BJUI
BJU INTERNATIONAL

Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial

Steven A. Kaplan, Tim Schneider*, Jenelle E. Foote†, Zhonghong Guan‡, Martin Carlsson‡ and Jason Gong‡, on behalf of the Second Fesoterodine Assessment and Comparison versus Tolterodine (FACT 2) Study Group

*Department of Urology, Weill Cornell Medical College, Cornell University, and ‡Pfizer Inc., New York, NY, USA, †Midtown Urology & Midtown Urology Surgical Center, Atlanta, GA, USA, and *Praxisklinik Urologie Rhein/Ruhr, Mülheim, Germany*

Accepted for publication 18 June 2010

Study Type – Therapy (RCT)
Level of Evidence 1b

What's known on the subject? and What does the study add?
A previous trial found greater efficacy with the maximum available dose of fesoterodine 8 mg compared with the maximum available dose of tolterodine ER 4 mg and placebo for improving overactive bladder symptoms, and patient-reported outcomes were demonstrated by a recent placebo-controlled, head-to-head trial.

The results of this trial, the largest to date to compare antimuscarinic efficacy, confirms the superior efficacy of fesoterodine 8 mg over tolterodine ER 4 mg for the treatment of OAB symptoms, and further emphasize the clinical advantage of the availability of an additional 8-mg dose over single-dose tolterodine ER 4 mg.

OBJECTIVE

- To show the superior efficacy of fesoterodine over tolterodine extended release (ER) in a placebo-controlled overactive bladder (OAB) trial with predefined treatment comparisons for both diary measures and patient-reported outcomes.

MATERIALS AND METHODS

- In this 12-week, double-blind, double-dummy trial, subjects reporting >1 urgency urinary incontinence (UUI) episode and ≥8 micturitions per 24 h at baseline were randomized to fesoterodine (4 mg for 1 week, 8 mg for 11 weeks), tolterodine ER 4 mg, or placebo.
- Subjects completed 3-day bladder diaries, the Patient Perception of Bladder Condition (PPBC) and the Urgency Perception Scale (UPS) at baseline and weeks 1, 4 and 12 and the OAB Questionnaire at baseline and week 12.

RESULTS

- A total of 2417 subjects were randomized. At week 12, fesoterodine 8 mg showed superiority over tolterodine ER 4 mg and placebo on UUI episodes (primary endpoint), micturitions, urgency and most other diary endpoints, and on the PPBC, UPS and all OAB Questionnaire scales and domains (all $P < 0.05$).
- Superiority of fesoterodine 8 mg over tolterodine ER 4 mg was seen as early as week 4 (3 weeks after escalation to fesoterodine 8 mg). At week 1, fesoterodine 4 mg was superior to placebo on most diary variables, the PPBC and the UPS (all $P < 0.05$). Dry mouth and constipation rates were 28% and 4% with fesoterodine, 13% and 3% with tolterodine ER, and 5% and 2% with placebo.
- Discontinuation rates as a result of adverse events were 5%, 3% and 2% for fesoterodine, tolterodine ER and placebo, respectively.

CONCLUSIONS

- In this randomized study, which is the largest to compare antimuscarinic efficacy performed to date, fesoterodine 8 mg was superior to tolterodine ER 4 mg for UUI episodes, micturitions and urgency episodes, as well as for self-reported patient assessments of bladder-related problems, urgency, symptom bother and health-related quality of life.
- The superiority of fesoterodine 8 mg over tolterodine ER 4 mg was observed as early as 3 weeks after escalation from fesoterodine 4 mg for most outcomes. These data may have important implications for the clinical management of OAB patients previously treated with tolterodine ER.

KEYWORDS

antimuscarinic, fesoterodine, tolterodine, head-to-head, efficacy, quality of life

INTRODUCTION

With the emergence of comparative effectiveness research as a driver of healthcare policy and reform, there is currently an emphasis on establishing the clinical value of one treatment over another [1]. A number of randomized, double-blind, placebo-controlled trials have compared the efficacy of antimuscarinics for the treatment of overactive bladder (OAB) symptoms [2–9]. The International Conference on Harmonisation Good Clinical Practice guidelines recommend the superiority design for comparisons between active treatments and with placebo [10]. However, most trials of antimuscarinic efficacy have been designed for comparison with placebo only; trials designed to compare the clinical efficacy of two antimuscarinics have either been based on a non-inferiority design or have lacked a placebo arm. Additionally, no placebo-controlled trials to date have reported predefined comparisons in both diary-based and patient-reported outcomes (PROs) measures.

Fesoterodine is an antimuscarinic agent that is rapidly and extensively converted by ubiquitous esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT); fesoterodine is not detectable in plasma after oral dosing, and all antimuscarinic effects are attributable to 5-HMT [11]. Tolterodine is also converted to 5-HMT, although this occurs primarily in the liver via cytochrome P450 2D6. A significant fraction of unconverted tolterodine is found in plasma, and both tolterodine and 5-HMT contribute to antimuscarinic effects [11]. After oral administration of tolterodine, there is considerable variability in the pharmacokinetic properties of 5-HMT and tolterodine between individuals with different cytochrome P450 2D6 phenotypes [12]. There is much less variability in 5-HMT pharmacokinetics after oral administration of fesoterodine [13].

By contrast to tolterodine extended release (ER), for which 4 mg is the one approved dose for treatment in the general population of patients with OAB [14], fesoterodine is available in both 4 and 8 mg once-daily doses [15,16]. Notably, a *post hoc* analysis of a placebo-controlled phase III trial of fesoterodine that included tolterodine ER as an active control [17] showed significantly greater improvements in urgency urinary incontinence (UUI) episodes and mean voided volume (MVV) per micturition with fesoterodine 8 mg compared to tolterodine ER 4 mg [18]. Consistent with these findings, a recent placebo-controlled, head-to-head trial showed that reductions in UUI episodes at 12 weeks (the primary endpoint) and increases in MVV per micturition and 3-day diary-dry rate (proportion of subjects with >0 UUI episodes on baseline bladder diaries who reported 0 UUI episodes at week 12; *post hoc* analysis) were significantly greater in subjects treated with fesoterodine 8 mg than in subjects treated with tolterodine ER 4 mg [9]. Subjects receiving fesoterodine 8 mg also had significantly greater improvements on the Patient-Perception of Bladder Condition (PPBC), Urgency Perception Sale (UPS) and the Overactive Bladder questionnaire (OAB-q) compared to subjects receiving tolterodine ER 4 mg (all *post hoc* analyses) [9].

The present study, which is the largest placebo-controlled, randomized, head-to-head antimuscarinic study peformed to date, is the second study to prospectively assess the superiority of the maximum available dose of fesoterodine (8 mg) over the maximum available dose of tolterodine ER (4 mg). Notably, all comparisons of diary-based endpoints and PROs in the present study were predefined, and this is the first placebo-controlled study for which the time course of the superiority of one antimuscarinic over another has been reported.

MATERIALS AND METHODS

STUDY DESIGN

This was a 12-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group, trial with a 2-week single-blind placebo run-in period, conducted at 210 centres in North America, South America, Europe, Asia and Africa between February 2008 and October 2009 (ClinicalTrials.gov Unique ID NCT00611026). Eligible subjects were randomized to fesoterodine, tolterodine ER or placebo in a 2 : 2 : 1 ratio. A randomization schedule with a block size of five was implemented, which was generated, secured, distributed and stored by Pfizer Global Clinical Data Services. The trial was approved by the appropriate Institutional Review Boards and Independent Ethics Committees and conducted in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable local regulatory requirements and laws. All subjects provided their written informed consent.

The United States and European fesoterodine product labels recommend a starting dose of fesoterodine of 4 mg once daily, which may be increased to 8 mg once daily based on individual response and tolerability [15,16]. In the present study, all subjects in the fesoterodine group received fesoterodine 4 mg for the first week followed by fesoterodine 8 mg for the next 11 weeks. All subjects in the tolterodine ER group received tolterodine ER 4 mg for all 12 weeks. Throughout the study, all subjects were instructed to take one tablet (fesoterodine 4 or 8 mg, or matching placebo) and one capsule (tolterodine ER 4 mg, or matching placebo) daily in the morning.

SUBJECTS

Eligible men and women (≥18 years) self-reported OAB symptoms for ≥3 months and had a mean of at least one UUI episode and ≥8 micturitions per 24 h in 3-day bladder diaries at baseline. Key exclusion criteria were: clinically significant hepatic or renal disease; voiding dysfunction attributable to lower genitourinary pathology or surgical treatment; neurological conditions (stroke, multiple sclerosis, spinal cord injury or Parkinson's disease); history of acute urinary retention requiring catheterization; symptoms of incontinence being predominately stress urinary incontinence in the opinion of the investigator; antimuscarinic treatment within 2 weeks before screening or electrostimulation, bladder training or pelvic floor exercises within 4 weeks of screening. Also excluded were female subjects who were pregnant, nursing or of childbearing potential, and who were heterosexually active without using adequate contraception measures.

OUTCOME MEASURES

Subjects completed 3-day diaries at baseline and weeks 1, 4 and 12; endpoints were changes from baseline in UUI episodes, micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes and frequency–urgency sum per 24 h, 3-day diary-dry rate and MVV per micturition. The primary endpoint was change in UUI episodes from baseline to week 12. Urgency episodes and severe urgency episodes were those rated ≥3 and ≥4, respectively, on the five-point

Urinary Sensation Scale (1 = no urgency, 5 = UUI) [19]. The frequency–urgency sum was defined as the sum of Urinary Sensation Scale ratings associated with all micturitions over the course of 24 h averaged over the diary period. Three-day diary-dry rate was defined as the proportion of subjects with >0 UUI episodes on baseline bladder diaries who reported 0 UUI episodes on post-baseline diary. Subjects also completed the PPBC [20] and UPS [21] at baseline and weeks 1, 4 and 12, and the OAB-q [22] at baseline and week 12.

STATISTICAL ANALYSIS

On the basis of a previously observed mean (SD) difference of 0.44 (2.36) between fesoterodine 8 mg and tolterodine ER 4 mg groups for changes in UUI episodes per 24 h from baseline to week 12 [17], 606 subjects per active treatment group were required for 90% power for comparisons at the 5% significance level. On the basis of the previously observed mean (SD) differences of 1.07 (2.85) between fesoterodine 8 mg and placebo groups and 0.63 (2.81) between tolterodine ER 4 mg and placebo groups [17], 303 subjects were required in the placebo group for ≥88% power for each comparison. Thus, 1515 subjects were required; assuming that 90% of randomized subjects would contribute to the full analysis set (FAS), it was originally planned to randomize 1675 subjects.

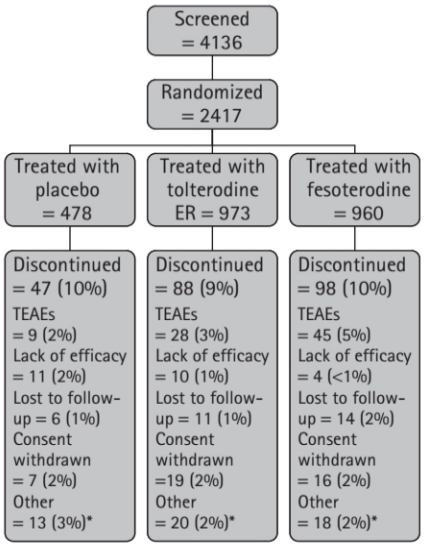
On the basis of the results of the first head-to-head trial of fesoterodine 8 mg vs tolterodine ER 4 mg [9], it was determined that non-parametric methods may be required for statistical analysis of some endpoints in the present study. A blinded sample size re-estimation was performed in January 2009 to calculate the conditional power of the present study based on the originally planned sample size of 1675 randomized subjects. The study was judged to be underpowered (68%) for non-parametric analysis as conducted in the previous study. To increase the power to 80%, the sample sizes were increased to 820, 820 and 410 subjects in the fesoterodine, tolterodine ER and placebo groups, respectively (total n = 2050). It was assumed that 95% of the randomized subjects would contribute to the FAS [9]; thus, at least 2160 randomized subjects were required.

Tolerability findings were assessed descriptively using the safety analysis set, which included all subjects who took one or more dose of double-blind study drug. Efficacy analyses were initially planned using the FAS, which included all subjects who took one or more dose of double-blind study drug and had at least one valid post-baseline efficacy assessment. Significant Good Clinical Practice violations and data irregularities were identified in theee study sites during a quality assurance audit conducted by the sponsor, during the study. All 77 subjects from these three sites were excluded from the FAS, although these subjects were included in the safety analysis set. This decision was documented in an amended statistical analysis plan and finalized before database unblinding. Sensitivity analyses of changes from baseline to week 12 for the primary endpoint (UUI episodes) and three secondary endpoints (MVV, micturitions per 24 h, and urgency episodes per 24 h) were conducted based on a supporting FAS that included the 77 subjects from these three sites. The sensitivity analyses showed that the results obtained for the primary and selected secondary endpoints based on the supporting FAS were consistent with those obtained based on the FAS.

All comparisons reported in the present study were prespecified. Treatment differences in the primary endpoint (changes in UUI episodes per 24 h from baseline to week 12) and all secondary endpoints were assessed using a closed testing procedure: the fesoterodine group was first compared with placebo and then with the tolterodine ER group if the difference vs placebo was significant. The tolterodine ER group was also compared with placebo. Numeric and percentage changes from baseline for each diary endpoint were considered in separate hierarchical order to preserve the α-level of 5% within each diary endpoint. Numeric changes were tested first, and percentage changes were tested only if the difference in numeric change was statistically significant.

The statistical analysis plan specified testing whether diary data met normality assumptions [23]. It was found that changes in UUI episodes, MVV and severe urgency episodes violated normality assumptions. Thus, changes in these variables were assessed using the non-parametric Van Elteren's test, a stratified Wilcoxon–Mann–Whitney test [24]. Changes in these variables are presented as Winsorized means, comprising a robust estimator of the sample mean that is calculated by replacing 5% of the sample distribution tails with values at the 5th and 95th percentiles, respectively. Changes in other diary endpoints and OAB-q scores were assessed using analysis of covariance (ANCOVA), with baseline value as a covariate and treatment and country as factors. Percentage changes from baseline in bladder diary endpoints were analyzed using ranked ANCOVA with terms for country, treatment and ranked baseline value as covariate. The Cochran–Mantel–Haenszel test stratified by country was used to assess treatment differences in 3-day diary-dry rate, four category changes in PPBC scores (≥2-point improvement, 1-point improvement, no change, deterioration), and three category changes in UPS scores (improvement, no change, deterioration).

*FIG. 1. Subject disposition. TEAEs, treatment-emergent adverse events (any causality). *Includes protocol violation, not meeting entrance criteria, and other reasons.*



RESULTS

SUBJECTS

Among 2417 subjects who were randomized, 2411 subjects received one or more dose of study medication (Fig. 1); 47 (10%), 88 (9%) and 98 (10%) subjects in the placebo,

TABLE 1 Baseline demographic and clinical characteristics

Characteristic	Placebo ($n = 478$)	Tolterodine ER 4 mg ($n = 973$)	Fesoterodine 8 mg ($n = 960$)
Women, *n* (%)	410 (86)	818 (84)	816 (85)
Age (years)			
Mean (SD)	59.5 (13.2)	58.1 (13.8)	57.9 (13.5)
Range	18.0–89.0	18.0–89.0	18.0–90.0
Race, *n* (%)			
White	384 (80)	758 (78)	744 (78)
Asian	47 (10)	99 (10)	101 (11)
Black	20 (4)	53 (5)	55 (6)
Other	27 (6)	63 (7)	60 (6)
OAB duration (years)			
Mean (SD)	6.3 (7.2)	6.5 (7.3)	6.6 (7.7)
Range	0.3–73.4	0.3–68.4	0.3–55.3
Subjects with >0 UUI episodes/24 h at baseline, *n* (%)	472 (99)	963 (99)	950 (99)
Number of subjects with previous antimuscarinic therapy	165 (34.5)	314 (32.3)	305 (31.8)
Bladder diary variables, mean (SD)			
UUI episodes per 24 h	2.4 (1.9)	2.6 (2.1)	2.6 (2.2)
MVV per micturition (mL)	147.3 (54.9)	142.1 (55.5)	146.2 (54.5)
Total micturitions per 24 h	11.7 (3.1)	11.9 (3.0)	11.7 (3.3)
Nocturnal micturitions per 24 h	2.1 (1.3)	2.3 (1.2)	2.2 (1.3)
Urgency episodes per 24 h	9.5 (3.9)	9.7 (3.6)	9.7 (4.0)
Severe urgency episodes per 24 h	6.0 (3.5)	6.3 (3.5)	6.4 (4.0)
Frequency–urgency sum per 24 h	40.8 (13.5)	41.8 (12.9)	41.7 (15.0)
PPBC, *n* (%)			
Not many problems at all (1)	4 (1)	4 (<1)	3 (<1)
Some very minor problems (2)	9 (2)	29 (3)	24 (3)
Some minor problems (3)	28 (6)	56 (6)	57 (6)
Some moderate problems (4)	151 (33)	296 (32)	289 (32)
Severe problems (5)	203 (45)	412 (44)	393 (43)
Many severe problems (6)	57 (13)	134 (14)	147 (16)
UPS, *n* (%)			
1	170 (38)	366 (39)	364 (40)
2	266 (59)	526 (56)	519 (57)
3	16 (4)	40 (4)	30 (3)
OAB-q, mean (SD)			
Symptom bother	57.4 (18.1)	59.3 (19.5)	59.4 (19.1)
Total HRQL	54.9 (20.7)	53.3 (22.8)	53.4 (21.3)
Concern	50.5 (23.5)	49.1 (26.0)	48.4 (24.9)
Coping	48.2 (25.4)	46.2 (27.2)	46.1 (25.7)
Sleep	53.4 (24.7)	51.3 (26.3)	52.2 (25.0)
Social Interaction	73.7 (23.2)	72.4 (24.3)	73.2 (23.2)

ER, extended release; HRQL, health-related quality of life; MVV, mean voided volume; OAB-q, Overactive Bladder Questionnaire; PPBC, Patient Perception of Bladder Condition; PRO, patient-reported outcomes; UPS, Urgency Perception Scale (1 = not able to hold urine; 2 = Able to hold urine, without leaking, until I reach a toilet immediately; 3 = Able to finish the ongoing work before going to the toilet, without leaking); UUI, urgency urinary incontinence. Demographic data represent the safety set (placebo, n = 478; tolterodine ER, n = 973; fesoterodine, n = 960); baseline diary variable data represent full analysis set (placebo, n = 462; tolterodine ER, n = 942; fesoterodine, n = 930) for all subjects reporting the symptom at baseline; PRO data represent the full analysis set.

tolterodine ER, and fesoterodine groups, respectively, discontinued the study. Baseline demographic and clinical characteristics were similar among the treatment groups (Table 1). Approximately 2% of subjects reported a mean of less than one UUI episode per 24 h during the 3-day diary period at baseline and were in violation of study inclusion criterion. These subjects were included in safety and efficacy analyses.

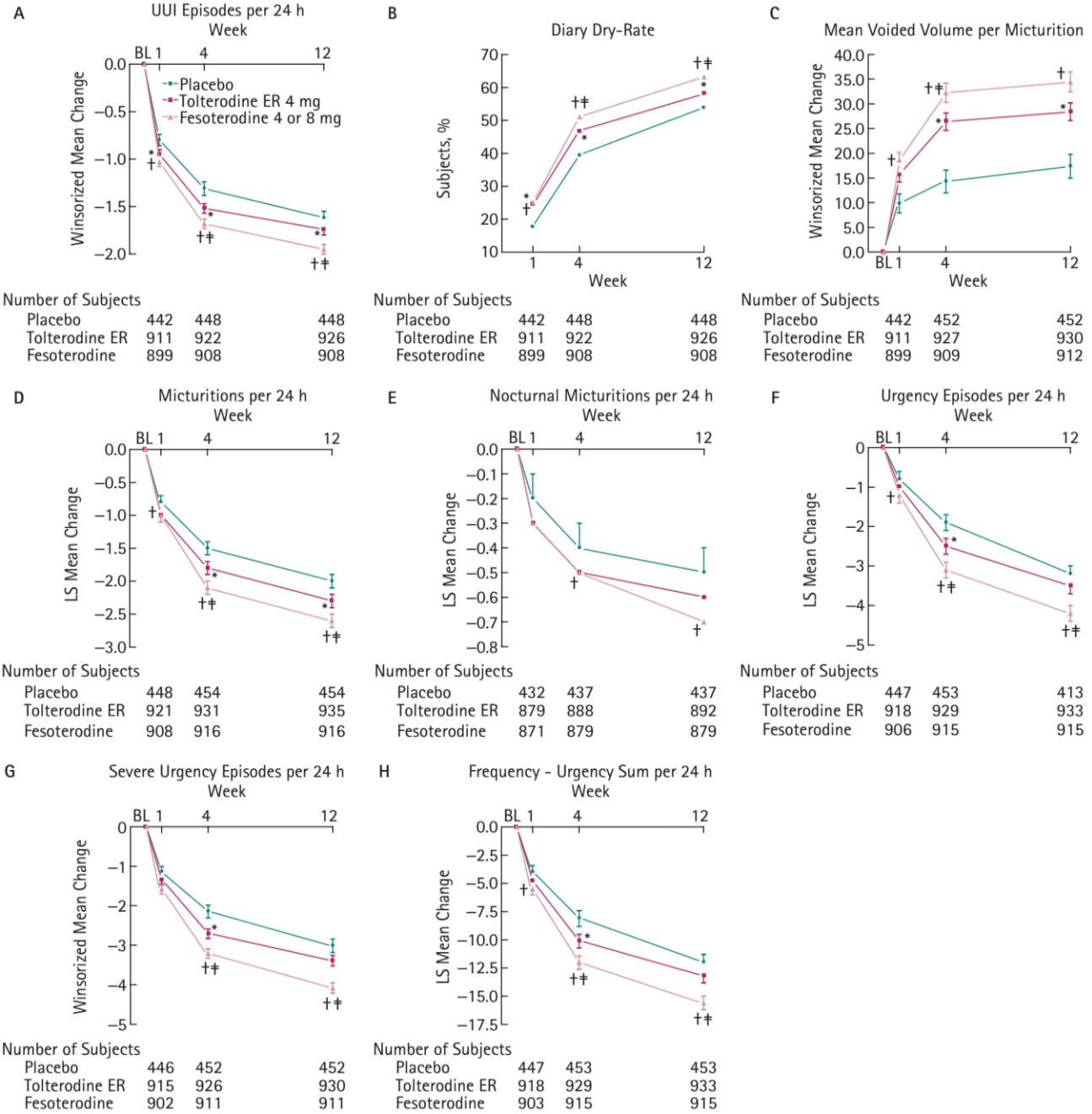
WEEK 12 OUTCOMES

At week 12, subjects receiving fesoterodine 8 mg had significantly greater mean improvements in most diary variables than subjects receiving tolterodine ER, including UUI episodes (the primary endpoint, $P = 0.0072$), micturitions ($P = 0.0016$), urgency episodes ($P < 0.0001$), severe urgency episodes ($P = 0.0001$) and frequency–urgency sum ($P < 0.0001$), but not nocturnal micturitions ($P = 0.1661$) or MVV ($P = 0.0525$) (Fig. 2A–H). The fesoterodine 8 mg group also had significantly greater mean improvements in all diary endpoints at week 12 compared to placebo (all $P < 0.0001$, except $P = 0.0134$ for nocturnal micturitions), whereas the tolterodine ER group showed significantly greater improvements in UUI episodes ($P = 0.0228$), MVV ($P = 0.0021$) and micturitions ($P = 0.0407$) vs placebo, but not in other diary variables ($P > 0.05$).

The median percentage reduction in UUI episodes at week 12 was 100% in all groups (Table 2). However, the treatment differences between the fesoterodine group and the tolterodine ER ($P = 0.0093$) and placebo ($P = 0.0001$) groups were statistically significant, reflecting an overall difference in the distribution of percentage changes in UUI in favour of fesoterodine. Consistent with this, the 3-day diary-dry rate at week 12 (proportion of subjects reporting no UUI episodes at endpoint among those with greater than zero UUI episodes at baseline) was significantly greater in the fesoterodine group vs tolterodine ER and placebo groups ($P = 0.0169$ and $P = 0.0003$; Fig. 2B). The treatment differences between the tolterodine ER and placebo groups with respect to median percentage reduction in UUI episodes ($P = 0.0805$) and diary-dry rate ($P = 0.0991$) at week 12 were not statistically significant.

Categorical changes in PPBC and UPS scores from baseline to week 12 were significantly better in the fesoterodine group compared

*FIG. 2. Change from baseline (BL) to weeks 1, 4 and 12 in UUI episodes per 24 h (**A**), MVV per micturition (**C**), total micturitions per 24 h (**D**), nocturnal micturitions per 24 h (**E**), urgency episodes per 24 h (**F**), severe urgency episodes per 24 h (**G**) and frequency–urgency sum per 24 h (**H**). Error bars represent the SEM. Also shown in (**B**) are the 3-day diary-dry rates at weeks 1, 4 and 12. Data represent the full analysis set for subjects reporting symptoms at baseline. Subjects in the fesoterodine group received fesoterodine 4 mg for the first week and then fesoterodine 8 mg for the remaining 11 weeks. ER, extended release; MVV, mean voided volume; UUI, urgency urinary incontinence. *P < 0.05 tolterodine ER vs placebo; †P < 0.05 fesoterodine vs placebo; ‡P < 0.05 fesoterodine vs tolterodine ER.*



with the tolterodine ER ($P = 0.0005$ and $P = 0.0016$) and placebo groups ($P < 0.0001$ and $P < 0.0001$; Fig. 3). Categorical changes in PPBC and UPS scores were also significantly better in the tolterodine ER group vs placebo ($P = 0.0107$ and $P = 0.0060$).

Compared with the tolterodine ER group, the fesoterodine 8 mg group had significantly greater improvements at week 12 on the OAB-q Symptom Bother scale ($P < 0.0001$), total health-related quality of life (HRQL) scale ($P = 0.0003$) and the Concern ($P <$ 0.0001), Coping ($P = 0.0004$), Sleep ($P = 0.0180$) and Social Interaction ($P = 0.0117$) domains (Fig. 4). The fesoterodine group also had significantly greater improvements vs placebo on the OAB-q Symptom Bother scale ($P < 0.0001$), HRQL scale ($P < 0.0001$) and the

TABLE 2 Median percentage changes in bladder diary variables from baseline

Bladder diary variable	Placebo ($n = 462$)	Tolterodine ER 4 mg ($n = 942$)	Fesoterodine 4 or 8 mg§ ($n = 930$)
UUI episodes per 24 h			
Week			
1	−40.8	−50.0*	−50.0†
4	−75.0	−88.9*	−100.0†‡
12	−100.0	−100.0	−100.0†‡
Micturitions per 24 h			
Week			
1	−7.1	−9.4	−9.0†
4	−13.4	−16.7*	−18.9†‡
12	−18.2	−20.8*	−23.5†‡
Nocturnal micturitions per 24 h			
Week			
1	−7.7	−14.3	−12.5
4	−20.0	−25.0	−25.0†
12	−27.3	−33.3	−33.3†
Urgency episodes per 24 h			
Week			
1	−9.4	−12.0	−11.8
4	−17.2	−26.3*	−32.1†‡
12	−31.0	−37.5	−45.5†‡
Severe urgency episodes per 24 h			
Week			
1	−19.7	−24.1	−25.0
4	−41.7	−55.6*	−61.1†‡
12	−61.0	−69.2	−79.3†‡

**P < 0.05 tolterodine vs placebo; †P < 0.05 fesoterodine vs placebo; ‡P < 0.05 fesoterodine vs tolterodine ER .§Subjects in the fesoterodine group received fesoterodine 4 mg for the first week and then fesoterodine 8 mg for the remaining 11 weeks. ER, extended release; UUI, urgency urinary incontinence. Data represent the full analysis set for all subjects reporting the symptom at baseline. P values are based on a ranked analysis of covariance model, with terms for country, treatment and ranked baseline value as covariate.*

Concern ($P < 0.0001$), Coping ($P < 0.0001$), Sleep ($P = 0.0003$) and Social Interaction ($P = 0.0011$) domains. The tolterodine ER group reported significantly greater improvements vs placebo on the OAB-q Symptom Bother ($P = 0.0458$) and HRQL ($P = 0.0429$) scales and the Coping ($P = 0.0229$) domain, but not on the Concern ($P = 0.0795$), Sleep ($P = 0.0923$) or Social Interaction ($P = 0.2208$) domains.

WEEK 4 OUTCOMES

At week 4, subjects receiving fesoterodine 8 mg showed significantly greater mean improvements vs subjects receiving tolterodine ER in UUI episodes ($P = 0.0148$), MVV ($P = 0.0130$), micturitions ($P = 0.0186$), urgency episodes ($P = 0.0005$), severe urgency episodes ($P = 0.0071$) and frequency–urgency sum ($P = 0.0006$), but not nocturnal micturitions ($P = 0.5906$; Fig. 2A–G). Subjects receiving fesoterodine 8 mg also had significantly greater improvements in all diary endpoints compared to placebo (all $P < 0.0001$, except $P = 0.0286$ for nocturnal micturitions). In the tolterodine ER group, improvements in UUI episodes ($P = 0.0019$), MVV ($P = 0.0002$), micturitions ($P = 0.0043$), urgency episodes ($P = 0.0054$), severe urgency episodes ($P = 0.0009$) and frequency–urgency sum ($P = 0.0034$), but not nocturnal micturitions ($P = 0.0794$), were significantly greater than in the placebo group.

The median percentage reduction in UUI episodes from baseline to week 4 was significantly greater in the fesoterodine group (−100%) compared to the tolterodine ER (−88.9%; $P = 0.0219$) and placebo groups (−75.0%; $P < 0.0001$), as well as in the tolterodine ER group vs placebo ($P = 0.0038$; Table 2). The 3-day diary-dry rates were significantly greater for fesoterodine vs tolterodine ER ($P = 0.0494$) and placebo ($P < 0.0001$) at week 4 (Fig. 2B).The difference between tolterodine ER and placebo in 3-day diary-dry rate was also significant at week 4 ($P = 0.0063$).

The categorical change in PPBC and UPS scores from baseline to week 4 was significantly better in the fesoterodine group compared to the tolterodine ER ($P = 0.0177$; $P = 0.0040$) and placebo groups ($P < 0.0001$ and $P = 0.0002$; Fig. 3). Changes in PPBC score in the tolterodine ER group were significantly better than in the placebo group ($P = 0.0001$), but the difference between tolterodine ER and placebo in change in UPS score was not significant ($P = 0.1485$).

WEEK 1 OUTCOMES

At week 1, there were no statistically significant differences between subjects receiving fesoterodine 4 mg and those receiving tolterodine ER for changes in any diary variable (all $P > 0.05$). Compared to placebo, the fesoterodine group had significantly greater improvements in UUI episodes ($P = 0.0006$), diary-dry rate ($P = 0.0008$), MVV ($P = 0.0020$), micturitions ($P = 0.0161$), urgency episodes ($P = 0.0374$) and frequency–urgency sum ($P = 0.0136$) at week 1, but not in severe urgency episodes ($P = 0.0576$) or nocturnal micturitions ($P = 0.3823$). Differences between the tolterodine ER and placebo groups were not statistically significant for any bladder diary variable ($P > 0.05$), except for UUI episodes ($P = 0.0202$) and diary-dry rate ($P = 0.0024$).

Compared to the tolterodine ER group, categorical changes in PPBC and UPS scores from baseline to week 1 in the fesoterodine group did not reach statistical significance ($P = 0.2817$ and $P = 0.3713$; Fig. 3). However, categorical changes in PPBC and UPS scores were significantly better in the fesoterodine ($P = 0.0009$ and $P = 0.0011$) and tolterodine ER ($P = 0.0279$ and $P = 0.0072$) groups at week 1 compared to placebo.

SAFETY AND TOLERABILITY

Both active treatments were well tolerated with nine (2%), 28 (3%) and 45 (5%) subjects in placebo, tolterodine ER and fesoterodine

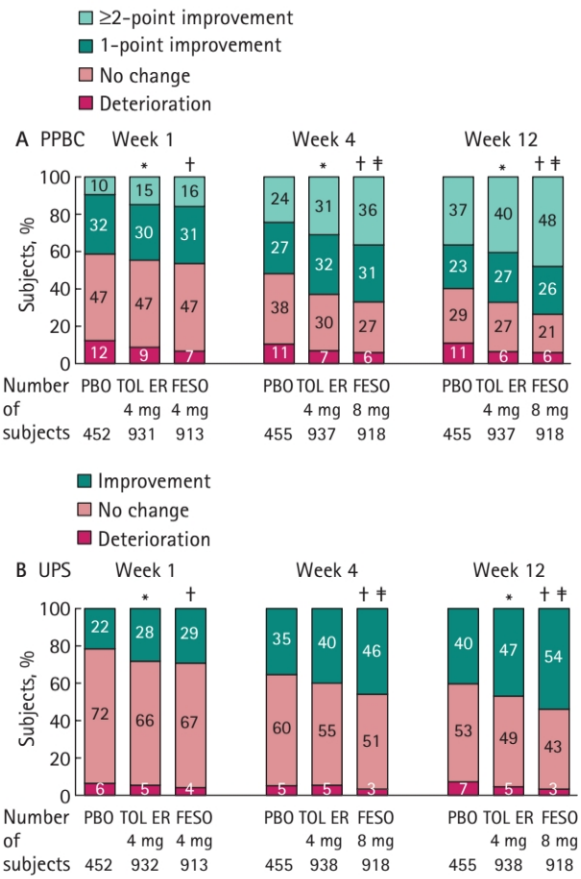


FIG. 3.
*Categorical changes in from baseline to weeks 1, 4 and 12 in Patient Perception of Bladder Condition (**A**) and Urgency Perception Scale (**B**) scores. Data represent the full analysis set. Subjects in the fesoterodine group received fesoterodine 4 mg for the first week and then fesoterodine 8 mg for the remaining 11 weeks. FESO, fesoterodine; PBO, placebo; PPBC, Patient-Perception of Bladder Condition; TOL ER, tolterodine extended release; UPS, Urgency Perception Scale. *P < 0.03 tolterodine ER vs placebo; †P < 0.002 fesoterodine vs placebo; ‡P = 0.02 fesoterodine vs tolterodine ER.*

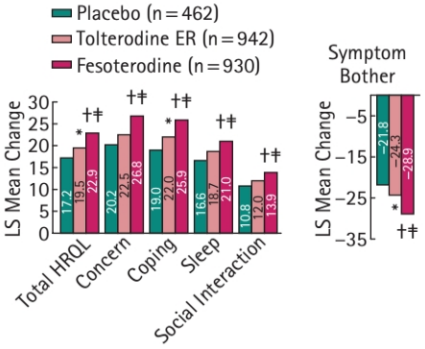


*FIG. 4. Changes from baseline to 12 weeks in Overactive Bladder Questionnaire scores. Data represent the full analysis set. ER, extended release; HRQL, health-related quality of life; LS, least squares. *P < 0.05 tolterodine ER vs placebo; †P < 0.001 fesoterodine vs placebo; ‡P < 0.02 fesoterodine vs tolterodine ER.*

*TABLE 3 Most-commonly reported treatment-emergent adverse events**

Event	Placebo ($n = 478$)	Tolterodine ER 4 mg ($n = 973$)	Fesoterodine 4 or 8 mg† ($n = 960$)
Dry mouth, *n* (%)	26 (5)	130 (13)	265 (28)
Headache, *n* (%)	6 (1)	20 (2)	27 (3)
Constipation, *n* (%)	7 (2)	30 (3)	42 (4)
Urinary tract infection, *n* (%)	5 (1)	12 (1)	14 (2)
Polyuria, *n* (%)	10 (2)	24 (3)	29 (3)

**All causality treatment-emergent adverse events reported by ≥2% subjects in the safety set in either active treatment group with higher incidence than placebo. †Subjects in the fesoterodine group received fesoterodine 4 mg for the first week and then fesoterodine 8 mg for the remaining 11 weeks. ER, extended release.*

groups, respectively, discontinuing owing to treatment-emergent adverse events of any causality. The most frequently reported treatment-emergent adverse events in all treatment groups were dry mouth, constipation and headache (Table 3); the large majority of all adverse events, including dry mouth, were of mild or moderate severity. Dry mouth was reported as severe by 0 (0%), one (<1%) and 20 (2%) subjects in the placebo, tolterodine ER and fesoterodine groups, respectively.

There was one fatal serious adverse event in the placebo group during the course of the study; this death was reported as unrelated to study treatment. Non-fatal serious adverse events of all causality occurring during treatment or within 7 days of the last dose were reported by seven (2%), six (1%) and 13 (1%) subjects in the placebo, tolterodine ER and fesoterodine groups, respectively. There were two serious adverse events in the fesoterodine group that were considered treatment related. The first occurred in a 49-year-old white woman who was temporarily withdrawn from the study after developing acute pyelonephritis on day 9, which subsequently resolved. The second occurred in a 72-year-old white man who developed acute urinary retention on day 13, which subsequently resolved after discontinuation of treatment and catheterization.

DISCUSSION

The present study is the largest double-blind, placebo-controlled, randomized study to compare antimuscarinic efficacy on OAB to date. It is also the first placebo-controlled, head-to-head superiority study of antimuscarinics designed to make predefined comparisons for both diary-based measures and PROs. The results show the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving UUI episodes (the primary endpoint), micturitions, urgency episodes, severe urgency episodes and frequency–urgency sum, but not nocturnal micturitions or MVV. Fesoterodine 8 mg also produced significantly greater improvements compared to tolterodine ER 4 mg in assessments by subjects of their OAB symptoms, as measured by the PPBC, UPS and OAB-q. The superiority

of fesoterodine 8 mg over tolterodine ER 4 mg was apparent at week 4 on all diary endpoints, except nocturnal micturitions, and also on the PPBC and UPS (OAB-q scores not captured at week 4).

These findings support those of a previous head-to-head trial designed to show the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for the treatment of OAB symptoms [9]; in that study, analyses comparing fesoterodine 8 mg and tolterodine ER 4 mg on 3-day diary-dry rates and PROs were not prespecified. Both studies found significantly greater improvements in UUI episodes, diary-dry rates and PPBC, UPS and OAB-q scores with fesoterodine 8 mg vs tolterodine ER 4 mg. In the present study, fesoterodine 8 mg was also associated with significantly greater improvements in micturitions, urgency episodes, severe urgency episodes and frequency–urgency sum compared to tolterodine ER 4 mg; treatment differences in these end points did not reach statistical significance in the previous head-to-head trial [9]. The previous study found that fesoterodine 8 mg was associated with a significantly greater increase in MVV than tolterodine ER 4 mg. In the present study, the increase in MVV was significantly greater with fesoterodine 8 mg than tolterodine ER 4 mg at week 4, but not at week 12. The results of these two trials taken together strongly support the superiority of fesoterodine 8 mg over tolterodine ER 4 mg on these endpoints and show the clinical value of the 8-mg fesoterodine dose, whereby patients who opt to escalate to the highest approved dose of fesoterodine (8 mg) are likely to achieve better symptom improvement than patients treated with the highest approved dose of tolterodine ER. The present findings are also consistent with a *post hoc* analysis of a phase III trial of fesoterodine that included tolterodine ER as an active control [17], which showed significantly greater improvements in UUI episodes and MVV per micturition with fesoterodine 8 mg vs tolterodine ER 4 mg [18].

In the present study, fesoterodine 8 mg was superior to tolterodine ER 4 mg on all study endpoints, except nocturnal micturitions, as early as week 4, which is 3 weeks after dose escalation to fesoterodine 8 mg. There were no significant differences between fesoterodine 4 mg and tolterodine ER 4 mg at week 1. However, fesoterodine 4 mg was associated with statistically significant improvements on all study endpoints vs placebo at week 1, whereas tolterodine ER 4 mg was associated with statistically significant improvements in UUI episodes and PPBC and UPS scores vs placebo at week 1. The apparent early efficacy of fesoterodine 4 mg and tolterodine ER 4 mg on OAB symptoms is important because these symptoms are often bothersome and can negatively impact HRQL [25]. Early efficacy at 1 week of treatment has been previously shown for tolterodine ER and other antimuscarinics [26–29].

Both the present study and the previous head-to-head study [9] showed that fesoterodine 8 mg produced significantly greater improvements than tolterodine ER 4 mg and placebo on several subjective, self-reported assessments of the severity of OAB symptoms and the impact of these symptoms on subjects' lives, including measures of symptom bother, HRQL, urgency and global severity of bladder-related problems. Moreover, fesoterodine 8 mg was associated with significantly greater improvements than tolterodine ER 4 mg on PROs as early as week 4, which parallels the results of diary assessments in the present study. These findings are notable because they suggest that the superiority of fesoterodine 8 mg over tolterodine ER 4 mg in the improvement of bladder diary variables reflect differences in efficacy that are clinically meaningful to patients with OAB.

Both active treatments were generally well tolerated in the present study. The generally higher occurrence of treatment-emergent adverse events in the fesoterodine 8 mg group compared to the tolterodine ER 4 mg and placebo groups mainly consisted of an increased incidence of dry mouth, and may be attributed to the study design, where dose escalation was not optional; therefore, the dose of fesoterodine may have been escalated in patients for whom 4 mg is the optimal fesoterodine dose.

A potential limitation of the present study was that dose escalation was not optional for subjects receiving fesoterodine; however, this investigation was focused on the maximum available doses of each agent. Whereas the use of the higher available dose of each active treatment was appropriate in the present study to show superiority, this may not directly reflect clinical practice. With flexible dosing, patients who achieve sufficient efficacy with fesoterodine 4 mg or adverse events limiting dose escalation would not escalate to the 8-mg dose, and patients who have unacceptable tolerability with fesoterodine 8 mg would likely be treated with the 4-mg dose. Future research may assess whether fesoterodine 4 mg or flexible-dose fesoterodine are associated with greater efficacy than tolterodine ER 4 mg.

In conclusion, in subjects with OAB symptoms including UUI, superior efficacy of fesoterodine 8 mg over tolterodine ER 4 mg was observed in key diary endpoints, as well as in improving subjects' assessments of bladder-related problems, urgency, symptom bother and HRQL. The present study also showed the superiority of fesoterodine 8 mg over tolterodine ER 4 mg and placebo on most endpoints as early as week 4. Both active treatments were generally well tolerated. These results, together with those of the previous head-to-head trial [9], offer substantial evidence supporting the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for the treatment of OAB symptoms for several diary endpoints; the availability of an additional 8-mg dose provides fesoterodine with a clinical advantage over single-dose tolterodine ER 4 mg.

ACKNOWLEDGEMENTS

This study was funded and conducted by Pfizer Inc. Editorial assistance was provided by Simon J. Slater, PhD, and Colin P. Mitchell, PhD, from Complete Healthcare Communications, Inc., and was funded by Pfizer Inc.

CONFLICT OF INTEREST

Steven A. Kaplan is a consultant, investigator, and lecturer for Pfizer Inc. Tim Schneider is an investigator and lecturer for Pfizer Inc. Jenelle E. Foote is a consultant, investigator, and lecturer for Pfizer Inc. Zhonghong Guan, Martin Carlsson, and Jason Gong are employees of Pfizer Inc.

REFERENCES

1 **Prioritization CoCER.** *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC: Then National Academies Press, 2009

2 **Diokno AC, Appell RA, Sand PK *et al.*** Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; **78**: 687–95

3 **Appell RA, Sand P, Dmochowski R *et al.*** Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc* 2001; **76**: 358–63

4 **Chapple CR, Martinez-Garcia R, Selvaggi L *et al.*** A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48**: 464–70

5 **Dmochowski RR, Sand PK, Zinner NR, Gittelman MC, Davila GW, Sanders SW.** Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003; **62**: 237–42

6 **Homma Y, Paick JS, Lee JG, Kawabe K.** Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. *BJU Int* 2003; **92**: 741–7

7 **Yamaguchi O, Marui E, Kakizaki H *et al.*** Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. *BJU Int* 2007; **100**: 579–87

8 **Junemann KP, Halaska M, Rittstein T *et al.*** Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. *Eur Urol* 2005; **48**: 478–82

9 **Herschorn S, Swift S, Guan Z *et al.*** Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int* 2010; **105**: 58–66

10 **ICH Expert Working Group.** Statistical principles for clinical trials E9. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*. 1998

11 **Michel MC.** Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. *Expert Opin Pharmacother* 2008; **9**: 1787–96

12 **Brynne N, Dalen P, Alvan G, Bertilsson L, Gabrielsson J.** Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamic of tolterodine. *Clin Pharmacol Ther* 1998; **63**: 529–39

13 **Malhotra B, Guan Z, Wood N, Gandelman K.** Pharmacokinetic profile of fesoterodine. *Int J Clin Pharmacol Ther* 2008; **46**: 556–63

14 **Detrol® LA (tolterodine tartrate).** *Full Prescribing Information*. New York: Pfizer Inc, 2008

15 **Toviaz® (fesoterodine fumarate).** *Full Prescribing Information*. New York: Pfizer Inc, 2008

16 **European Medicines Agency (EMEA).** EPARs for authorized medicinal products for human use. European Public Assessment Report for Toviaz (Product Information). Updated August 2009. Available at: http://www.emea.europa.eu/humandocs/Humans/EPAR/toviaz/toviaz.htm. Accessed 20 October 2009

17 **Chapple C, Van Kerrebroeck P, Tubaro A *et al.*** Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol* 2007; **52**: 1204–12

18 **Chapple C, Van Kerrebroeck P, Juenemann K, Wang J, Brodsky M.** Comparison of fesoterodine and tolterodine in subjects with overactive bladder. *BJU Int* 2008; **102**: 1128–32

19 **Coyne KS, Tubaro A, Brubaker L, Bavendam T.** Development and validation of patient-reported outcomes measures for overactive bladder: a review of concepts. *Urology* 2006; **68**: 9–16

20 **Coyne KS, Matza LS, Kopp Z, Abrams P.** The validation of the Patient Perception of Bladder Condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur Urol* 2006; **49**: 1079–86

21 **Cardozo L, Coyne KS, Versi E.** Validation of the Urgency Perception Scale. *BJU Int* 2005; **95**: 591–6

22 **Coyne K, Revicki D, Hunt T *et al.*** Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res* 2002; **11**: 563–74

23 **Box GEP, Hunter WG, Hunter JS.** *Statistics for Experimenters*. New York: Wiley, 1978

24 **Van Elteren PH.** On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst* 1960; **37**: 351–61

25 **Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I.** The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int* 2008; **101**: 1388–95

26 **Herschorn S, Heesakkers J, Castro-Diaz D, Wang JT, Brodsky M, Guan Z.** Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms. *Curr Med Res Opin* 2008; **24**: 3513–21

27 **Siami P, Seidman LS, Lama D.** A multicenter, prospective, open-label study of tolterodine extended-release 4 mg for overactive bladder: the speed of onset of therapeutic assessment trial (STAT). *Clin Ther* 2002; **24**: 616–28

28 **Zinner N, Gittelman M, Harris R, Susset J, Kanelos A, Auerbach S.** Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol* 2004; **171**: 2311–5

29 **Cardozo L, Hessdorfer E, Milani R *et al.*** Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. *BJU Int* 2008; **102**: 1120–7

Correspondence: Steven A. Kaplan, Institute of Bladder and Prostate Health, Weill Cornell Medical College, Cornell University, Department of Urology, 1300 York Avenue, New York, NY 10021, USA.
e-mail: kaplans@med.cornell.edu

Abbreviations: **ER**, extended release; **FAS**, full analysis set; **5-HMT**, 5-hydroxymethyl tolterodine; **HRQL**, health-related quality of life; **MVV**, mean voided volume; **OAB**, overactive bladder; **OAB-q**, Overactive Bladder Questionnaire; **PPBC**, Patient Perception of Bladder Condition; **PRO**, patient-reported outcome; **UPS**, Urgency Perception Scale; **UUI**, urgency urinary incontinence.