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Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies

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Abstract

Background: Oral pharmacotherapies to treat overactive bladder (OAB) are used less in men despite a similar prevalence of storage symptoms as women. The efficacy and safety of once-daily mirabegron 50 mg was evaluated in male OAB patients from five phase III studies that included placebo or antimuscarinic (tolterodine ER 4 mg or solifenacin 5 mg) as a comparator.

Methods: Three pooled 12-week placebo-controlled studies (mirabegron 50 mg *versus* placebo) and one 12-week non-inferiority phase IIIb study (BEYOND; mirabegron 50 mg *versus* solifenacin 5 mg) were used for efficacy (daily micturition frequency, urgency and incontinence episodes) and safety analyses. An additional 52-week active-controlled phase III safety study (mirabegron 50 mg *versus* tolterodine ER 4 mg) was included in the safety analysis. Male patients aged ⩾18 years with OAB for ⩾3 months were included in the analyses. Patients may also have a history of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)/benign prostatic enlargement (BPE) or concomitant use of α_1-blockers.

Results: In the pooled studies, mirabegron 50 mg demonstrated superiority *versus* placebo (treatment difference: –0.37 [95% confidence interval (CI): –0.74, –0.01]) for reducing micturition frequency; improvements in urgency and incontinence were not significantly different between mirabegron 50 mg and placebo. In BEYOND, mirabegron 50 mg was comparable with solifenacin 5 mg for reducing micturition frequency, urgency, and incontinence episodes. Mirabegron was well tolerated at 12 and 52 weeks and overall treatment-emergent adverse events (AEs) were similar to those with placebo.

Conclusions: In a male OAB population with or without LUTS associated with BPH/BPE, mirabegron 50 mg provided similar improvements in urgency, frequency, and incontinence as solifenacin 5 mg, and is a well-tolerated alternative to antimuscarinics. In the three pooled 12-week studies, significant differences were not seen for urgency and incontinence *versus* placebo, although mirabegron 50 mg did demonstrate significant improvements *versus* placebo for frequency.

Keywords: benign prostatic enlargement, benign prostatic hyperplasia, LUTS, male patients, mirabegron, overactive bladder

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Introduction

Lower urinary tract symptoms (LUTS) can be classified into storage, voiding, and post-micturition symptoms. Most patients experience a diversity of LUTS, which often develop *via* similar pathophysiology. Nevertheless, male and female LUTS are often regarded as two distinct conditions, related to prostate pathology in men and bladder pathology in women.[1] The prevalence of storage (51.3% and 59.2%), voiding (25.7% and

19.5%), and post-micturition LUTS (16.9% and 14.2%) are generally similar between men and women, respectively.[2] This includes overactive bladder (OAB), defined as urinary urgency usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathologies.[3,4] OAB affects approximately 12% of men and women aged >40 years, and its prevalence increases with advancing age.[2] OAB can impact significantly on quality of life (QoL) in men and women[5,6] and is generally perceived as more bothersome than voiding symptoms;[7] the latter is usually associated with benign prostatic obstruction (BPO) in men.

Despite the similar prevalence of OAB symptoms in men and women, there are important differences in predominating symptoms and their management. Men are more likely to experience urgency, frequency and nocturia accompanied by LUTS associated with voiding dysfunction,[1,6,7] whereas women are twice as likely to experience incontinence (including stress and mixed incontinence).[6,7]

Oral antimuscarinics or β_3-adrenoceptor agonists (mirabegron) are recommended as first-line pharmacotherapy for the treatment of OAB.[8] Long-term persistence of treatment is often poor with antimuscarinics due to inadequate efficacy or anticholinergic adverse events (AEs), such as dry mouth or constipation,[9,10] and in male patients there remains a perception of an increased risk of acute urinary retention, despite that risk being low.[11] Mirabegron has demonstrated similar efficacy to antimuscarinics, without the bothersome AEs associated with antimuscarinics, in pivotal 12-week phase III studies and pooled data,[12–16] including phase III studies in Japanese and Asian populations,[17,18] and long-term tolerability in a 52-week phase III study.[19] This improved tolerability profile is reflected by significantly higher 12-month adherence and persistence rates in patients taking mirabegron *versus* antimuscarinics.[20] In a previous phase II study in males with LUTS/bladder outlet obstruction (BOO), mirabegron did not adversely affect voiding urodynamics [maximum urinary flow (Q_{max}), detrusor pressure at maximum urinary flow ($P_{det \cdot Qmax}$), or detrusor contractility] and was not associated with acute urinary retention after 12 weeks' treatment.[21] Additionally, mirabegron was efficacious for several OAB outcome variables.[21] However, mirabegron is not recommended in patients with severe uncontrolled hypertension.[22]

In men with LUTS, the 2015 European Association of Urology guidelines recommend antimuscarinics or β_3-adrenoceptor agonists to treat moderate-to-severe LUTS where bladder storage symptoms predominate, and a combination of α_1-adrenoceptor antagonist (α_1-blocker) and antimuscarinic to treat troublesome moderate-to-severe LUTS if symptom relief with either monotherapy is insufficient.[23] Male patients often receive α_1-blockers first to treat bladder storage symptoms (i.e. urgency) due to the perception that benign prostatic enlargement (BPE) is the underlying cause; however, storage LUTS remain bothersome in two-thirds of such men.[24]

Combining an antimuscarinic or mirabegron with an α_1-blocker improves efficacy *versus* monotherapy in males with LUTS/BPE.[25–27] However, the potential for anticholinergic AEs is higher with antimuscarinics, which may worsen treatment persistence.[9] There have also been reports of increased post-void residual (PVR) volume in men with BPO treated with mirabegron or antimuscarinics combined with an α_1-blocker; however, these were volumes considered clinically irrelevant (i.e. <50 ml).[24–27]

Despite the underrepresentation of male OAB patients in phase III trials (~20–25% of the study population), there is growing evidence about the efficacy and safety of mirabegron in men. The objective of this critical analysis of male data from five phase III studies was to evaluate the efficacy of mirabegron 50 mg once daily based on 12-week pooled data[15] from three phase III studies (SCORPIO,[12] ARIES,[13] CAPRICORN[14]) and a phase IIIb non-inferiority study (BEYOND),[16] and to evaluate 12-week safety from these studies and a 52-week phase III safety study (TAURUS).[19]

Methods

Study design and population

Efficacy and safety have been previously reported in the overall OAB population in the five phase III studies included in this analysis of male data.[12–16,19] The five studies consisted of three 12-week placebo-controlled phase III studies [SCORPIO (ClinicalTrials.gov identifier: NCT00689104), ARIES (ClinicalTrials.gov identifier: NCT00662909), and CAPRICORN (ClinicalTrials.gov identifier: NCT00912964)], one 12-week non-inferiority phase IIIb study [BEYOND (ClinicalTrials.gov identifier: NCT01638000)], and one

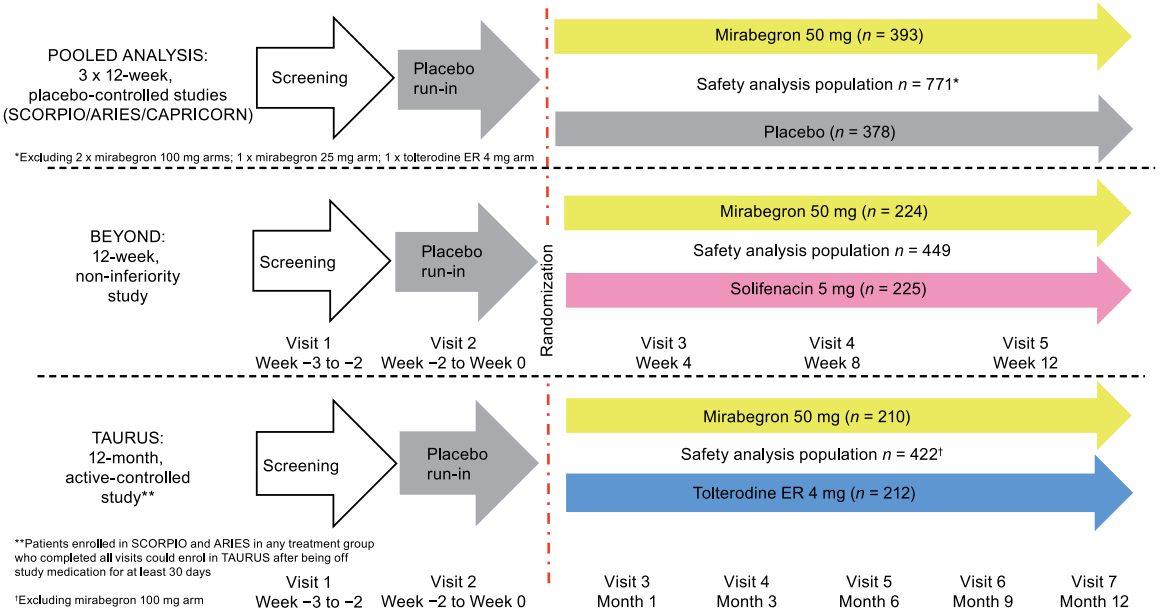

Figure 1. Summary of the study designs for the phase III randomized controlled trials included in the analysis of male patients.

52-week phase III active-controlled safety study [TAURUS (ClinicalTrials.gov identifier: NCT00688688)] (Figure 1). Patients enrolled in SCORPIO and ARIES in any treatment group who completed all visits could enroll in TAURUS after discontinuing study medication for at least 30 days. Mirabegron 25 mg was only studied in one (CAPRICORN) of the five phase III studies. Due to the limited number of male patients administered once-daily 25 mg mirabegron [recommended starting dose in the United States (US) and several other countries], the 25 mg data were excluded in addition to those for the unlicensed 100 mg mirabegron dose (SCORPIO, ARIES, and TAURUS).

Men enrolled in these studies were aged ⩾18 years with OAB for ⩾3 months, and the studies could include men with a history of LUTS associated with BPH/BPE and/or concomitant use of α_1-blockers (Tables 1 and 2). In BEYOND, the population consisted of patients dissatisfied (based on the Treatment Satisfaction Likert questionnaire) with the efficacy of their last antimuscarinic (excluding solifenacin). Following a 2-week, single-blind, placebo run-in to determine baseline symptoms and eligibility, patients were randomized if, during a 3-day micturition diary period, they recorded ⩾8 micturitions/24 h and ⩾3 urgency episodes, based on urgency grade 3 or 4 according to the Patient Perception of Intensity of Urgency Scale (PPIUS)[28] with or without urgency incontinence. Patients with clinically significant BOO at risk of urinary retention were excluded from the pooled studies or TAURUS (at the discretion of the investigator), and excluded from BEYOND if PVR volume was >200 ml (Supplementary material S1: Key inclusion and exclusion criteria and Supplementary material S2: Randomization and blinding).

Efficacy assessment

Efficacy was assessed according to sub-analyses of pooled data from SCORPIO, ARIES, and CAPRICORN (mirabegron 50 mg or placebo once daily), and data from BEYOND (mirabegron 50 mg or solifenacin 5 mg [active comparator] once daily) after 12 weeks' treatment. Safety was the primary objective for the 52-week TAURUS study and was not designed or powered for efficacy comparisons so efficacy results are not presented. The pooled male sub-analysis for mean number of micturitions/24 h and mean number of incontinence episodes/24 h was prespecified prior to database lock and unblinding of treatment groups for the three studies included in the pooled analysis (i.e. prior to analyzing any data from any study by sex). The pooled male sub-analysis for mean number of urgency episodes/24 h was a *post hoc* analysis. In BEYOND, the analysis for micturition frequency was

Table 1. Summary of phase III studies investigating efficacy and safety of mirabegron in a male OAB population.

	Study				
	SCORPIO (046)	**ARIES (047)**	**CAPRICORN (074)**	**TAURUS (049)**	**BEYOND**
Study duration	12 weeks	12 weeks	12 weeks	52 weeks	12 weeks
Study design	Phase III, randomized, placebo-controlled, double-blind	Phase III, randomized, placebo-controlled, double-blind	Phase III, randomized, placebo-controlled, double-blind	Phase III, randomized, active-controlled, double-blind	Phase IIIb, non-inferiority, randomized, double-blind
Patient population	Adults with OAB ⩾ 3 months	Adults with OAB ⩾ 3 months	Adults with OAB ⩾ 3 months	Adults with OAB ⩾ 3 months	Adult OAB patients dissatisfied with their previous antimuscarinic due to lack of efficacy
Treatment arms/daily dose	Placebo; mirabegron 50 mg, mirabegron 100 mg,† tolterodine ER 4 mg‡	Placebo, mirabegron 50 mg, mirabegron 100 mg†	Placebo, mirabegron 25 mg,* mirabegron 50 mg	Mirabegron 50 mg, mirabegron 100 mg,† tolterodine ER 4 mg	Mirabegron 50 mg, solifenacin 5 mg
Total proportion of males in the overall SAF	549/1978 (27.8%)	341/1328 (25.7%)	408/1305 (31.3%)	634/2444 (25.9%)	449/1870 (24.0%)
Total proportion of males in the overall FAS	534/1906 (28.0%)	320/1270 (25.2%)	394/1251 (31.5%)	615/2382 (25.8%)	443/1833 (24.2%)
Treatment arms included in efficacy analysis (FAS)	Placebo ($n = 362$), mirabegron 50 mg ($n = 382$)			Not applicable	Mirabegron 50 mg ($n = 222$), solifenacin 5 mg ($n = 221$)
Treatment arms included in SAF	Placebo ($n = 378$), mirabegron 50 mg ($n = 393$)			Mirabegron 50 mg ($n = 210$), tolterodine ER 4 mg ($n = 212$)	Mirabegron 50 mg ($n = 224$), solifenacin 5 mg ($n = 225$)
Efficacy data available by sex	Change from baseline to EoT: • Mean number of micturitions/24 h • Mean number of incontinence episodes/24 h • Mean number of urgency episodes (grade 3 or 4)/24 h			No *post hoc* efficacy analysis in males was conducted as this study was designed primarily to assess 12-month safety	Change from baseline to EoT: • Mean number of micturitions/24 h • Mean number of incontinence episodes/24 h • Mean urgency episodes (grade 3 or 4)/24 h
Safety data available by sex	• Incidence of TEAEs • Change from baseline in vital signs (blood pressure and pulse rate) • AEs of special interest (antimuscarinic AEs, urinary retention) • Change from baseline in PVR			• Incidence of TEAEs • Change from baseline in vital signs (blood pressure and pulse rate) • AEs of special interest (antimuscarinic AEs, urinary retention)	• Incidence of TEAEs • AEs of special interest (antimuscarinic AEs, urinary retention)

*Mirabegron 25 mg results excluded as this dose was restricted to a single study (074); †Mirabegron 100 mg results not shown as this is not a licensed dose; ‡Tolterodine ER 4 mg active-control excluded from pooled analysis.
The efficacy and safety endpoints only reflect those included in this publication and do not represent all endpoints investigated in the total population in ARIES, SCORPIO, CAPRICORN, BEYOND, and TAURUS.
AE, adverse event; EoT, end of treatment; ER, extended release; FAS, full analysis set; OAB, overactive bladder; PVR, post-void residual; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

Table 2. Male patient demographics and baseline characteristics (FAS).

	Pooled studies (SCORPIO/ ARIES/CAPRICORN)		TAURUS		BEYOND	
	Placebo (n = 362)	Mirabegron 50 mg (n = 382)	Mirabegron 50 mg (n = 204)	Tolterodine ER 4 mg (n = 206)	Mirabegron 50 mg (n = 222)	Solifenacin 5 mg (n = 221)
Sex, n (% of total study population)						
Male/total	362/1328 (27.3)	382/1324 (28.9)	204/789 (25.9)	206/791 (26.0)	222/921 (24.1)	221/912 (24.2)
Age, years						
Mean (SD)	62.1 (12.8)	62.8 (11.3)	61.6 (11.5)	61.7 (12.0)	58.1 (15.1)	59.5 (14.6)
Range	23–86	21–85	24–87	24–83	22–87	19–87
Race						
White	329 (90.9)	356 (93.2)	194 (95.1)	197 (95.6)	220 (99.1)	217 (98.2)
Black/African American	25 (6.9)	16 (4.2)	7 (3.4)	5 (2.4)	0	1 (0.5)
Asian	4 (1.1)	8 (2.1)	3 (1.5)	2 (1.0)	1 (0.5%)	3 (1.4)
Other	4 (1.1)	2 (0.5)	0	2 (1.0)	1 (0.5)	0
BMI, kg/m^2						
Mean (SD)	28.6 (5.5)	28.2 (4.8)	28.1 (4.4)	28.4 (4.8)	27.1 (4.0)	27.6 (4.0)
Range	15.9–56.6	19.4–45.5	19.4–51.9	19.4–45.1	20–41	20–44
Type of OAB, n (%)						
Urgency incontinence	130 (35.9)	141 (36.9)	76 (37.3)	67 (32.5)	74 (33.3)	78 (35.3)
Mixed	16 (4.4)	30 (7.9)	6 (2.9)	12 (5.8)	19 (8.6)	14 (6.3)
Frequency	216 (59.7)	211 (55.2)	122 (59.8)	127 (61.7)	129 (58.1)	129 (58.4)
Use of α_1-blocker at baseline	78 (21.5)	82 (21.5)	40 (19.6)	43 (20.9)	45 (20.3)	50 (22.6)
History of BPH†, n (%)	147 (40.6)	142 (37.2)	84 (41.2)	78 (37.9)	73 (32.9)	80 (36.2)
Duration of OAB, months						
Mean (SD)	66.9 (78.6)	73.4 (86.7)	77.9 (94.6)	62.7 (56.6)	55.7 (75.4)	51.7 (68.0)
Range	3–688	3–688	3–534	5–427	3.2–568.0	3.0–568.0
Previous OAB drug, n (%)						
Yes	133 (36.7)	153 (40.1)	91 (44.6)	96 (46.6)	222 (100.0)	221 (100.0)
Reasons for previous OAB drug discontinuation,‡ n (%)						
Insufficient effect						
Yes	95 (71.4)	108 (70.6)	62 (68.1)	60 (62.5)	222 (100.0)	221 (100.0)
No	38 (28.6)	45 (29.4)	29 (31.9)	36 (37.5)	0	0
Poor tolerability						
Yes	30 (22.6)	29 (19.0)	14 (15.4)	22 (22.9)	34 (15.3)	43 (19.5)
No	103 (77.4)	124 (81.0)	77 (84.6)	74 (77.1)	188 (84.7)	178 (80.5)
Mean number of incontinence episodes/24 h (FAS)*						
Mean (SD)	0.9 (2.09)	1.0 (1.97)	0.7 (1.74)	0.7 (1.80)		
Range	0–26	0–15	0–11	0–17		

(continued)

Table 2. (Continued)

	Pooled studies (SCORPIO/ ARIES/CAPRICORN)		TAURUS		BEYOND	
	Placebo (n = 362)	**Mirabegron 50 mg (n = 382)**	**Mirabegron 50 mg (n = 204)**	**Tolterodine ER 4 mg (n = 206)**	**Mirabegron 50 mg (n = 222)**	**Solifenacin 5 mg (n = 221)**
Mean number of incontinence episodes/24 h (FAS-I)	(n = 154)	(n = 168)	(n = 77)	(n = 76)	(n = 58)	(n = 59)
Mean (SD)	2.1 (2.77)	2.2 (2.45)	1.9 (2.41)	1.9 (2.55)	2.13 (1.85)	2.31 (2.16)
Range	0–26	0–15	0–11	0–17	0.3–6.7	0.3–7.7
Mean number of micturitions/24 h						
Mean (SD)	11.7 (3.4)	12.0 (3.4)	11.4 (2.8)	11.4 (3.0)	11.8 (3.1)	11.6 (2.4)
Range	4–40	7–33	6–25	7–25	8–27	8–22
Mean number of urgency episodes/24 h						
Mean (SD)	5.0 (3.2)	5.4 (3.9)	5.2 (3.5)	4.8 (3.6)	7.6 (4.9)	7.3 (4.4)
Range	0–15	0–33	1–18	1–19	1–27	1–22

*In BEYOND, summaries for incontinence episodes are only for patients with baseline value >0 (i.e. FAS-I).
†History of BPH was defined using the following selected preferred terms based on MedDRA version 9.1 for the pooled studies and TAURUS and MedDRA version 12.1 for the BEYOND study for medical history: BPH, prostatic obstruction, prostatism, benign neoplasm of prostate, prostatic adenoma, transurethral prostatectomy, prostatomegaly, nocturia, terminal dribbling, urine flow decreased, strangury, and urinary hesitation.
‡Patients could choose more than one reason for discontinuation.
BMI, body mass index; BPH, benign prostatic hyperplasia; ER, extended release; FAS, full analysis set; FAS-I, full analysis set-incontinence; OAB, overactive bladder; SD, standard deviation.

prespecified, and analysis on incontinence and urgency were *post hoc*.

Patients completed a 3-day micturition diary prior to clinic visits at baseline, 4, 8, and 12 weeks/end of treatment (EoT; last on-treatment assessment including patients who did not complete week 12 visit). The three key OAB symptoms were assessed based on the 24-h change from baseline to EoT: mean number of micturitions; mean number of urgency episodes (PPIUS grade 3 or 4); and mean number of incontinence episodes. Nocturia is often multifactorial and clinical trials do not differentiate between nocturnal polyuria and nocturia,[29] hence its exclusion.

Safety assessment

Safety was assessed based on pooled data in males from SCORPIO, ARIES, and CAPRICORN (mirabegron 50 mg or placebo), *post hoc* analysis in BEYOND (mirabegron 50 mg or solifenacin 5 mg), and the 52-week TAURUS study [mirabegron 50 mg or tolterodine extended-release (ER) 4 mg (active control)].

Assessments included the incidence of treatment-emergent AEs (TEAEs), including those of special interest (e.g. antimuscarinic-related AEs and urinary retention). Vital signs were assessed using patient-recorded 5-day diaries (pooled analysis and TAURUS) and/or by the investigator on site (pooled analysis, TAURUS, and BEYOND). Patient-recorded vital signs in men are presented only for the pooled studies and TAURUS since this analysis was not conducted in BEYOND. Hypertension was reported as an AE according to three prespecified criteria in the pooled studies and TAURUS: systolic blood pressure (SBP) $>$140 mmHg and/or diastolic blood pressure (DBP) $>$90 mmHg at two consecutive visits post-baseline in normotensive patients at baseline; SBP increased by $\geq$20 mmHg and/or DBP increased by $\geq$10 mmHg at two consecutive visits post-baseline in hypertensive patients at baseline; treatment with an antihypertensive was initiated to treat hypertension or the dose of a prior antihypertensive was increased due to increased blood pressure. In contrast, hypertension as an AE was based on spontaneous reporting in BEYOND. Change in PVR volume from baseline to EoT was also assessed in men with or without a history of LUTS associated with benign prostatic hyperplasia (BPH)/BPE in the pooled analysis. PVR volume was not measured in TAURUS and only measured at screening in BEYOND.

Statistical analysis

Demographic and baseline characteristics were summarized by descriptive statistics. Micturition frequency and urgency were assessed in the full analysis set (FAS; patients receiving $\geq$1 dose of double-blind treatment at baseline and $\geq$1 post-baseline micturition measurement) and incontinence was assessed in the FAS-incontinence (FAS-I; FAS patients with $\geq$1 incontinence episode at baseline).

In the pooled analysis, changes from baseline in daily micturitions, urgency episodes, and incontinence episodes for the comparison of mirabegron 50 mg *versus* placebo were analyzed using an analysis of covariance (ANCOVA) model including treatment, sex, study, and treatment-by-sex interaction as fixed factors, and baseline as a covariate.

In BEYOND, non-inferiority analyses of daily micturitions in the per protocol set were similar to the FAS;[16] to be consistent with the pooled data, only outcomes in the FAS are reported. Change from baseline in daily micturitions, urgency episodes, and incontinence episodes was analyzed using an ANCOVA model with treatment, age ($<$65 years and $\geq$65 years), number of prior antimuscarinics (1 antimuscarinic and $\geq$2 antimuscarinics), and geographic region as fixed factors, and baseline as a covariate.

Least squares mean estimates and two-sided 95% confidence intervals (CIs) for mean changes from baseline were derived within treatment groups and between mirabegron 50 mg and placebo or solifenacin 5 mg.

Descriptive statistics were presented for the safety analysis set (SAF; randomized patients who received $\geq$1 dose of double-blind treatment). Vital signs on the pooled studies were analyzed using the same ANCOVA model as the efficacy variables. Vital signs for TAURUS were assessed using an ANCOVA model with treatment group, previous study history, sex, geographical region, and treatment-by-sex interaction as fixed factors, and baseline as a covariate.

Results

Demographic and baseline characteristics

Overall, 1187 men were included in the FAS and 1642 men in the SAF (Table 1 and Figure 1). In the pooled 12-week studies and the 52-week TAURUS study, of the male patients who had

prior OAB treatment (41%), approximately 70% had discontinued treatment because of insufficient efficacy; discontinuation of a previous antimuscarinic due to insufficient efficacy was a prerequisite for inclusion in BEYOND. Patient demographics and baseline characteristics were consistent across treatment groups and generally similar across studies, although patients in BEYOND had a higher average number of urgency episodes/24 h at baseline (>7 episodes) *versus* the pooled studies (~5 episodes) (Table 2). Approximately 37% of men had a history of LUTS associated with BPH/BPE and 22% were receiving an α_1-blocker, indicating a substantial proportion had underlying LUTS/BPO. In the FAS-I, baseline incontinence (~2.0 episodes/24 h) was comparable across the pooled studies, TAURUS, and BEYOND.

Efficacy

In the FAS, mirabegron 50 mg was associated with a statistically significantly greater reduction in daily micturitions *versus* placebo in the pooled analysis (Figure 2a). Adjusted mean (95% CI) change from baseline to EoT was −1.29 (−1.55, −1.04) and −0.92 (−1.18, −0.66) in the mirabegron 50 mg and placebo groups, respectively: significant treatment difference in favor of mirabegron *versus* placebo of −0.37 (95% CI: −0.74, −0.01). In BEYOND, an adjusted mean (95% CI) change from baseline to EoT of −2.97 (−3.32, −2.63) and −3.10 (−3.45, −2.76) for micturition frequency was observed with mirabegron 50 mg and solifenacin 5 mg, respectively: mean treatment difference *versus* mirabegron 50 mg of −0.13 (−0.62, 0.36), favoring solifenacin 5 mg, but was not statistically significant.

The mean number of urgency episodes (PPIUS grade 3 or 4)/24 h was improved with mirabegron in the pooled studies and BEYOND. However, there was a significant placebo effect in the pooled analysis, with an adjusted mean (95% CI) change from baseline to EoT of −1.60 (−1.93, −1.27) and −1.88 (−2.23, −1.54) with mirabegron 50 mg and placebo, respectively: mean treatment difference *versus* placebo of +0.28 (−0.19, 0.76). In BEYOND, the adjusted mean (95% CI) change from baseline to EoT was −4.43 (−4.88, −3.98) and −4.67 (−5.12, −4.22) with mirabegron 50 mg and solifenacin 5 mg, respectively: mean treatment difference *versus* mirabegron of −0.24 (−0.88, 0.40), favoring solifenacin 5 mg, but not statistically significant (Figure 2b).

In the FAS-I, improvements in daily incontinence episodes were similar with mirabegron 50 mg and placebo in the pooled analysis. Adjusted mean (95% CI) change from baseline to EoT in the mean number of incontinence episodes/24 h was −1.48 (−1.78, −1.18) and −1.41 (−1.72, −1.10) with mirabegron 50 mg and placebo, respectively: mean treatment difference *versus* placebo of −0.07 (−0.50, 0.36) favoring mirabegron 50 mg. In BEYOND, the adjusted mean (95% CI) change from baseline to EoT was −2.02 (−2.27, −1.77) and −1.74 (−1.99, −1.49) with mirabegron 50 mg and solifenacin 5 mg, respectively: mean treatment difference *versus* mirabegron 50 mg of +0.28 (–0.08, 0.64), which favored mirabegron, but was not statistically significant (Figure 2c).

Safety

After 12 weeks of treatment, the overall incidence of TEAEs was similar between mirabegron 50 mg (46.1%) and placebo (45.2%) in the pooled studies, and between mirabegron 50 mg (24.5%) and solifenacin 5 mg (26.2%) in BEYOND. After 52 weeks' treatment, the incidence of TEAEs in TAURUS was higher than the other studies, likely due to additional observation time, but was similar between mirabegron 50 mg (60.0%) and tolterodine ER 4 mg (62.3%). In each case, the incidence of TEAEs in men was similar to the overall OAB population (Table 3). Common TEAEs (≥2% in any group) in the pooled studies (mirabegron 50 mg *versus* placebo), BEYOND (mirabegron 50 mg *versus* solifenacin 5 mg), and TAURUS (mirabegron 50 mg *versus* tolterodine ER 4 mg), respectively, were nasopharyngitis (5.9% *versus* 2.1%; 2.2% *versus* 1.3%; and 3.3% *versus* 3.3%), headache (2.5% *versus* 1.3%; 3.1% *versus* 1.3%; and 2.4% *versus* 3.3%), constipation (2.0% *versus* 1.6%; 1.8% *versus* 2.7%; and 2.9% *versus* 1.9%), and dry mouth (1.5% *versus* 2.4%; 3.5% *versus* 6.7%; and 3.3% *versus* 8.0%) (Table 3). Arterial hypertension, reported according to three prespecified criteria, was the most frequently reported TEAE in the pooled studies (~10% with placebo and mirabegron 50 mg) and TAURUS (~12% with mirabegron 50 mg and tolterodine ER 4 mg). In BEYOND, hypertension according to spontaneous reporting as an AE was reported in 0.4% of men treated with mirabegron 50 mg or solifenacin 5 mg. Overall, three cases of acute urinary retention were reported, two in the pooled analysis [placebo $n = 1$ (0.3%) at day 83; mirabegron 50 mg $n = 1$ (0.3%) at day 47] and one in TAURUS [tolterodine ER 4 mg $n = 1$ (0.5%) at day 21].

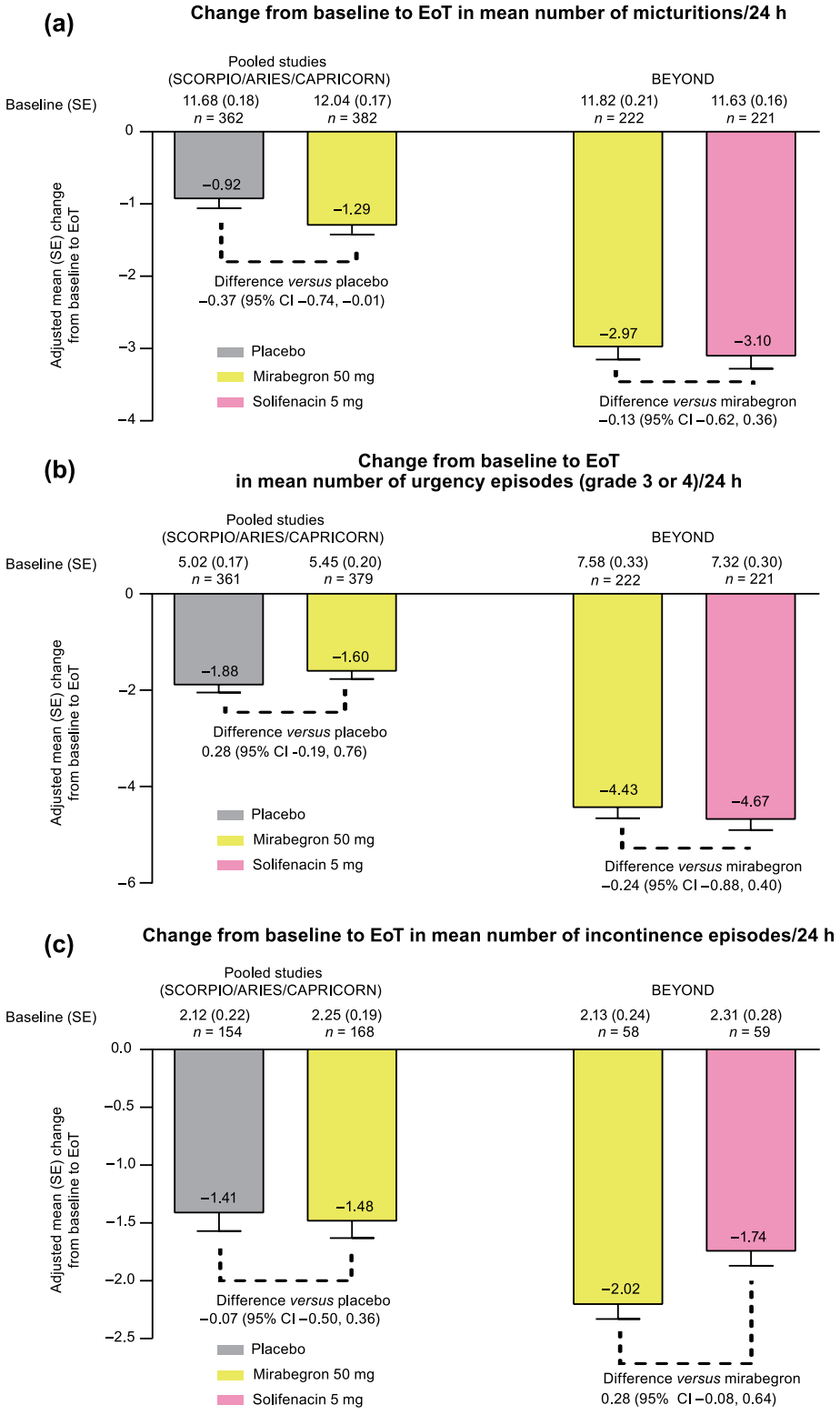

Figure 2. Adjusted mean change from baseline to EoT in male patients for the key OAB efficacy parameters in the pooled phase III studies (SCORPIO, ARIES, CAPRICORN), and phase IIIb study (BEYOND): (a) mean number of micturitions/24 h (FAS), (b) mean number of urgency episodes (grade 3 or 4 of PPIUS)/24 h (FAS), and (c) mean number of incontinence episode/24 h (FAS-I).
CI, confidence interval; EoT, end of treatment; FAS, full analysis set; FAS-I, full analysis set-incontinence; OAB, overactive bladder; PPIUS, Patient Perception of Intensity of Urgency Scale; SE, standard error.

Table 3. Overall incidence of TEAEs, most common TEAEs (⩾2% in any treatment group), and TEAEs of special interest in male patients from the pooled phase III studies, 12-month study, and phase IIIb study (SAF).

TEAE (preferred term), *n* (%)	Pooled studies (12 weeks) (SCORPIO/ARIES/CAPRICORN)		TAURUS (52 weeks)		BEYOND (12 weeks)	
	Placebo (*n* = 378)	Mirabegron 50 mg (*n* = 393)	Mirabegron 50 mg (*n* = 210)	Tolterodine ER 4 mg (*n* = 212)	Mirabegron 50 mg (*n* = 224)	Solifenacin 5 mg (*n* = 225)
Overall TEAE in males	171/378 (45.2)	181/393 (46.1)	126/210 (60.0)	132/212 (62.3)	55/224 (24.5)	59/225 (26.2)
Overall TEAE in total population	658/1380 (47.7)	647/1375 (47.1)	485/812 (59.7)	508/812 (62.6)	274/936 (29.3)	282/934 (30.2)
Common TEAEs (⩾2% in any group)						
Hypertension	35 (9.3)	43 (10.9)	26 (12.4)	25 (11.8)	–	–
Nasopharyngitis	8 (2.1)	23 (5.9)	7 (3.3)	7 (3.3)	5 (2.2)	3 (1.3)
Headache	5 (1.3)	10 (2.5)	5 (2.4)	7 (3.3)	7 (3.1)	3 (1.3)
Cough	–	–	5 (2.4)	1 (0.5)	–	–
Constipation	6 (1.6)	8 (2.0)	6 (2.9)	4 (1.9)	4 (1.8)	6 (2.7)
Diarrhea	–	–	2 (1.0)	5 (2.4)	–	–
Dry mouth	9 (2.4)	6 (1.5)	7 (3.3)	17 (8.0)	8 (3.5)	15 (6.7)
Urinary tract infection	–	–	4 (1.9)	5 (2.4)	–	–
Dizziness	–	–	5 (2.4)	7 (3.3)	–	–
Back pain	8 (2.1)	4 (1.0)	9 (4.3)	2 (0.9)	–	–
Tachycardia	–	–	2 (1.0)	8 (3.8)	–	–
Nausea	–	–	1 (0.5)	6 (2.8)	–	–
Fatigue	–	–	2 (1.0)	5 (2.4)	–	–
Influenza	–	–	3 (1.4)	6 (2.8)	–	–
Pain in extremity	–	–	5 (2.4)	1 (0.5)	–	–
Cystitis	–	–	3 (1.4)	5 (2.4)	–	–
TEAEs of special interest						
Urinary retention	1 (0.3)	1 (0.3)	0	3 (1.4)	1 (0.1)	0
Acute urinary retention	1 (0.3)	1 (0.3)	0	1 (0.5)	0	0
Blurred vision	0	1 (0.3)	3 (1.4)	1 (0.5)	2 (0.2)	0
Dyspepsia	4 (1.1)	2 (0.5)	1 (0.5)	4 (1.9)	1 (0.1)	1 (0.1)
Hypertension	35 (9.3)	43 (10.9)	26 (12.4)	25 (11.8)	4 (0.4)	4 (0.4)

ER, extended release; SAF, safety analysis set; TEAE, treatment-emergent adverse events

In the pooled analysis at EoT, mean SBP and DBP increased by ~1 mmHg and 0.5 mmHg, respectively, and mean pulse rate increased by approximately 1 beat per minute (bpm) with mirabegron 50 mg *versus* placebo. In TAURUS, changes in SBP and DBP after 52 weeks were of a similar magnitude to the 12-week pooled studies, and the difference between mirabegron 50 mg and tolterodine ER 4 mg was also similar to the 12-week studies (Table 4).

In the pooled analysis, there were no notable changes in PVR volume at EoT with mirabegron 50 mg or placebo in patients with or without history of LUTS associated with BPH/BPE (Figure 3). Overall, two patients experienced a post-baseline PVR >300 ml [placebo $n = 1$ (339 ml) and mirabegron 50 mg $n = 1$ (450 ml)], although baseline PVR volumes were already relatively high [172 ml (placebo) and 161 ml (mirabegron 50 mg)].

Discussion

In this analysis of male OAB patients, including a significant proportion with a history of LUTS associated with BPH/BPE (~37%) or use of α_1-blockers at baseline (~22%), mirabegron 50 mg demonstrated superiority *versus* placebo, and was comparable with solifenacin 5 mg in improving micturition frequency. In the pooled studies, despite a clear improvement in urgency with mirabegron 50 mg, the result did not differentiate from placebo possibly due to a high placebo response. Although incontinence is uncommon in men, it was improved with mirabegron 50 mg by a similar magnitude as solifenacin 5 mg, but mirabegron 50 mg did not differentiate from placebo in the pooled studies.

Although OAB affects men and women equally in terms of prevalence and impact on QoL, it is important to recognize sex differences in etiology, underlying pathology and symptom presentation. Men tend to report more LUTS with greater severity than the general OAB population, and are particularly bothered by urgency, frequency, and nocturia.[7,30,31] The proportion of men with OAB in this analysis was relatively high (24–29%) compared with the Healthcore Integrated Research Database (17%),[32] but was less than the EPIC study (35%).[5] The FAS population was representative of male OAB patients in clinical practice with low baseline incontinence (~0.9 episodes/24 h).

The incidence of TEAEs in men treated with mirabegron 50 mg was similar to the overall population and placebo, suggesting there is no requirement for dose adjustment based on sex. The incidence of dry mouth was two-fold higher with solifenacin or tolterodine *versus* mirabegron, and was the most frequent TEAE reported in BEYOND. The higher incidence of TEAEs in TAURUS with mirabegron 50 mg and tolterodine ER 4 mg was expected given the longer duration of treatment. The lower incidence of TEAEs in BEYOND could be attributed to selection bias of patients previously treated with antimuscarinics and hence more likely to tolerate bothersome AEs. Arterial hypertension, the most frequent TEAE in the pooled studies and TAURUS, was reported at a similar rate with mirabegron, tolterodine, and placebo, and comparable with the overall population in these studies. Arterial hypertension was almost absent in BEYOND, which is probably explained by the different reporting criteria (prespecified *versus* spontaneous reporting) and frequency of assessment (on-site investigator *versus* 5-day diaries). The change in vital signs in men treated with mirabegron 50 mg was comparable with vital sign results from a recent systematic literature review of cardiovascular safety with mirabegron, which reported a mean increase in SBP/DBP and pulse rate of ⩽1 mmHg and 1 bpm, respectively, with mirabegron 50 mg *versus* placebo, and a rate of arterial hypertension of 8.7% and 8.5% with mirabegron 50 mg and placebo, respectively.[33]

These data offer an interesting insight in patients with a history of LUTS associated with BPH/BPE and OAB, and confirm the safety of mirabegron and solifenacin in this population. In the pooled studies, PVR volume, an important predictor of acute urinary retention, was comparable between mirabegron and placebo, and was unaffected by history of LUTS associated with BPH/BPE. Acute urinary retention was reported in only 3 cases (placebo $n = 1$; mirabegron 50 mg $n = 1$; tolterodine ER 4 mg $n = 1$).

Approximately half of men with symptomatic BPE also have bladder storage symptoms,[24,34] and it is these storage symptoms, mainly urgency, frequency, and nocturia, which usually prompt them to seek advice. However, the underlying cause of storage LUTS may be unrelated to BPE. Furthermore, it is often difficult to differentiate symptoms of detrusor overactivity and BPO without a comprehensive urodynamic assessment.[35]

Table 4. Change from baseline to EoT in vital signs as measured by patient diary in the morning and afternoon (SAF).

Vital signs	Pooled studies (SCORPIO/ARIES/CAPRICORN)		TAURUS	
	Placebo	Mirabegron 50 mg	Mirabegron 50 mg	Tolterodine ER 4 mg
SBP (a.m.), mmHg	*n* = 363	*n* = 383	*n* = 205	*n* = 206
Baseline mean (SE)	132.2 (0.87)	132.6 (0.81)	133.3 (1.03)	132.2 (1.02)
Adjusted change from baseline (SE) [95% CI]	0.2 (0.47)	1.7 (0.46)	1.7 (0.66) [0.4, 3.0]	0.9 (0.66) [−0.4, 2.2]
Mean difference *versus* placebo (SE) [95% CI]	–	1.5 (0.65) [0.2, 2.8]	N/A	N/A
SBP (p.m.), mmHg	*n* = 361	*n* = 383	*n* = 204	*n* = 206
Baseline mean (SE)	130.9 (0.79)	131.5 (0.73)	132.2 (0.90)	131.3 (0.93)
Adjusted change from baseline (SE) [95% CI]	1.4 (0.49)	1.9 (0.48)	1.9 (0.65) [0.6, 3.2]	1.2 (0.65) [−0.1, 2.4]
Mean difference *versus* placebo (SE) [95% CI]	–	0.5 (0.68) [−0.8, 1.9]	N/A	N/A
DBP (a.m.), mmHg	*n* = 363	*n* = 383	*n* = 205	*n* = 206
Baseline mean (SE)	78.6 (0.50)	79.3 (0.44)	79.5 (0.61)	79.0 (0.61)
Adjusted change from baseline (SE) [95% CI]	0.0 (0.29)	0.6 (0.29)	−0.2 (0.41) [−1.0, 0.6]	0.3 (0.41) [−0.5, 1.1]
Mean difference *versus* placebo (SE) [95% CI]	–	0.5 (0.41) [−0.3, 1.3]	N/A	N/A
DBP (p.m.), mmHg	*n* = 361	*n* = 383	*n* = 204	*n* = 206
Baseline mean (SE)	76.5 (0.47)	76.9 (0.46)	77.4 (0.63)	77.0 (0.60)
Adjusted change from baseline (SE) [95% CI]	0.8 (0.32)	1.0 (0.31)	0.6 (0.42) [−0.2, 1.4]	0.6 (0.42) [−0.2, 1.5]
Mean difference *versus* placebo (SE) [95% CI]	–	0.2 (0.44) [−0.6, 1.1]	N/A	N/A
Pulse rate (a.m.), bpm	*n* = 363	*n* = 383	*n* = 205	*n* = 206
Baseline mean (SE)	67.5 (0.56)	67.3 (0.55)	69.3 (0.79)	66.5 (0.73)
Adjusted change from baseline (SE) [95% CI]	0.3 (0.34)	1.3 (0.33)	−0.6 (0.44) [−1.4, 0.3]	0.4 (0.45) [−0.5, 1.3]
Mean difference *versus* placebo (SE) [95% CI]	–	1.0 (0.47) [0.1, 1.9]	N/A	N/A
Pulse rate (p.m.), bpm	*n* = 361	*n* = 383	*n* = 204	*n* = 206
Baseline mean (SE)	73.2 (0.60)	72.9 (0.55)	73.2 (0.73)	71.4 (0.76)
Adjusted change from baseline (SE) [95% CI]	0.2 (0.35)	0.8 (0.34)	−1.1 (0.47) [−2.1, −0.2]	0.8 (0.47) [−0.2, 1.7]
Mean difference *versus* placebo (SE) [95% CI]	–	0.6 (0.49) [−0.3, 1.6]	N/A	N/A

Adjusted change from baseline was generated from the ANCOVA model with treatment, sex, study, and treatment-by-sex as fixed factors, and baseline as a covariate. Difference of the adjusted means *versus* placebo was calculated by subtracting the adjusted mean of placebo from the adjusted mean of the treatment group.
ANCOVA, analysis of covariance; bpm, beats per minute; CI, confidence interval; DBP, diastolic blood pressure; ER, extended release; EoT, end of treatment; N/A, not applicable; SBP, systolic blood pressure; SAF, safety analysis set; SE, standard error.

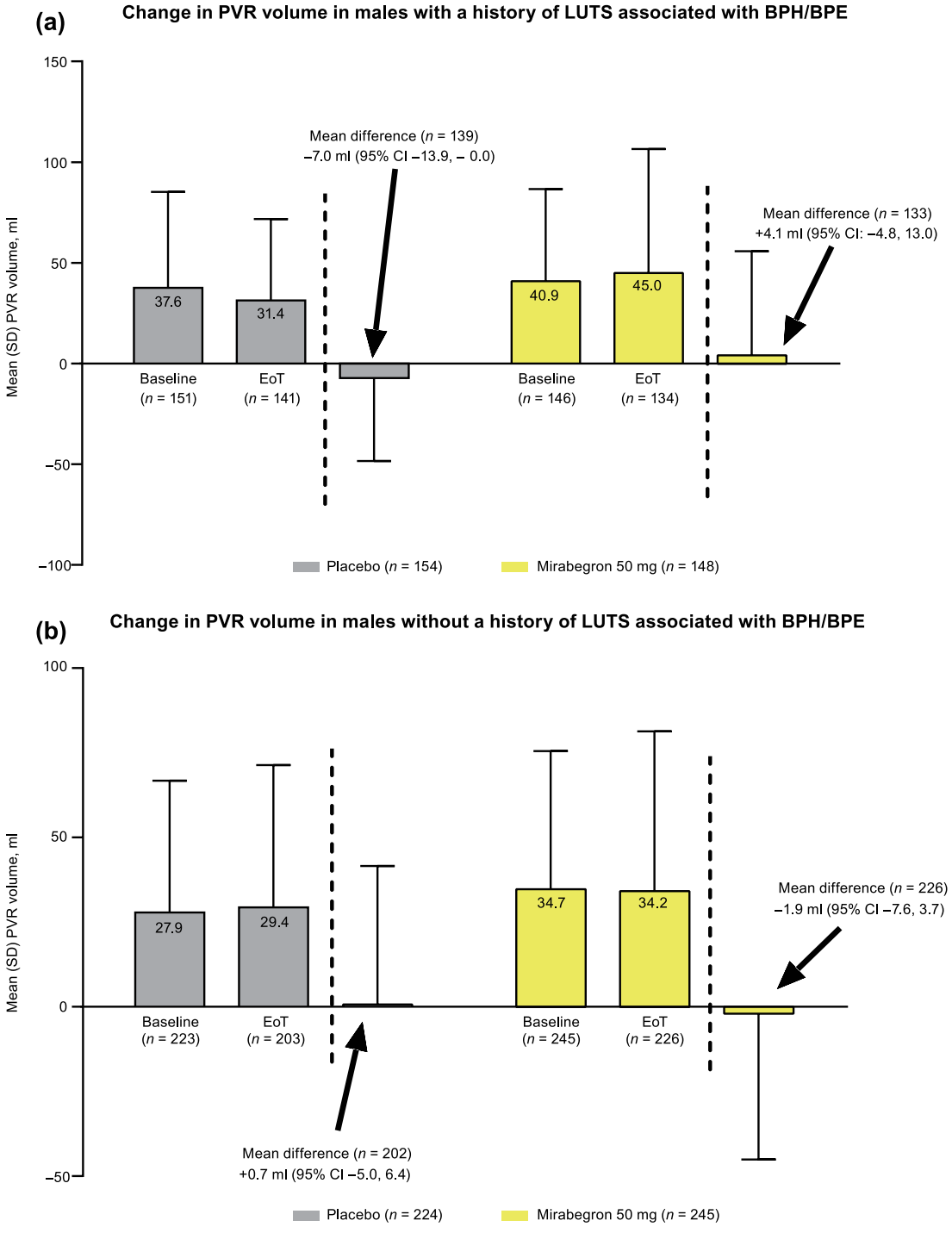

Figure 3. Change from baseline to EoT in PVR volume (pooled 12-week studies only) (SAF): (a) males with a history of LUTS associated with BPH/BPE, and (b) males without a history of LUTS associated with BPH/BPE.
BPE, benign prostatic enlargement; BPH, benign prostatic hyperplasia; CI, confidence interval; EoT, end of treatment; LUTS, lower urinary tract symptoms; PVR, post-void residual; SAF, safety analysis set; SD, standard deviation.

Consequently, storage LUTS are often treated with α_1-blockers assuming underlying BPO without an additional medication to target residual storage symptoms. This results in the insufficient control of urgency and frequency in as many as two-thirds of males with LUTS.[24]

Mirabegron has previously been shown to be efficacious and well tolerated in a phase II study investigating urodynamics and safety in 200 men with LUTS/BOO.[21] Micturition frequency, urgency, and incontinence episodes/24 h were reduced by a similar magnitude with mirabegron 50 mg *versus* placebo (−1.35, −1.60, and −0.89, respectively) as the pooled 12-week studies, and differences were statistically significant for urgency ($p < 0.01$) and frequency ($p < 0.05$). Furthermore, there were no detrimental effects on voiding phase urodynamics such as Q_{max}, $P_{det \cdot Qmax}$, or bladder contractility index. The overall incidence of TEAEs (mirabegron 40.0% *versus* placebo 43.1%) in men with LUTS/BOO was comparable with the pooled 12-week studies, and there were no reports of acute urinary retention.[21] The rate of hypertension in males with LUTS/BOO was comparable between the mirabegron 50 mg (4.3%) and placebo (3.1%) groups.[21]

The absence of any detrimental effect on voiding phase parameters (Q_{max} and $P_{det \cdot Qmax}$) with mirabegron in males with LUTS/BPE is related to its mode of action. Stimulation of the β_3-adrenoceptor mediates detrusor relaxation and increases bladder capacity during the storage phase, but there are no changes during the voiding phase, thus there are no effects on micturition pressure, flow rate, or residual volume. Concerns that antimuscarinics may impair voiding pressure during bladder emptying and thereby increase the risk of acute urinary retention, particularly in men with underlying BPO, appear to be unfounded based on two literature reviews of antimuscarinics in men with LUTS.[11,36] After comparing acute urinary retention rates in the general male population and in men with LUTS (PVR ⩽ 200 ml), the risk with antimuscarinics with or without α_1-blockers may be increased during short-term treatment but, if patients do not develop acute urinary retention within the first 3–4 months, their subsequent risk is lower than the untreated, symptomatic population.[11] Furthermore, a smaller study suggested long-term antimuscarinic use (>1 year) was a risk factor for increasing PVR volume by >50 ml.[37] Although significant increases in PVR volumes have been reported (>20 ml to <40 ml) in men with storage symptoms and BPE following combination therapy with antimuscarinic plus α_1-blocker,[26] or mirabegron plus α_1-blocker,[27] these were considered clinically irrelevant, as reflected by the single case of acute urinary retention in the latter study.[27] These data support the safety for mirabegron and solifenacin in patients with LUTS associated with BPH and PVR < 200 ml.

The efficacy observed with mirabegron in this analysis, primarily deriving from US and European male data, is consistent with unpublished male data from a Japanese phase III study.[17] In Japanese males with OAB, a similar benefit in reducing micturition frequency was observed with mirabegron 50 mg (−1.03) *versus* placebo (−0.74); a treatment difference of −0.30 (95% CI: −1.21, 0.61). However, relative improvements in urinary incontinence and urgency were not demonstrated. In a more diverse Asian population (Taiwan, Korea, China, and India),[18] unpublished male data indicate that mirabegron 50 mg *versus* placebo improved micturition frequency (−2.25 *versus* −1.69) and incontinence (−1.30 *versus* −0.80); however, as observed with the US/European data and Japanese data, improvements in urgency did not differentiate from placebo. Interestingly, a clear treatment effect was observed for volume voided per micturition (the most objective bladder diary outcome) in favor of mirabegron (11.46 ml) *versus* placebo (−0.73 ml).

Study limitations

One of the main limitations is the small amount of pooled data available at the time of this male sub-analysis. The 12-week data were pooled as a requirement of the US and European regulatory submission process in 2012 and, therefore, only included North American and European studies. Studies conducted outside these regions with data available at the time of pooling (i.e. Japanese phase III data[17]) were not included. There are plans to integrate mirabegron phase II–IV data from all geographic regions, which will provide a larger sample size for men to be analyzed at the 12-week time point. When available, these results should add to the volume of available data on men with OAB. However, in the interim, the unpublished efficacy data in Japanese and Asian men are presented in the discussion to highlight potential regional differences.

The limited number of studies that shared the same design and population will have undoubtedly contributed to the observed heterogeneity with mirabegron. For instance, the inclusion of superiority *versus* non-inferiority study designs and studies that allowed only prior-treated patients *versus* those that also allowed naïve

patients. Further factors known to affect homogeneity of OAB treatment effect estimates, which differed between the studies in this analysis, include small patient numbers, severity of incontinence and urgency at baseline, and placebo response rates. A high placebo response is not unusual in OAB trials and may be a consequence of counselling and lifestyle changes, self-reported diaries, subjective assessment of urgency, trials of shorter duration, and the concomitant use of α_1-blockers. Markedly higher placebo responses were evident in male patients *versus* female patients for urgency (−1.88 *versus* −1.06) and incontinence (−1.41 *versus* −1.03), but not micturitions (−0.92 *versus* −1.31) in the pooled studies, which contributed in part to the lower treatment effect *versus* placebo observed in male patients for these two variables. In the overall populations in OAB registration trials, treatment differences between active drug and placebo are often limited due to the high placebo response inherent in OAB trials. The reduction in micturition frequency in this male OAB population is lower than seen in the overall OAB population, yet the results are statistically significant. The relatively small sample size in this analysis could have impacted the urgency and incontinence results, especially taking into consideration that a smaller proportion of male OAB patients have urinary incontinence compared with females. Ongoing mirabegron phase IV male OAB studies shall provide more conclusive evidence in the future. Although women are more likely to experience incontinence than men, a significant proportion of male patients experience some element of post-micturition dribble,[38] which could be perceived by the patient as incontinence, and is less likely to be responsive to treatment. Therefore, one might expect to observe reductions in urgency incontinence of a similar magnitude in men *versus* women. Nevertheless, the limited response observed in men in this analysis is consistent with a recent literature review and meta-analysis of OAB medications, which found incontinence outcomes less favorable in men.[39] The authors attributed this to discrepancies in anatomy and pathophysiology, particularly comorbid conditions such as BPH, which can precipitate episodes of post-micturition dribble and overflow incontinence.[39] Furthermore, this analysis was not powered for the male population and lacked a common comparator across the studies, so efficacy and safety results are not interpretable for relative comparisons. The use of an active comparator (solifenacin) in BEYOND, in patients who were unresponsive to previous antimuscarinic therapy, could be seen to potentially bias the results in favor of mirabegron. However, this was not evident in the overall population or in male patients, which supports the original evidence-based premise that solifenacin is effective in both treatment-naïve OAB patients and those who failed previous antimuscarinic therapy, and supported the decision to use solifenacin as an active comparator for this non-inferiority study. The inclusion of a placebo group in BEYOND might have allowed a more meaningful assessment of the treatment effect observed with mirabegron and solifenacin.

The limitations of this analysis could be addressed in the future *via* a network meta-analysis with corresponding female data after accounting for differences between the male and female populations, which would allow direct and indirect treatment comparisons and estimation of relative efficacy (including patient-reported outcomes) and safety with mirabegron by sex; male and female data from the phase III Japanese and Asian studies[17,18] could also be potentially included. *Post hoc* analyses could explore which male patient factors influence efficacy and safety of mirabegron (e.g. age, previous or concomitant medical therapy for LUTS/BPH, duration and severity of symptoms, previously treated *versus* treatment-naïve) and whether a similar response is observed in men treated with the 25-mg mirabegron dose. Future analyses could also benefit from the inclusion of efficacy and safety data from phase II studies and efficacy data in treatment-naïve patients from TAURUS.[19]

The two large randomized controlled trials [ClinicalTrials.gov identifiers: NCT02757768 and NCT02656173] designed to investigate the efficacy and safety of add-on mirabegron in men with OAB symptoms taking an α-blocker (tamsulosin hydrochloride) for LUTS due to BPH are currently recruiting participants. A small Japanese study has already reported significant improvements in OAB and good tolerability following add-on mirabegron to tamsulosin *versus* tamsulosin monotherapy in men with OAB and BPE.[27]

Conclusion

In male OAB patients with or without underlying BPE, mirabegron 50 mg improved urgency, frequency, and incontinence, as did solifenacin 5 mg in BEYOND. Although statistically significant

differences were not seen for urgency and incontinence *versus* placebo in the pooled studies, mirabegron 50 mg did demonstrate statistically significant improvements in frequency *versus* placebo. Mirabegron 50 mg is a well-tolerated alternative to antimuscarinics, without the same potential concerns over voiding difficulty. No significant increase in PVR volume or in the incidence of acute urinary retention was observed with mirabegron. More robust randomized controlled studies are required to confirm the benefit of mirabegron in men, to explore why mirabegron is more effective in improving frequency than other OAB symptoms, and to investigate mirabegron monotherapy and add-on therapy to α_1-blockers in men with and without underlying BPE/BPO, with the focus on improving storage symptoms of frequency, urgency, and nocturia. *Post hoc* analyses could also explore whether certain patient categories (e.g. age, severity of symptoms) are more predictive of treatment success.

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Institutional Review Board approval of the protocol, and informed patient consent was obtained prior to each study commencing. Studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines and applicable laws and regulations.

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Conflict of interest statement

A.T. has received consultancy fees from Allergan (Dublin, Ireland), Astellas (Tokyo, Japan), AMS/Boston Scientific (Marlborough, USA), Bayer (Leverkusen, Germany), GSK (Middlesex, UK), and Shionogy (Florham Park, USA); investigator for GSK, Shionogy, Bayer, and Pierre Fabre (Paris, France).

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References

1. Sexton CC, Coyne KS, Kopp ZS, *et al.* The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. *BJU Int* 2009; 103(Suppl. 3): 12–23.
2. Irwin DE, Milsom I, Hunskaar S, *et al.* Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006; 50: 1306–1314.
3. Abrams P, Cardozo L, Fall M, *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167–178.
4. Drake MJ. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. *Neurourol Urodyn* 2014; 33: 622–624.
5. Coyne KS, Sexton CC, Irwin DE, *et al.* 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: 1388–1395.

6. Stewart WF, Van Rooyen JB, Cundiff GW, *et al*. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003; 20: 327–336.
7. Agarwal A, Eryuzlu LN, Cartwright R, *et al*. What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. *Eur Urol* 2014; 65: 1211–1217.
8. Gormley EA, Lightner DJ, Faraday M, *et al*. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *J Urol* 2015; 193: 1572–1580.
9. Benner JS, Nichol MB, Rovner ES, *et al*. Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010; 105: 1276–1282.
10. Wagg A, Compion G, Fahey A, *et al*. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012; 110: 1767–1774.
11. Oelke M, Speakman M, Desgrandchamps F, *et al*. Acute urinary retention rates in the general male population and in adult men with lower urinary tract symptoms participating in pharmacotherapy trials – a literature review. *Urology* 2015; 86: 654–665.
12. Khullar V, Amarenco G, Angulo JC, *et al*. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *Eur Urol* 2013; 63: 283–295.
13. Nitti VW, Auerbach S, Martin N, *et al*. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *J Urol* 2013; 189: 1388–1395.
14. Herschorn S, Barkin J, Castro-Diaz D, *et al*. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology* 2013; 82: 313–320.
15. Nitti V, Khullar V, van Kerrebroeck P, *et al*. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract* 2013; 67: 619–632.
16. Batista JE, Kölbl H, Herschorn S, *et al*. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: results of a non-inferiority, randomised, phase IIIb trial. *Ther Adv Urol* 2015; 7: 167–179.
17. Yamaguchi O, Marui E, Kakizaki H, *et al*. Phase III, randomised, double-blind, placebo-controlled study of the β3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. *BJU Int* 2014; 113: 951–960.
18. Kuo HC, Lee KS, Na Y, *et al*. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder in Asia. *Neurourol Urodyn* 2015; 34: 685–692.
19. Chapple CR, Kaplan SA, Mitcheson D, *et al*. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β_3-adrenoceptor agonist, in overactive bladder. *Eur Urol* 2013; 63: 296–305.
20. Wagg A, Franks B, Ramos B, *et al*. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: early experience in Canada. *Can Urol Assoc J* 2015; 9: 343–350.
21. Nitti VW, Rosenberg S, Mitcheson DH, *et al*. Urodynamics and safety of the β_3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. *J Urol* 2013; 190: 1320–1327.
22. Astellas Pharma US, Inc. Prescribing information for MYRBETRIQ® (mirabegron) extended-release tablets, for oral use, http://www.us.astellas.com/docs/Myrbetriq_WPI.pdf (2016, accessed 31 March 2017).
23. Gravas S, Bach T, Bachmann A, *et al*. European Association of Urology Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS) including benign prostatic obstruction, http://uroweb.org/wp-content/uploads/EAU-Guidelines-Non-Neurogenic-Male-LUTS-Guidelines-2015-v2.pdf (2015, accessed 31 March 2017).
24. Lee JY, Kim HW, Lee SJ, *et al*. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int* 2004; 94: 817–820.
25. Masumori N, Tsukamoto T, Yanase M, *et al*. The add-on effect of solifenacin for patients with remaining overactive bladder after treatment with tamsulosin for lower urinary tract symptoms suggestive of benign prostatic obstruction. *Adv Urol*. Epub ahead of print 26 October 2010. DOI: 10.1155/2010/205251.
26. Lee KS, Choo MS, Kim DY, *et al*. Combination treatment with propiverine hydrochloride plus

doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. *J Urol* 2005; 174: 1334–1338.

27. Ichihara K, Masumori N, Fukuta F, *et al.* A randomized controlled study of the efficacy of tamsulosin monotherapy and its combination with mirabegron for overactive bladder induced by benign prostatic obstruction. *J Urol* 2015; 193: 921–926.
28. Notte SM, Marshall TS, Lee M, *et al.* Content validity and test-retest reliability of Patient Perception of Intensity of Urgency Scale (PPIUS) for overactive bladder. *BMC Urol* 2012; 12: 26.
29. Oelke M, Adler E, Marschall-Kehrel D, *et al.* Nocturia – state of the art and critical analysis of current assessment and treatment strategies. *World J Urol* 2014; 32: 1109–1117.
30. Irwin DE, Milsom I, Kopp Z, *et al.* Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. *Eur Urol* 2009; 56: 14–20.
31. Oelke M, Wiese B and Berges R. Nocturia and its impact on health-related quality of life and health care seeking behaviour in German community-dwelling men aged 50 years or older. *World J Urol* 2014; 32: 1155–1162.
32. Andersson KE, Sarawate C, Kahler KH, *et al.* Cardiovascular morbidity, heart rates and use of antimuscarinics in patients with overactive bladder. *BJU Int* 2010; 106: 268–274.
33. Rosa GM, Ferrero S, Nitti VW, *et al.* Cardiovascular safety of β_3-adrenoceptor agonists for the treatment of patients with overactive bladder syndrome. *Eur Urol* 2016; 69: 311–323.
34. Knutson T, Edlund C, Fall M, *et al.* BPH with coexisting overactive bladder dysfunction–an everyday urological dilemma. *Neurourol Urodyn* 2001; 20: 237–247.
35. Oelke M, Baard J, Wijkstra H, *et al.* Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *Eur Urol* 2008; 54: 419–426.
36. Athanasopoulos A, Chapple C, Fowler C, *et al.* The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. *Eur Urol* 2011; 60: 94–105.
37. Sung Yong C, Hyun Dong S, In Rae C, *et al.* The risk factors increasing post-void residual urine volume after long term anticholinergics therapy over 1 year in patients with benign prostatic hyperplasia accompanied with overactive bladder. *Eur Urol Suppl* 2009; 8: 237.
38. Furuya S, Ogura H, Tanaka M, *et al.* Incidence of postmicturition dribble in adult males in their twenties through fifties (English abstract). *Acta Urologica Japonica* 1997; 43: 407–410.
39. Hartmann KE, McPheeters ML, Biller DH, *et al. Treatment of overactive bladder in women*. Evidence Report/Technology Assessment No.187 (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290–2007–10065-I). AHRQ Publication No. 09-E017. Rockville, MD: Agency for Healthcare Research and Quality, 2009.