problems | 3 | (0.9) | 10 | (1.4) | 9 | (1.3) |
| Causes me (some) moderate problems | 85 | (24.4) | 178 | (25.4) | 164 | (24.2) |
| Causes me severe problems | 175 | (50.3) | 340 | (48.6) | 337 | (49.8) |
| Causes me many severe problems | 82 | (23.6) | 171 | (24.4) | 161 | (23.8) |
| Week 12 | | | | | | |
| Does not cause me any problems at all | 12 | (3.4) | 42 | (6.0) | 43 | (6.4) |
| Causes me some very minor problems | 41 | (11.8) | 112 | (16.0) | 135 | (19.9) |
| Causes me some minor problems | 59 | (17.0) | 130 | (18.6) | 164 | (24.2) |
| Causes me (some) moderate problems | 105 | (30.2) | 234 | (33.4) | 206 | (30.4) |
| Causes me severe problems | 91 | (26.1) | 139 | (19.9) | 93 | (13.7) |
| Causes me many severe problems | 40 | (11.5) | 43 | (6.1) | 36 | (5.3) |
| Week 12 vs. Baseline | | | | | | |
| Deterioration | 25 | (7.2) | 38 | (5.4) | 27 | (4.0) |
| No Change | 122 | (35.1) | 172 | (24.6) | 151 | (22.3) |
| Minor Improvement | 105 | (30.2) | 210 | (30.0) | 170 | (25.1) |
| Major Improvement | 96 | (27.6) | 280 | (40.0) | 329 | (48.6) |
| p-value vs. placebo[b] | | | 0.0008 | | <0.0001 | |
| p-value vs. Fesoterodine 4 mg[b] | | | | | 0.0057 | |

CMH = Cochran-Mantel-Haenszel; FAS = Full analysis set; PPBC = Patient Perception of Bladder Condition; N/n = number; vs = versus.

a. Number of non-missing values for change from Baseline to Week 12.

b. p-value based on a CMH test with modified ridit scoring controlling for country.

UPS: The change from Baseline to Week 12 in UPS was statistically significantly different for the treatment comparison fesoterodine 8 mg vs. placebo (p=0.0007) based on a 3-category analysis (Table 11). A statistically significant difference in UPC at Week 12 was also determined for the comparison between the fesoterodine 8 mg vs. 4 mg groups (p=0.0091). The proportion of subjects for whom treatment qualified as "improvement" in UPS was higher in the fesoterodine treatment groups in comparison to placebo; 50.5% of subjects in the fesoterodine 8 mg group, 43.1% of subjects in the fesoterodine 4 mg group, and 37.9% of subjects in the placebo group. There was no statistically significant difference in the UPS at Week 12 relative to Baseline between the fesoterodine 4 mg and the placebo groups (p=0.3901).

**Table 11. Change from Baseline in UPS at Treatment Week 12 – FAS**

| Urgency Perception Scale | Placebo | | Fesoterodine 4 mg | | Fesoterodine 8 mg | |
|---|---|---|---|---|---|---|
| "I am usually …." | n | (%) | n | (%) | n | (%) |
| n[a] | 348 | (100.0) | 700 | (100.0) | 677 | (100.0) |
| Baseline | | | | | | |
| Not able to hold urine | 180 | (51.7) | 333 | (47.6) | 329 | (48.6) |
| Able to hold urine (without leaking) until I reach a toilet if I go to the toilet immediately | 164 | (47.1) | 349 | (49.9) | 332 | (49.0) |
| Able to finish what I am doing before going to the toilet (without leaking) | 4 | (1.1) | 18 | (2.6) | 16 | (2.4) |
| Week 12 | | | | | | |
| Not able to hold urine | 107 | (30.7) | 151 | (21.6) | 112 | (16.5) |
| Able to hold urine (without leaking) until I reach a toilet if I go to the toilet immediately | 188 | (54.0) | 393 | (56.1) | 395 | (58.3) |
| Able to finish what I am doing before going to the toilet (without leaking) | 53 | (15.2) | 156 | (22.3) | 170 | (25.1) |
| Week 12 vs. Baseline | | | | | | |
| Deterioration | 23 | (6.6) | 37 | (5.3) | 30 | (4.4) |
| No Change | 193 | (55.5) | 361 | (51.6) | 305 | (45.1) |
| Improvement | 132 | (37.9) | 302 | (43.1) | 342 | (50.5) |
| p-value vs. placebo[b] | - | - | 0.3901 | - | 0.0007 | - |
| p-value vs. Fesoterodine 4 mg[b] | - | - | - | - | 0.0091 | - |

CMH = Cochran-Mantel-Haenszel; FAS=Full analysis set; N/n=number; UPS = Urgency Perception Scale; vs = versus.

a. Number of non-missing values for change from Baseline to Week 12.
b. p-value based on a CMH test with modified ridit scoring controlling for country.

Change in OAB-q Symptom Bother Score at Week 12 Relative to Baseline: The decrease in OAB-q symptom bother score at Week 12 relative to Baseline was statistically significantly greater in the fesoterodine 8 mg group than in the placebo group ($p<0.0001$). The decrease in OAB-q symptom bother score was also statistically significantly greater in the fesoterodine 8 mg vs. 4 mg group ($p=0.0002$; Table 12). The decrease in OAB-q symptom bother score at Week 12 relative to Baseline was also statistically significantly greater in the fesoterodine 4 mg vs. the placebo group ($p<0.0001$).

**Table 12. ANCOVA of Change From Baseline in OAB-q at Week 12 – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| OAB-q symptom bother score | | | |
| n[a] | 347 | 701 | 678 |
| Baseline | | | |
| Mean (SD) | 70.09 ( 18.28) | 68.57 ( 18.66) | 68.76 ( 18.58) |
| Median (min, max) | 72.50 ( 20.00, 100.00) | 70.00 ( 15.00, 100.00) | 70.00 ( 12.50, 100.00) |
| Week 12 | | | |
| Mean (SD) | 48.30 ( 26.73) | 39.32 ( 24.20) | 35.17 ( 24.05) |
| Median (min, max) | 47.50 ( 0.00, 100.00) | 35.00 ( 0.00, 100.00) | 30.00 ( 0.00, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | -21.79 ( 25.51) | -29.25 ( 25.46) | -33.58 ( 26.20) |
| Median (min, max) | -17.50 ( -85.00, 37.50) | -25.00 ( -97.50, 52.50) | -32.50 (-100.00, 37.50) |
| LS mean (SE) | -22.41 ( 1.43) | -30.19 ( 1.09) | -34.88 ( 1.10) |
| 95% CI for mean | ( -25.21, -19.61) | ( -32.33, -28.06) | ( -37.05, -32.71) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS mean difference (SE) | - | -7.78 ( 1.53) | -12.47 ( 1.54) |
| 95% CI | - | ( -10.78, -4.78) | -15.49, -9.45) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | -4.69 ( 1.26) |
| 95% CI | - | - | ( -7.15, -2.22) |
| p-value[c] | - | - | 0.0002 |

ANCOVA = Analysis of covariance; CI = confidence interval; FAS = Full analysis set; LS = least squares; max = maximum; min = minimum; N/n = number; SD = standard deviation; SE = standard error; vs = versus.

a. Number of non-missing values for change from Baseline to Week 12.
b. p-value based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country centered Baseline value and centered Baseline by treatment interaction.

Change in Score of Each HRQL Domain of OAB-q and Total Score at Week 12 Relative to Baseline: High scores on HRQL scale were indicative of better HRQL, and an increase in score was indicative of improvement.

The scores of the HRQL scale domains (and total score) showed statistically significant increases, from Baseline to Week 12, in both fesoterodine treatment groups and the placebo group (all p-values: <0.0001; Table 13).

The improvement in each domain and also in the total score of the HRQL scale was statistically significantly greater in the fesoterodine 8 mg group compared with the placebo group (all p-values: <0.0001). There was also a statistically significant improvement in the fesoterodine 8 mg vs. the 4 mg group for the coping domain (p=0.0006), concern domain (p=0.0010), sleep domain (p=0.0034), social interaction domain (p=0.0004), and the HRQL total score (p=0.0003).

For the comparison fesoterodine 4 mg vs. placebo, statistically significant improvements were determined in each HRQL domain, ie, for the coping domain (p=0.0005), concern

domain ($p<0.0001$), sleep domain ($p=0.0164$), and social interaction domain ($p=0.0023$), and the HRQL total score ($p=0.0003$).

**Table 13. ANCOVA of Change From Baseline in Score of Each HRQL Domain of OAB-q and HRQL Total Score at Week 12 – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Coping domain | | | |
| n[a] | 347 | 701 | 677 |
| Baseline | | | |
| Mean (SD) | 37.18 (26.29) | 39.65 (26.73) | 37.81 (26.02) |
| Median (min, max) | 32.50 (0.00, 100.00) | 35.00 (0.00, 100.00) | 32.50 (0.00, 100.00) |
| Week 12 | | | |
| Mean (SD) | 59.09 (30.34) | 66.37 (27.87) | 69.84 (27.52) |
| Median (min, max) | 65.00 (0.00, 100.00) | 72.50 (0.00, 100.00) | 77.50 (0.00, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | 21.91 (28.95) | 26.72 (27.68) | 32.03 (29.38) |
| Median (min, max) | 15.00 (-50.00, 100.00) | 20.00 (-55.00, 100.00) | 30.00 (-35.00, 100.00) |
| LS Mean (SE) | 20.91 (1.55) | 26.69 (1.18) | 31.38 (1.19) |
| 95% CI for mean | (17.88, 23.95) | (24.38, 29.00) | (29.03, 33.72) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | 5.78 (1.66) | 10.46 (1.67) |
| 95% CI | - | (2.53, 9.03) | (7.20, 13.73) |
| p-value[c] | - | 0.0005 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS Mean difference (SE) | - | - | 4.68 (1.36) |
| 95% CI | - | - | (2.01, 7.36) |
| p-value[c] | - | - | 0.0006 |
| Concern domain | | | |
| n[a] | 347 | 701 | 677 |
| Baseline | | | |
| Mean (SD) | 40.01 (25.36) | 42.31 (26.29) | 40.85 (24.94) |
| Median (min, max) | 37.14 (0.00, 100.00) | 40.00 (0.00, 100.00) | 40.00 (0.00, 100.00) |
| Week 12 | | | |
| Mean (SD) | 61.57 (29.55) | 69.59 (26.96) | 72.80 (26.32) |
| Median (min, max) | 65.71 (0.00, 100.00) | 77.14 (0.00, 100.00) | 80.00 (0.00, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | 21.56 (27.83) | 27.28 (27.77) | 31.95 (29.12) |
| Median (min, max) | 17.14 (-54.29, 97.14) | 22.86 (-65.71, 100.00) | 28.57 (-45.71, 100.00) |
| LS Mean (SE) | 20.27 (1.51) | 26.82 (1.15) | 31.18 (1.16) |
| 95% CI for mean | (17.32, 23.22) | (24.57, 29.08) | (28.90, 33.47) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS Mean difference (SE) | - | 6.55 (1.61) | 10.91 (1.62) |
| 95% CI | - | (3.39, 9.72) | (7.73, 14.09) |
| p-value[c] | - | <0.0001 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS mean difference (SE) | - | - | 4.36 (1.33) |
| 95% CI | - | - | (1.76, 6.96) |
| p-value[c] | - | - | 0.0010 |
| Sleep domain | | | |
| n[a] | 347 | 701 | 677 |
| Baseline | | | |

## Table 13. ANCOVA of Change From Baseline in Score of Each HRQL Domain of OAB-q and HRQL Total Score at Week 12 – FAS

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Mean (SD) | 41.61 (26.54) | 43.62 (26.29) | 43.93 (27.48) |
| Median (min, max) | 36.00 (0.00, 100.00) | 40.00 (0.00, 100.00) | 40.00 (0.00, 100.00) |
| Week 12 | | | |
| Mean (SD) | 60.73 (28.94) | 66.05 (26.90) | 69.33 (26.61) |
| Median (min, max) | 64.00 (0.00, 100.00) | 72.00 (0.00, 100.00) | 76.00 (0.00, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | 19.11 (25.43) | 22.43 (26.50) | 25.41 (28.55) |
| Median (min, max) | 16.00 (-48.00, 92.00) | 20.00 (-76.00, 96.00) | 20.00 (-52.00, 100.00) |
| LS Mean (SE) | 18.25 (1.45) | 21.97 (1.10) | 25.71 (1.12) |
| 95% CI for mean | (15.42, 21.09) | (19.80, 24.14) | (23.51, 27.90), |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS mean difference (SE) | - | 3.72 (1.55) | 7.46 (1.56) |
| 95% CI | - | (0.68, 6.76) | (4.40, 10.51) |
| p-value[c] | - | 0.0164 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS mean difference (SE) | - | - | 3.74 (1.27) |
| 95% CI | - | - | (1.24, 6.23) |
| p-value[c] | - | - | 0.0034 |
| Social interaction domain | | | |
| n[a] | 347 | 701 | 677 |
| Baseline | | | |
| Mean (SD) | 64.75 (27.18) | 66.84 (27.36) | 64.54 (27.70) |
| Median (min, max) | 68.00 (0.00, 100.00) | 72.00 (0.00, 100.00) | 68.00 (0.00, 100.00) |
| Week 12 | | | |
| Mean (SD) | 78.25 (25.55) | 83.17 (21.72) | 85.61 (20.78) |
| Median (min, max) | 88.00 (0.00, 100.00) | 92.00 (0.00, 100.00) | 96.00 (0.00, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | 13.50 (24.68) | 16.33 (25.26) | 21.06 (25.24) |
| Median (min, max) | 8.00 (-60.00, 96.00) | 12.00 (-72.00, 100.00) | 16.00 (-44.00, 100.00) |
| LS Mean (SE) | 12.61 (1.17) | 16.43 (0.89) | 20.11 (0.90) |
| 95% CI for mean | (10.32, 14.90) | (14.68, 18.18) | (18.34, 21.88) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS mean difference (SE) | - | 3.82 (1.25) | 7.50 (1.26) |
| 95% CI | - | (1.36, 6.28) | (5.03, 9.97) |
| p-value[c] | - | 0.0023 | <0.0001 |
| Treatment difference vs. Fesoterodine 4 mg | | | |
| LS mean difference (SE) | - | - | 3.68 (1.03) |
| 95% CI | - | - | (1.65, 5.70) |
| p-value[c] | - | - | 0.0004 |
| HRQL total score | | | |
| n[a] | 347 | 701 | 677 |
| Baseline | | | |
| Mean (SD) | 44.37 (22.84) | 46.63 (23.30) | 45.23 (22.78) |
| Median (min, max) | 42.40 (0.00, 94.40) | 46.40 (0.00, 97.60) | 44.80 (0.00, 100.00) |
| Week 12 | | | |

**Table 13. ANCOVA of Change From Baseline in Score of Each HRQL Domain of OAB-q and HRQL Total Score at Week 12 – FAS**

| Value | Placebo | Fesoterodine 4 mg | Fesoterodine 8 mg |
|---|---|---|---|
| Mean (SD) | 63.94 (26.54) | 70.57 (23.99) | 73.72 (23.54) |
| Median (min, max) | 68.00 (0.00, 100.00) | 76.00 (0.00, 100.00) | 80.80 (2.40, 100.00) |
| Numerical change from Baseline to Week 12 | | | |
| Mean (SD) | 19.57 (24.50) | 23.94 (24.42) | 28.49 (25.49) |
| Median (min, max) | 15.20 (-44.80, 92.00) | 19.20 (-60.00, 96.80) | 26.40 (-33.60, 98.40) |
| LS Mean (SE) | 18.57 (1.33) | 23.70 (1.02) | 27.94 (1.03) |
| 95% CI for mean | (15.96, 21.17) | (21.71, 25.70) | 25.92, 29.95) |
| p-value[b] | <0.0001 | <0.0001 | <0.0001 |
| Treatment difference vs. placebo | | | |
| LS mean difference (SE) | - | 5.14 (1.43) | 9.37 (1.43) |
| 95% CI | - | (2.34, 7.94) | (6.56, 12.18) |
| p-value[c] | - | 0.0003 | <0.0001 |
| Treatment difference vs. fesoterodine 4 mg | | | |
| LS mean difference (SE) | - | - | 4.23 (1.17) |
| 95% CI | - | - | (1.93, 6.53) |
| p-value[c] | - | - | 0.0003 |

ANCOVA = Analysis of covariance; BL = baseline; CI = confidence interval; FAS = Full analysis set; HRQL = Health-Related Quality of Life; LS = least squares; max = maximum; min = minimum; N/n = number; OAB-q = Overactive Bladder Questionnaire; SD = standard deviation; SE = standard error; vs = versus.

a. Number of non-missing values for change from Baseline to Week 12.
b. p-value based on paired t-test comparing Baseline with post-baseline values.
c. Based on an ANCOVA model with terms for treatment, pooled country, centered baseline value and centered baseline by treatment interaction.

**Safety Results:** A summary of the incidences of all causality treatment emergent AEs (TEAEs) reported by ≥1% of subjects in any treatment group is presented in Table 14.

**Table 14: Incidence of Treatment-Emergent Adverse Events (All Causalities) in ≥1% of Subjects in Any Treatment Group – Safety Analysis Set**

| Number (%) of Subjects With Adverse Events by System Organ Class MedDRA Preferred Term | Placebo N=386 | Fesoterodine 4 mg N=790 | Fesoterodine 8 mg N=779 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Total preferred term events | 184 (47.7) | 481 (60.9) | 609 (78.2) |
| Eye disorders | 5 (1.3) | 14 (1.8) | 19 (2.4) |
| Dry eye | 3 (0.8) | 8 (1.0) | 10 (1.3) |
| Gastrointestinal disorders | 33 (8.5) | 141 (17.8) | 241 (30.9) |
| Constipation | 7 (1.8) | 12 (1.5) | 31 (4.0) |
| Diarrhea | 4 (1.0) | 13 (1.6) | 5 (0.6) |
| Dry mouth | 13 (3.4) | 102 (12.9) | 203 (26.1) |
| Dyspepsia | 0 | 8 (1.0) | 10 (1.3) |
| Nausea | 3 (0.8) | 11 (1.4) | 10 (1.3) |
| General disorders and administration site conditions | 10 (2.6) | 13 (1.6) | 15 (1.9) |
| Fatigue | 4 (1.0) | 7 (0.9) | 7 (0.9) |
| Infections and infestations | 45 (11.7) | 85 (10.8) | 80 (10.3) |
| Bronchitis | 4 (1.0) | 7 (0.9) | 5 (0.6) |
| Nasopharyngitis | 18 (4.7) | 24 (3.0) | 17 (2.2) |
| Urinary tract infection | 5 (1.3) | 16 (2.0) | 17 (2.2) |
| Injury, poisoning and procedural complications | 5 (1.3) | 14 (1.8) | 10 (1.3) |
| Metabolism and nutrition disorders | 4 (1.0) | 4 (0.5) | 10 (1.3) |
| Musculoskeletal and connective tissue disorders | 11 (2.8) | 29 (3.7) | 18 (2.3) |
| Back pain | 1 (0.3) | 9 (1.1) | 8 (1.0) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 4 (1.0) | 2 (0.3) | 3 (0.4) |
| Nervous system disorders | 6 (1.6) | 33 (4.2) | 24 (3.1) |
| Dizziness | 1 (0.3) | 10 (1.3) | 2 (0.3) |
| Headache | 2 (0.5) | 8 (1.0) | 12 (1.5) |
| Psychiatric disorders | 3 (0.8) | 5 (0.6) | 11 (1.4) |
| Renal and urinary disorders | 10 (2.6) | 10 (1.3) | 18 (2.3) |
| Respiratory, thoracic and mediastinal disorders | 6 (1.6) | 19 (2.4) | 23 (3.0) |
| Skin and subcutaneous tissue disorders | 5 (1.3) | 15 (1.9) | 19 (2.4) |
| Surgical and medical procedures | 4 (1.0) | 3 (0.4) | 0 |
| Vascular disorders | 4 (1.0) | 8 (1.0) | 5 (0.6) |

SAE and AE results are not separated out in this table.
MedDRA version 15.1 coding dictionary applied.
AE = adverse event; N, n=number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Dry mouth was the most commonly reported all causality TEAE preferred term and the incidence increased with fesoterodine dose strength, reported by 26.1% (203 subjects) of the subjects in the fesoterodine 8 mg group, 12.9% (102 subjects) in the fesoterodine 4 mg group, and 3.4% (13 subjects) in the placebo group. Almost all of these events were considered by the Investigator to be related to treatment, for 25.8% (201 subjects) of the subjects in the fesoterodine 8 mg group, 12.7% (100 subjects) in the fesoterodine 4 mg group, and 3.1% (12 subjects) in the placebo group (Table 15).

**Table 15. Incidence of Treatment-Emergent Adverse Events (Treatment Related) in ≥1% of Subjects in Any Treatment Group – Safety Analysis Set**

| Number (%) of Subjects With Adverse Events by System Organ Class<br>MedDRA Preferred Term | Placebo N=386<br>n (%) | Fesoterodine 4 mg N=790<br>n (%) | Fesoterodine 8 mg N=779<br>n (%) |
|---|---|---|---|
| Total preferred term events | 57 (14.8) | 213 (27.0) | 380 (48.8) |
| Eye disorders | 4 (1.0) | 11 (1.4) | 15 (1.9) |
| Dry eye | 3 (0.8) | 8 (1.0) | 9 (1.2) |
| Gastrointestinal disorders | 22 (5.7) | 116 (14.7) | 224 (28.8) |
| Constipation | 6 (1.6) | 11 (1.4) | 30 (3.9) |
| Dry mouth | 12 (3.1) | 100 (12.7) | 201 (25.8) |
| General disorders and administration site conditions | 6 (1.6) | 7 (0.9) | 11 (1.4) |
| Infections and infestations | 3 (0.8) | 4 (0.5) | 9 (1.2) |
| Nervous system disorders | 1 (0.3) | 20 (2.5) | 12 (1.5) |
| Renal and urinary disorders | 4 (1.0) | 5 (0.6) | 10 (1.3) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.3) | 7 (0.9) | 15 (1.9) |
| Skin and subcutaneous tissue disorders | 3 (0.8) | 7 (0.9) | 10 (1.3) |

SAE and AE results are not separated out in this table.
MedDRA version 15.1 coding dictionary applied.
AE = adverse event; N, n=number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

A summary of SAEs is provided in Table 16.

## Table 16. Serious Adverse Events

| Serial Number | MedDRA Preferred Term | Therapy Stop Day[a] | Event Onset Day/ Stop Day[b,c] | Action Taken (Drug Level) | Causality Investigator/ Sponsor | Outcome | Seriousness |
|---|---|---|---|---|---|---|---|
| **Placebo** | | | | | | | |
| 1 | Back pain | 83 | 72/84 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved with sequel | Hospitalization |
| 2 | Staphylococcal abscess | 85 | 48/58 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved with sequel | Hospitalization |
| 3 | Labyrinthitis | 8 | 5/34 | Temporarily withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 4 | Hemorrhoids | 92 | 5/NA | Dose not changed | Unrelated/ Unrelated | Recovering/ Resolving | Hospitalization |
| 5 | Breast cancer | 85 | 63/NA | Dose not changed | Unrelated/ Unrelated | Not recovered/ Not resolving | Important medical event |
| 6 | Wound | 85 | 60/60 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 7 | Lower limb fracture | 40 | 41/NA | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved with sequel | Hospitalization |
| 8 | Pancreatitis acute | 27 | 27/31 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 9 | Pleural effusion | 92 | 18/19 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 10 | Breast cancer | 80 | 31/NA | Dose not changed | Unrelated/ Unrelated | Unknown | Hospitalization |
| 11 | Atrial fibrillation | 74 | 81/86 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| **Fesoterodine 4 mg** | | | | | | | |
| 1 | Post procedural hemorrhage | 98 | 20/27 | Temporarily withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 2 | Cerebrovascular accident | 38 | 72/92 | Post-therapy | Unrelated/ Unrelated | Recovered/ Resolved with sequel | Hospitalization Important medical event |
| 3 | Appendicitis | 89 | 11/14 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 4 | Peripheral artery thrombosis | 86 | 9/11 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization Important medical event |
| 5 | Ulcerative keratitis | 84 | 29/NA | Dose not changed | Unrelated/ Unrelated | Recovering/ Resolving | Hospitalization |
| | Herpes simplex ophthalmic | 84 | 29/NA | Dose not changed | Unrelated/ Unrelated | Recovering/ Resolving | Hospitalization |
| 6 | Myocardial infarction | 62 | 24/24 | Post-therapy | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization Important medical event |
| 7 | Pelvic inflammatory disease | 84 | 76/77 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| | Uterine hemorrhage | 84 | 76/77 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 8 | Benign ovarian | 16 | 3/17 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |

## Table 16. Serious Adverse Events

| Serial Number | MedDRA Preferred Term | Therapy Stop Day[a] | Event Onset Day/ Stop Day[b,c] | Action Taken (Drug Level) | Causality Investigator/ Sponsor | Outcome | Seriousness |
|---|---|---|---|---|---|---|---|
| | tumor | | | | | | |
| 9 | Viral infection | 61 | 53/86 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 10 | Pulmonary embolism | 85 | 94/100 | Post-therapy | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 11 | Dehydration | 85 | 62/65 | Temporarily withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| | Syncope | 85 | 66/69 | Temporarily withdrawn | Related/ Unrelated | Recovered/ Resolved | Hospitalization |
| 12 | Chest pain | 29 | 14/14 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| Fesoterodine 8 mg | | | | | | | |
| 1 | Pancreatitis | 41 | 41/51 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 2 | Pulmonary embolism | 1 | 2/NA | Unknown | Unrelated/ Unrelated | Fatal | Fatal |
| | Hypertensive heart disease | 1 | NA/NA | Unknown | Unrelated/ Unrelated | Fatal | Fatal |
| 3 | Breast cancer | 85 | 86/NA | Post-therapy | Unrelated/ Unrelated | Not recovered/ Not resolved | Important medical event |
| 4 | Colon cancer | 19 | 23/NA | Permanently withdrawn | Unrelated/ Unrelated | Not recovered/ Not resolved | Hospitalization |
| 5 | Gastrointestinal carcinoma | 31 | 9/72 | Permanently withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Important medical event |
| 6 | Peripheral ischemia | 79 | 55/57 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 7 | Dermatitis allergic | 91 | 25/48 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 8 | Chronic obstructive pulmonary disease | 114 | 118/NA | Post-therapy | Unrelated/ Unrelated | Recovering/ Resolving | Hospitalization |
| | Chronic obstructive pulmonary disease | 114 | 32/35 | Dose not changed | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| | Pneumonia | 114 | 73/83 | Post-therapy | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 9 | Atrial fibrillation | 102 | 16/26 | Temporarily withdrawn | Unrelated/ Unrelated | Recovered/ Resolved | Hospitalization |
| 10 | Pyelonephritis | 57 | 57/NA | Permanently withdrawn | Unrelated/ Unrelated | Recovering/ Resolving | Hospitalization |
| 11 | Colitis ischemic | 14 | 45/51 | Permanently withdrawn | Related/ Unrelated | Recovered/ Resolved | Hospitalization |
| 12 | Prostate cancer | 95 | -14/NA | Not applicable | Unrelated/ Unrelated | Unknown | Important medical event |
| 13 | Bladder cancer | 84 | 88/NA | Post-therapy | Unrelated/ Unrelated | Fatal | Hospitalization Important medical event |

MedDRA (v15.1) coding dictionary applied.
ID = Identification; MedDRA = Medical Dictionary for Regulatory Activities; NA = not available or not applicable;

**Table 16. Serious Adverse Events**

| Serial Number | MedDRA Preferred Term | Therapy Stop Day[a] | Event Onset Day/ Stop Day[b,c] | Action Taken (Drug Level) | Causality Investigator/ Sponsor | Outcome | Seriousness |
|---|---|---|---|---|---|---|---|

OC = Oracle Clinical; SAE = Serious Adverse Event; SDW = safety data warehouse.
a. Therapy stop day was calculated as OC last active therapy date minus OC first active therapy date plus one.
b. Onset study day was calculated as SDW onset date minus OC first active therapy date plus one.
c. Event stop day was calculated as SDW SAE stop date minus OC first active therapy date plus one.

Two of all serious adverse events (SAEs) reported in the study (including post-therapy period), colitis ischemic in the fesoterodine 8 mg and syncope in the fesoterodine 4 mg group, were considered by the investigators to be related to treatment (Table 16). None of these SAEs was considered by the sponsor to be related to study medication; both SAEs were resolved.

Discontinuations: The number of subjects who had their dose reduced or temporarily discontinued due to all-causality TEAEs was 13 (1.7%) subjects in the fesoterodine 8 mg group, 9 (1.1%) subjects in the fesoterodine 4 mg group, and 4 (1.0%) subjects in the placebo group. Treatment-emergent AEs for which study drug was stopped temporarily and considered serious by the investigator occurred in 2 subjects (pneumonia and atrial fibrillation) in the fesoterodine 8 mg group, 4 subjects (post procedural hemorrhage, Herpes simplex ophthalmic, dehydration and syncope) in the fesoterodine 4 mg group, and 1 subject (labyrinthitis) in the placebo group.

Considering TEAE that occurred in ≥2 subjects in any treatment group, dry mouth was the most common treatment-emergent incident, leading to discontinuation of 18 (2.3%) subjects in the fesoterodine 8 mg group, 2 (0.3%) subjects in the fesoterodine 4 mg group, but no subjects in the placebo group.

Further TEAE leading to discontinuation (≥2 subjects) in each treatment group included:

- Fesoterodine 8 mg: nausea (2 subjects; 0.3%), fatigue (2 subjects; 0.3%), abdominal distension (2 subjects; 0.3%), constipation (2 subjects; 0.3%), colon cancer (2 subjects; 0.3%), and headache (2 subjects; 0.3%);
- Fesoterodine 4 mg: dry eye (3 subjects; 0.4%), vertigo (2 subjects; 0.3%), constipation (2 subjects; 0.3%);
- Placebo: rash (2 subjects; 0.3%).

Almost all of these TEAEs leading to discontinuation were considered by the investigator to be treatment-related, except colon cancer in 2 subjects of the fesoterodine 8 mg group and rash in 1 subject of the placebo group Table 17.

## Table 17. Summary of Withdrawals Due to Adverse Events – Safety Analysis Set

| Number (%) of Subjects With Adverse Events by System Organ Class<br>MedDRA Preferred Term | Placebo N=386<br>n (%) | Fesoterodine 4 mg N=790<br>n (%) | Fesoterodine 8 mg N=779<br>n (%) |
|---|---|---|---|
| Cardiac disorders | 1 (0.3) | 1 (0.1) | 0 |
| Atrial fibrillation | 1 (0.3) | 0 | 0 |
| Myocardial infarction | 0 | 1 (0.1) | 0 |
| Ear and labyrinth disorders | 0 | 2 (0.3) | 1 (0.1) |
| Vertigo | 0 | 2 (0.3) | 1 (0.1) |
| Eye disorders | 1 (0.3) | 4 (0.5) | 0 |
| Dry eye | 1 (0.3) | 4 (0.5) | 0 |
| Gastrointestinal disorders | 2 (0.5) | 7 (0.9) | 27 (3.5) |
| Abdominal discomfort | 1 (0.3) | 0 | 0 |
| Abdominal distension | 0 | 0 | 2 (0.3) |
| Abdominal pain | 0 | 1 (0.1) | 1 (0.1) |
| Colitis ischemic | 0 | 0 | 1 (0.1) |
| Constipation | 0 | 2 (0.3) | 2 (0.3) |
| Diarrhea | 0 | 1 (0.1) | 0 |
| Dry mouth | 0 | 2 (0.3) | 18 (2.3) |
| Dyspepsia | 0 | 0 | 1 (0.1) |
| Gastroesophageal reflux disease | 0 | 1 (0.1) | 0 |
| Nausea | 0 | 1 (0.1) | 3 (0.4) |
| Palatal edema | 0 | 0 | 1 (0.1) |
| Pancreatitis | 0 | 0 | 1 (0.1) |
| Pancreatitis acute | 1 (0.3) | 0 | 0 |
| General disorders and administration site conditions | 2 (0.5) | 1 (0.1) | 4 (0.5) |
| Chest pain | 0 | 1 (0.1) | 0 |
| Chills | 1 (0.3) | 0 | 0 |
| Fatigue | 0 | 0 | 3 (0.4) |
| Edema | 0 | 0 | 1 (0.1) |
| Suprapubic pain | 1 (0.3) | 0 | 0 |
| Immune system disorders | 0 | 0 | 2 (0.3) |
| Allergic edema | 0 | 0 | 1 (0.1) |
| Hypersensitivity | 0 | 0 | 1 (0.1) |
| Infections and infestations | 0 | 3 (0.4) | 3 (0.4) |
| Bacteriuria | 0 | 1 (0.1) | 0 |
| Lower respiratory tract infection | 0 | 0 | 1 (0.1) |
| Pyelonephritis | 0 | 0 | 1 (0.1) |
| Urinary tract infection | 0 | 1 (0.1) | 1 (0.1) |
| Viral infection | 0 | 1 (0.1) | 0 |
| Injury, poisoning and procedural complications | 1 (0.3) | 0 | 1 (0.1) |
| Epicondylitis | 0 | 0 | 1 (0.1) |
| Lower limb fracture | 1 (0.3) | 0 | 0 |
| Investigations | 0 | 0 | 1 (0.1) |
| Weight increased | 0 | 0 | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 2 (0.5) | 4 (0.5) | 1 (0.1) |
| Arthralgia | 0 | 1 (0.1) | 0 |
| Back pain | 1 (0.3) | 1 (0.1) | 1 (0.1) |
| Intervertebral disc protrusion | 1 (0.3) | 0 | 0 |
| Joint swelling | 0 | 1 (0.1) | 0 |
| Pain in extremity | 0 | 1 (0.1) | 0 |

**Table 17. Summary of Withdrawals Due to Adverse Events – Safety Analysis Set**

| Number (%) of Subjects With Adverse Events by System Organ Class<br>MedDRA Preferred Term | Placebo N=386<br>n (%) | Fesoterodine 4 mg N=790<br>n (%) | Fesoterodine 8 mg N=779<br>n (%) |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (inclusive cysts and polyps) | 0 | 0 | 2 (0.3) |
| Colon cancer | 0 | 0 | 2 (0.3) |
| Nervous system disorders | 1 (0.3) | 2 (0.3) | 3 (0.4) |
| Headache | 0 | 1 (0.1) | 2 (0.3) |
| Hypoesthesia | 1 (0.3) | 0 | 0 |
| Somnolence | 0 | 1 (0.1) | 1 (0.1) |
| Psychiatric disorders | 0 | 1 (0.1) | 1 (0.1) |
| Aggression | 0 | 1 (0.1) | 0 |
| Sleep disorder | 0 | 0 | 1 (0.1) |
| Renal and urinary disorders | 2 (0.5) | 2 (0.3) | 2 (0.3) |
| Bladder pain | 1 (0.3) | 0 | 0 |
| Bladder prolapse | 0 | 1 (0.1) | 0 |
| Dysuria | 1 (0.3) | 0 | 1 (0.1) |
| Micturition urgency | 1 (0.3) | 0 | 0 |
| Nephrolithiasis | 0 | 0 | 1 (0.1) |
| Pollakiuria | 1 (0.3) | 0 | 0 |
| Urinary retention | 0 | 1 (0.1) | 0 |
| Respiratory, thoracic and mediastinal disorders | 1 (0.3) | 1 (0.1) | 3 (0.4) |
| Nasal dryness | 0 | 0 | 1 (0.1) |
| Oropharyngeal pain | 0 | 1 (0.1) | 1 (0.1) |
| Pharyngeal edema | 0 | 0 | 1 (0.1) |
| Throat irritation | 1 (0.3) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 3 (0.8) | 0 | 1 (0.1) |
| Dermatitis | 1 (0.3) | 0 | 0 |
| Pruritus | 0 | 0 | 1 (0.1) |
| Rash | 2 (0.5) | 0 | 0 |
| Vascular disorders | 0 | 0 | 1 (0.1) |
| Hypertension | 0 | 0 | 1 (0.1) |

MedDRA (v15.1) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Deaths: A total of 2 subjects, both in the fesoterodine 8 mg group, died. One subject died due to hypertensive heart disease and pulmonary embolism on Day 13. The Investigator and Sponsor considered this death to be unrelated to treatment with the study drug. A second subject died during the post-therapy phase due to bladder cancer on Day 241. The Investigator and Sponsor considered this death to be unrelated to treatment with the study drug.

**CONCLUSIONS:**

- The primary objective of this study was achieved, which demonstrated the superior efficacy of 8 mg over 4 mg fesoterodine on UUI episode reduction in subjects with OAB. The study demonstrated statistical significance in UUI episode reduction from Baseline to Week 12 for the treatment difference between fesoterodine 8 mg (LS mean change:

-3.12 episodes) and fesoterodine 4 mg (LS mean change: -2.85 episodes) or placebo (LS mean change: -2.22 episodes).

- The fesoterodine 8 mg group also showed statistically significant improvements to fesoterodine 4 mg and placebo for change from Baseline to Weeks 12 and 4 in the mean number of micturition and micturition-related urgency episodes.

- At Week 12, the Diary Dry Rate (the proportion of subjects with UUI=0) in the fesoterodine 8 mg group was statistically significantly superior to the rate in the fesoterodine 4 mg group or placebo.

- Statistically significant improvements in change from Baseline to Week 12 in PPBC, UPS, OAB-q symptom bother score, total and each domain of the HRQL scale were observed in the fesoterodine 8 mg group compared to fesoterodine 4 mg and placebo. The clinical relevance of the outcome is supported by the differences noted in the validated PRO.

- The safety and tolerability profile of fesoterodine was consistent with the known profile for antimuscarinic products. No new safety concern was identified and the most common AEs were dry mouth and constipation.