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Platinum Priority – Incontinence

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Efficacy and Tolerability of Mirabegron, a β_3-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European–Australian Phase 3 Trial

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Abstract

Background: Mirabegron, a β_3-adrenoceptor agonist, has been developed for the treatment of overactive bladder (OAB).
Objective: To assess the efficacy and tolerability of mirabegron versus placebo.
Design, setting, and participants: Multicenter randomised double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial conducted in 27 countries in Europe and Australia in patients ≥18 yr of age with symptoms of OAB for ≥3 mo.
Intervention: After a 2-wk single-blind placebo run-in period, patients were randomised to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release 4 mg orally once daily for 12 wk.
Outcome measurements and statistical analysis: Patients completed a micturition diary and quality-of-life (QoL) assessments. Co–primary efficacy end points were change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 h. The primary comparison was between mirabegron and placebo with a secondary comparison between tolterodine and placebo. Safety parameters included adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, and postvoid residual volume.
Results and limitations: A total of 1978 patients were randomised and received the study drug. Mirabegron 50-mg and 100-mg groups demonstrated statistically significant improvements (adjusted mean change from baseline [95% confidence intervals]) at the final visit in the number of incontinence episodes per 24 h (−1.57 [−1.79 to −1.35] and −1.46 [−1.68 to −1.23], respectively, vs placebo −1.17 [−1.39 to −0.95]) and number of micturitions per 24 h (−1.93 [−2.15 to −1.72] and −1.77 [−1.99 to −1.56], respectively, vs placebo −1.34 [−1.55 to −1.12]; $p < 0.05$ for all comparisons). Statistically significant improvements were also observed in other key efficacy end points and QoL outcomes. The incidence of treatment-emergent AEs was similar across treatment groups. The main limitation of this study was the short (12-wk) duration of treatment.
Conclusions: Mirabegron represents a new class of treatment for OAB with proven efficacy and good tolerability.
Trial identification: This study is registered at ClinicalTrials.gov, identifier NCT00689104.

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1. Introduction

Overactive bladder syndrome (OAB) affects >400 million people worldwide [1]. The prevalence of OAB increases with age, affecting 30–40% of the population >75 yr of age [2,3].

Treatment options for OAB include antimuscarinics as first-line pharmacotherapy [4,5]; however, OAB patients may have a suboptimal response or find that antimuscarinic therapy is limited by associated adverse events (AEs), with dry mouth the most common and bothersome AE [6,7]. For these patients there has not been another class of oral therapeutic agents available; therefore, there is a need for a new treatment option for OAB that is effective and well tolerated, with a distinct mechanism of action.

An important role has been proposed for the β_3-adrenergic receptor (β_3-AR) in promoting urine storage in the bladder by inducing detrusor relaxation [8,9]. Mirabegron is a β_3-AR agonist that has been developed for the treatment of OAB. The effects of mirabegron on the symptoms of OAB have been examined in completed phase 2 (NCT01604928 and NCT00337090) and phase 3 studies (NCT00689104, NCT00662909, NCT00912964, and NCT00688688), and it is the first drug in this class to be approved for the treatment of symptoms of OAB. The results of one of these studies (NCT00689104), a large phase 3 trial conducted in Europe and Australia, are presented here. The purpose of this study was to assess the efficacy, safety, and tolerability of mirabegron 50 mg and 100 mg once daily in a multinational and multicenter randomised double-blind, parallel-group placebo- and tolterodine extended-release (ER)-controlled trial in patients with OAB. The tolterodine ER control served to place the efficacy and safety of mirabegron in context with that of an established antimuscarinic OAB treatment; however, no statistical comparisons were performed for mirabegron versus tolterodine ER.

2. Materials and methods

2.1. Study design and participants

This 12-wk multinational and multicenter randomised double-blind, parallel-group placebo- and active-controlled trial was conducted at 189 sites in 27 countries in Europe and Australia. The study population consisted of men and women ≥18 yr of age with symptoms of OAB for ≥3 mo. Patients were selected for randomisation if they met all inclusion criteria including an average micturition frequency of eight or more times per 24-h period and at least three episodes of urgency, with or without incontinence, during a 3-d micturition diary period. Key OAB-related exclusion criteria included stress incontinence or stress-predominant mixed incontinence at screening, or an average total daily urine volume >3000 ml as recorded in a 3-d micturition diary period (see the Appendix for the full inclusion and exclusion criteria). All patients provided written informed consent. The study was approved by the institutional review board of each study site and conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation guidelines, and all applicable laws and regulations. After screening, patients were enrolled in a 2-wk single-blind, placebo run-in period. Upon completion of this run-in period, patients meeting selection criteria were randomly assigned in a 1:1:1:1 ratio to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine ER 4 mg orally once daily for 12 wk (Fig. 1).

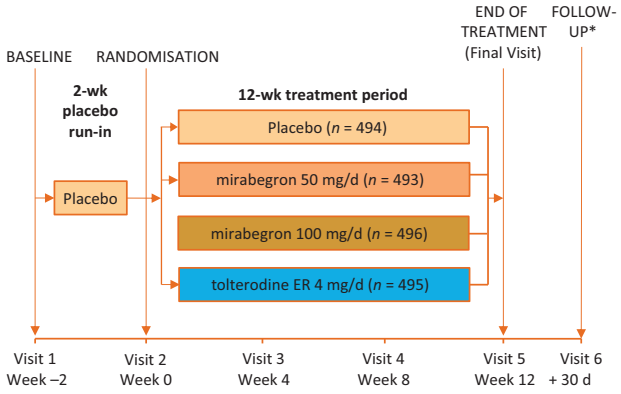

Fig. 1 – Study design. Numbers of patients are for the safety analysis set population. ER = extended release. *Evaluation of adverse events and concomitant medication by telephone or visit for a period of 30 d.

2.2. Randomisation and masking

Randomisation was accomplished using a computer-generated randomisation scheme prepared by Pierrel Research Europe GmbH (Essen, Germany) with stratification by country; allocation to treatment groups at each site was accomplished via an interactive response system. During the placebo run-in period, patients were blinded to the identity of the study drug, and during the double-blind treatment, both patients and investigators were blinded to the identity of the randomised drug assignment.

2.3. Efficacy and safety assessments

To assess the efficacy of mirabegron, patients completed a paper micturition diary for a 3-d period before clinic visits at baseline and at weeks 4, 8, and 12 (final visit). Co–primary efficacy end points were a change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 h. The primary comparison was between mirabegron and placebo with a secondary comparison between tolterodine and placebo. Key secondary efficacy end points included change from baseline to final visit in mean volume voided per micturition, and changes from baseline to week 4 in mean number of incontinence episodes and micturitions per 24 h. The percentage of responders at final visit (patients with ≥50% decrease from baseline in mean number of incontinence episodes per 24 h) and the percentage of responders with no incontinence episodes were also assessed.

Additional secondary efficacy variables were included to assess patient perception of improvement in health-related quality of life (QoL). These included the OAB Questionnaire (OAB-q), the Patient Perception of Bladder Condition (PPBC), and the Treatment Satisfaction-Visual Analog Scale (TS-VAS).

Safety assessments included reporting of AEs, clinical laboratory assessments, vital signs, physical examination, electrocardiogram (ECG) findings, and measurement of postvoid residual (PVR) volume. Notable shifts in PVR volume from baseline to final visit were defined as those >300 ml or those that changed from a baseline PVR volume of <150 ml to >150 ml but <300 ml. An independent cardiovascular adjudication committee determined all deaths and serious potential cardiovascular AEs using the categorisation of Antiplatelet Trialists' Collaboration/Major Adverse Cardiovascular Events (APTC/MACE) or non-APTC/MACE.

2.4. Statistical analyses

A sample size of 362 evaluable patients per treatment group would provide approximately 90% power to detect a reduction of 0.7 (standard deviation: 2.7) in the mean number of micturitions per 24 h in either mirabegron group versus placebo. A two-sided significance level of 0.027 was used based on the Dunnett test, which takes into account multiplicity for the two mirabegron dose group comparisons with placebo. Assuming that 65% of the population will be incontinent at baseline, 234 evaluable patients per treatment group would be included in the analysis for the mean number of incontinence episodes per 24 h. A power analysis done for a Wilcoxon rank-sum test based on ordered categories revealed a power of 97%. Assuming that at least 85% of randomised patients were evaluable and a dropout rate of 20% during the placebo run-in period, a total of 2160 patients were to be enrolled in the study.

Efficacy was assessed using either the full analysis set (FAS), which included all randomised patients who took at least one dose of the study drug and had at least a baseline and one postbaseline micturition measurement, or the FAS incontinence (FAS-I), which consisted of all FAS patients who had at least one incontinence episode at baseline. Safety analyses were performed on the safety analysis set (SAF), consisting of all randomised patients who took at least one dose of the study drug.

Efficacy analyses at the final visit were performed using the last observation carried forward method. Pairwise comparison was performed between both mirabegron groups and placebo and between the tolterodine group and placebo. No comparisons between mirabegron and tolterodine were performed. Multiplicity among the primary end points and key secondary end points was controlled at a 5% type 1 error rate using a stepwise parallel gatekeeping procedure. At each stage, the difference in mean change from baseline between a mirabegron dose group and placebo had to be statistically significant before proceeding to the next stage. The Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage when both mirabegron groups were compared with placebo and at the $\alpha = 0.025$ level when only one mirabegron group was compared with placebo. There was no multiplicity adjustment for additional secondary variables or for comparisons between tolterodine and placebo.

Inferential analyses for change from baseline in incontinence episodes were performed using a separate stratified rank analysis of covariance (ANCOVA) for each pairwise treatment group difference (mirabegron 50 and 100 mg vs placebo). All other change from baseline efficacy end points and vital sign variables were analysed using an ANCOVA model, including treatment, sex, and geographic region as fixed factors and baseline as a covariate. Responder end points were analysed using a logistic regression model that included treatment, sex, geographic region, and baseline. See the Appendix for the detailed statistical methodology.

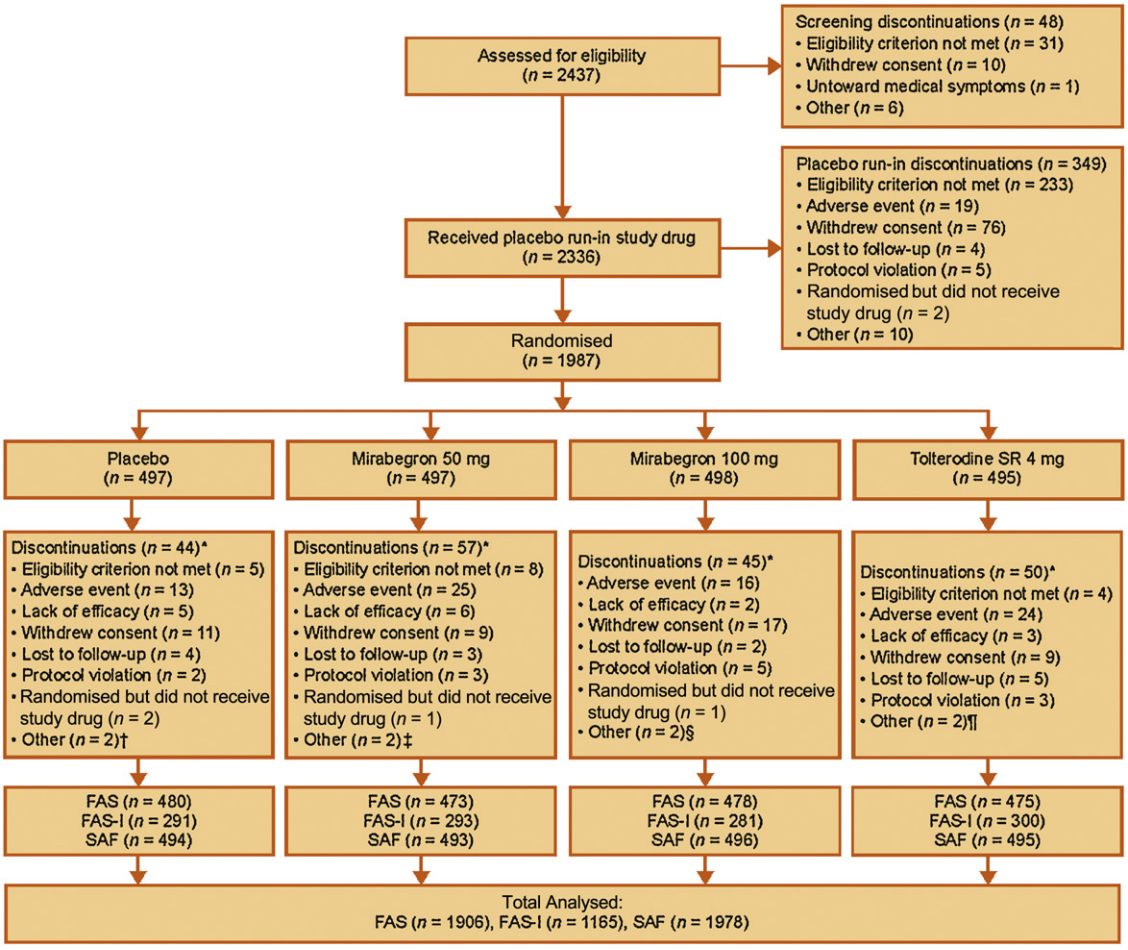

Fig. 2 – Study profile. FAS = full analysis set; FAS-I = full analysis set incontinence; SAF = safety analysis set; SR = sustained release. *Discontinuations are reported for randomised patients. †Other: personal reasons; blood pressure too difficult to measure. ‡Other: unable to commit to study schedule due to work commitments; patient was travelling and could not return in time to begin the study. §Other: excluded in error; patient had to move out of town. ¶Other: personal reasons; familial troubles.

3. Results

3.1. Patient demographics

A total of 2336 patients with symptoms of OAB for ≥3 mo were enrolled, of whom 1987 successfully completed the run-in phase and were randomised into the study (Fig. 2); 1978 randomised patients received the study drug. The number and proportion of patients who discontinued the study was comparable across all treatment groups.

Demographic and baseline characteristics were consistent across treatment groups for patients in the SAF (n = 1978; Table 1), FAS (n = 1906), and FAS-I (n = 1165) populations. OAB history characteristics were comparable across all treatment groups within each population; variations were consistent with FAS-I patients reporting at least one incontinence episode at baseline (Table 2). Approximately half of the patients had received previous treatment with OAB medication. Insufficient effect (approximately 67% of patients) and poor tolerability (approximately 27% of patients) were cited as primary reasons for the discontinuation of OAB drugs.

3.2. Efficacy

The mirabegron 50-mg and 100-mg groups showed statistically significant reductions in the mean number of incontinence episodes per 24 h compared with placebo (mean decreases of 1.57 and 1.46 for mirabegron 50 mg and 100 mg, respectively, vs 1.17 for placebo; $p < 0.05$ for both comparisons) (Table 3; Fig. 3). Similarly, statistically significant reductions were demonstrated with mirabegron 50 mg and 100 mg for the co–primary efficacy end point of change from baseline to final visit in the mean number of micturitions per 24 h (mean decreases of 1.93 and 1.77 for mirabegron 50 mg and 100 mg, respectively, vs 1.34 for placebo; $p < 0.05$ for both comparisons) (Table 3; Fig. 3). Improvements in co–primary efficacy end points were also observed with tolterodine ER but did not reach statistical significance compared with placebo ($p = 0.11$ for both).

For the key secondary efficacy end points, statistically significant reductions in the number of incontinence episodes and micturitions per 24 h were evident at week 4 (first measured time point) for both doses of mirabegron compared with placebo ($p < 0.05$ for both comparisons; Table 4), which was maintained over time (weeks 8 and 12). Mean difference versus placebo was only statistically significant for the tolterodine ER 4-mg group at week 4 (Table 4). Compared with placebo, all active treatment groups achieved statistically significant improvements from baseline in mean volume voided per micturition ($p < 0.05$; Table 4). The mirabegron 50 mg group achieved a statistically significant improvement from baseline to final visit in the mean number of episodes with urgency (grade 3 or 4) per 24 h (Table 4).

At the final visit, the percentage of responders (patients in the FAS-I with ≥50% decrease from baseline in the mean number of incontinence episodes per 24 h) in both mirabegron groups was greater than observed in the placebo group (mirabegron 50 mg: 72.0% vs 60.1%; odds ratio [OR]: 1.75; 95% confidence interval [CI], 1.23–2.49; $p = 0.002$; mirabegron 100 mg: 67.6% vs 60.1%; OR: 1.45; 95% CI, 1.02–2.05; $p = 0.037$). The percentage of responders who were incontinent at baseline and became dry at postbaseline was numerically, but nonsignificantly, higher in the mirabegron 50-mg group than in the placebo group, and this difference was maintained or increased from week 4 through the final visit (45.1% for mirabegron 50 mg compared with 40.5% for placebo at final visit; OR: 1.23; 95%

Table 1 – Demographic and baseline characteristics*

	Placebo	Mirabegron		Tolterodine ER 4 mg
		50 mg	100 mg	
Parameter category	(n = 494)	(n = 493)	(n = 496)	(n = 495)
Sex, n (%)				
Male	138 (27.9)	136 (27.6)	141 (28.4)	134 (27.1)
Female	356 (72.1)	357 (72.4)	355 (71.6)	361 (72.9)
Age, yr				
Mean (SD)	59.2 (12.30)	59.1 (12.36)	59.0 (12.71)	59.1 (12.89)
n (%) by age group				
≥65 yr	181 (36.6)	178 (36.1)	183 (36.9)	192 (38.8)
≥75 yr	44 (8.9)	46 (9.3)	46 (9.3)	37 (7.5)
Race, n (%)				
White	490 (99.2)	488 (99.0)	492 (99.2)	490 (99.0)
Black or African American	2 (0.4)	1 (0.2)	1 (0.2)	3 (0.6)
Asian	0	2 (0.4)	2 (0.4)	2 (0.4)
Other†	2 (0.4)	2 (0.4)	1 (0.2)	0
Body mass index, kg/m^2				
n	493	493	495	495
Mean (SD)	27.8 (4.96)	27.5 (4.86)	28.0 (4.95)	27.8 (4.96)

ER = extended release; SD = standard deviation.

* Safety analysis set.

† Other race: placebo: Romanian and Ghanaian; mirabegron 50 mg: Pakistani and Native American; mirabegron 100 mg: Latin American.

Table 2 – Overactive bladder history by treatment group

Parameter category	Placebo	Mirabegron		Tolterodine ER 4 mg
		50 mg	100 mg	
FAS analysis population	(*n* = 480)	(*n* = 473)	(*n* = 478)	(*n* = 475)
Type of OAB, *n* (%)[†]				
Urgency incontinence	201 (41.9)	192 (40.6)	179 (37.4)	184 (38.7)
Frequency	177 (36.9)	173 (36.6)	183 (38.3)	186 (39.2)
Mixed	102 (21.3)	108 (22.8)	116 (24.3)	105 (22.1)
Prior OAB surgery, *n* (%)				
Yes	22 (4.6)	33 (7.0)	28 (5.9)	17 (3.6)
Previous OAB drug, *n* (%)				
Yes	238 (49.6)	240 (50.7)	237 (49.6)	231 (48.6)
Reason for previous OAB drug discontinuation, *n* (%)[‡]				
Insufficient effect	159 (66.8)	160 (66.7)	159 (67.1)	155 (67.1)
Poor tolerability	68 (28.6)	65 (27.1)	64 (27.0)	56 (24.2)
Duration of OAB symptoms, mo				
Mean (SD)	76.9 (92.15)	78.7 (85.68)	85.3 (95.24)	76.3 (93.40)
Median	50.5	49.9	53.4	47.2
Range	3–688	3–637	3–567	3–711
FAS-I analysis population	(*n* = 291)	(*n* = 293)	(*n* = 281)	(*n* = 300)
Type of OAB, *n* (%)[†]				
Urgency incontinence	156 (53.6)	143 (48.8)	140 (49.8)	142 (47.3)
Frequency	47 (16.2)	59 (20.1)	43 (15.3)	65 (21.7)
Mixed	88 (30.2)	91 (31.1)	98 (34.9)	93 (31.0)
Prior OAB surgery, *n* (%)				
Yes	14 (4.8)	29 (9.9)	22 (7.8)	11 (3.7)
Previous OAB drug, *n* (%)				
Yes	167 (57.4)	164 (56.0)	167 (59.4)	160 (53.3)
Reason for previous OAB drug discontinuation, *n* (%)[‡]				
Insufficient effect	112 (67.1)	105 (64.0)	121 (72.5)	102 (63.8)
Poor tolerability	46 (27.5)	50 (30.5)	45 (26.9)	44 (27.5)
Duration of OAB symptoms, mo				
Mean (SD)	90.4 (105.08)	84.6 (89.59)	96.5 (97.67)	80.9 (95.03)
Median	62.5	54.0	63.3	50.7
Range	3–688	3–637	3–519	3–711

FAS = full analysis set; FAS-I = full analysis set incontinence; OAB = overactive bladder; SD = standard deviation.
[†] Predominant types of OAB were defined as follows: urgency incontinence = urge incontinence only; mixed = mixed stress/urge incontinence with urge as a predominant factor; frequency = frequency/urgency.
[‡] Patients could choose more than one reason for discontinuation of previous OAB drug.

CI, 0.86–1.76; $p = 0.26$). Table 4 shows the results for the 100-mg mirabegron group.

All three active treatment groups demonstrated a statistically significant improvement from baseline to final visit compared with placebo on the TS-VAS, OAB-q, and PPBC at each assessment point (Table 5).

3.3. *Tolerability*

The incidence of treatment-emergent AEs (TEAEs) was similar across the placebo, mirabegron 50-mg and 100-mg, and tolterodine ER 4-mg groups (Table 6). Most TEAEs were mild or moderate in all treatment groups. Importantly, the incidence of dry mouth in the mirabegron 50-mg and 100-mg groups was similar to placebo (2.8%, 2.8%, and 2.6%, respectively). Dry mouth was more than three-fold higher in patients receiving tolterodine ER 4 mg (10.1%). Hypertension was reported in the mirabegron 50-mg and 100-mg groups (5.9% and 5.4%, respectively), but the incidence was lower than placebo (7.7%) or tolterodine ER 4-mg treated patients (8.1%).

The number of patients discontinuing study drug due to a TEAE was low, at 2.6%, 4.9%, 3.2%, and 4.4% for placebo, mirabegron 50-mg, mirabegron 100-mg, and tolterodine ER 4-mg groups, respectively.

Cardiovascular-related events were closely monitored in this study. The proportion of patients with hypertension TEAEs was higher in the tolterodine ER 4-mg and placebo groups than in either mirabegron group. The incidence of TEAEs of QTc prolongation or its sequelae, arrhythmia, and atrial fibrillation are shown in Table 6. Only one patient had a TEAE adjudicated as an APTC/MACE cardiovascular event: A patient in the tolterodine ER 4-mg group experienced a cardiovascular death due to a ruptured cerebral aneurysm 10 d after the last dose of the study drug.

At the final visit, mirabegron was associated with small dose-dependent increases in AM and PM pulse rates compared with placebo (AM: 0.8 bpm, 95% CI, 0.0–1.6 and 1.6 bpm, 95% CI, 0.8–2.4; PM: 0.7 bpm, 95% CI, –0.1 to 1.5 and 2.0 bpm, 95% CI, 1.2–2.8 for mirabegron 50 mg and 100 mg, respectively) that were similar to those seen with

Table 3 – Co–primary efficacy end points

Statistic	Placebo	Mirabegron		Tolterodine ER 4 mg
		50 mg	100 mg	
Mean number of incontinence episodes per 24 h (FAS-I)				
	(*n* = 291)	(*n* = 293)	(*n* = 281)	(*n* = 300)
Baseline				
Mean (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)
Median	2.00	2.00	2.33	1.67
Range	0.3–13.3	0.3–16.7	0.3–14.0	0.3–11.7
Final visit				
Mean (SE)	1.54 (0.145)	1.22 (0.133)	1.37 (0.134)	1.42 (0.145)
Median	0.67	0.33	0.33	0.33
Range	0.0–17.7	0.0–17.7	0.0–19.3	0.0–14.7
Change from baseline				
Mean (SE)	−1.13 (0.126)	−1.62 (0.137)	−1.51 (0.128)	−1.21 (0.137)
Median	−1.00	−1.00	−1.33	−1.00
Range	−11.7 to 10.0	−12.0 to 5.7	−11.3 to 9.7	−10.3 to 9.3
ANCOVA model*				
Adjusted mean change from baseline (SE)	−1.17 (0.113)	−1.57 (0.113)	−1.46 (0.115)	−1.27 (0.112)
95% two-sided CI	(−1.39 to −0.95)	(−1.79 to −1.35)	(−1.68 to −1.23)	(−1.49 to −1.05)
Mean difference vs placebo (SE)	NA	−0.41 (0.160)	−0.29 (0.162)	−0.10 (0.159)
95% two-sided CI	NA	(−0.72 to −0.09)	(−0.61 to 0.03)	(−0.42 to 0.21)
p value†	NA	0.003§	0.010§	0.11
Mean number of micturitions per 24 h (FAS)				
	(*n* = 480)	(*n* = 473)	(*n* = 478)	(*n* = 475)
Baseline				
Mean (SE)	11.71 (0.143)	11.65 (0.137)	11.51 (0.124)	11.55 (0.128)
Median	11.00	11.00	11.00	11.00
Range	5.3–25.0	6.7–25.7	6.7–23.3	6.0–22.7
Final visit				
Mean (SE)	10.35 (0.144)	9.70 (0.139)	9.76 (0.144)	9.97 (0.162)
Median	10.00	9.00	9.00	9.33
Range	4.3–24.3	4.0–25.3	4.0–24.0	3.7–35.7
Change from baseline				
Mean (SE)	−1.37 (0.115)	−1.94 (0.116)	−1.75 (0.110)	−1.57 (0.123)
Median	−1.17	−1.67	−2.00	−1.67
Range	−13.0 to 6.7	−14.0 to 7.3	−9.0 to 8.7	−10.3 to 13.0
ANCOVA model*				
Adjusted mean change from baseline (SE)	−1.34 (0.110)	−1.93 (0.111)	−1.77 (0.100)	−1.59 (0.111)
95% two-sided CI	(−1.55 to −1.12)	(−2.15 to −1.72)	(−1.99 to −1.56)	(−1.80 to −1.37)
Mean difference vs placebo (SE)	NA	−0.60 (0.156)	−0.44 (0.156)	−0.25 (0.156)
95% two-sided CI	NA	(−0.90 to −0.29)	(−0.74 to −0.13)	(−0.55 to 0.06)
p value‡	NA	<0.001§	0.005§	0.11

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FAS-I = full analysis set incontinence; NA = not applicable; SE = standard error.

* The ANCOVA model included treatment group, sex, and geographic region as fixed factors and baseline as a covariate.

† Nominal *p* values were from pairwise comparisons versus placebo within the stratified rank ANCOVA, a nonparametric analysis.

‡ Nominal *p* values were from pairwise comparisons versus placebo within the ANCOVA model, a parametric analysis.

§ Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustments.

tolterodine ER 4 mg. Adjusted mean changes from baseline in systolic and diastolic blood pressure measurements were <1.5 mm Hg; these were similar across treatment groups and between the normotensive and hypertensive population. Increases in heart rate were consistent with increases in pulse rate. No consistent ECG trends were identified. The proportion of patients with notable shifts in PVR volume was comparable across treatment groups: 1 (0.2%), 2 (0.4%), and 1 (0.2%) patient(s) in the mirabegron 50-mg, 100-mg, and tolterodine ER 4-mg groups had PVR volumes >300 ml at the final visit. Changes in haematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups.

4. Discussion

Antimuscarinic therapy is the current standard first-line pharmacotherapy for OAB. However, although these agents are generally effective, some patients experience a suboptimal response to treatment or experience frequent, bothersome AEs, the most common of which is dry mouth. Patients with suboptimal responses to antimuscarinic treatment or who are unwilling to continue treatment due to the associated AEs have no other oral drug available as a treatment option.

With the β_3-AR implicated in promoting urine storage in the bladder, research has focused on the effects of β_3-AR

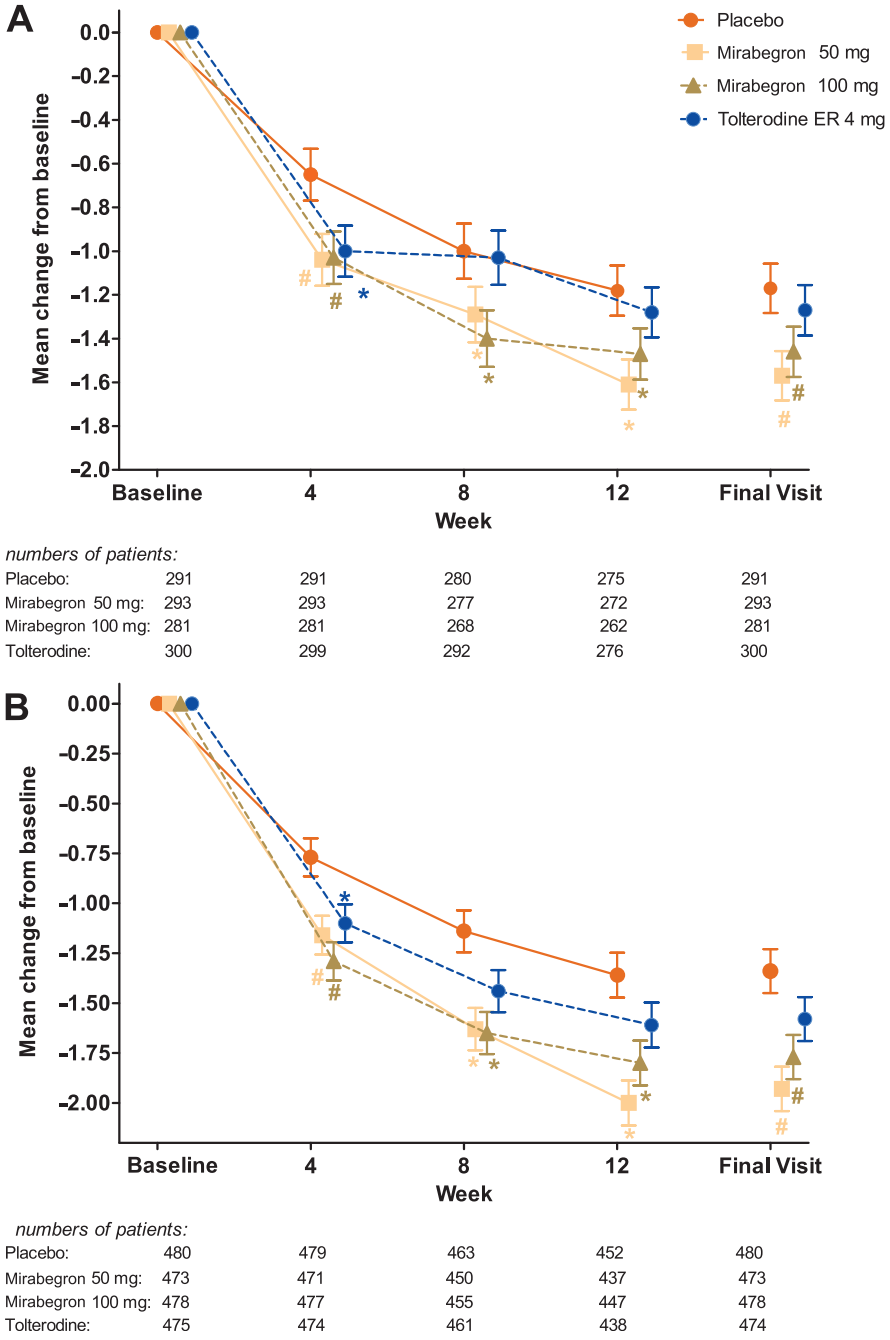

Fig. 3 – Adjusted mean change from baseline at each visit for co–primary efficacy end points. (A) Mean number of incontinence episodes per 24 h (full analysis set incontinence); (B) mean number of micturitions per 24 h (full analysis set). ER = extended release. *Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustments. #Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustments.

agonists on the symptoms of OAB. A recent phase 2 study demonstrated the potential of solabegron, which significantly reduced the symptoms of OAB in women with moderate to severe OAB [10]. However, mirabegron is the first drug in this class to have completed phase 3 registration studies and, following approval for the treatment of OAB in both Japan and the United States, represents a new oral agent for the treatment of OAB. In the current study, mirabegron at doses of 50 mg and 100 mg once daily for 12 wk demonstrated clinical efficacy in the treatment of the symptoms of urgency, urinary incontinence, and frequency. This is supported by data demonstrating QoL improvements with mirabegron, as measured by the TS-VAS, PPBC, and symptom bother score of the OAB-q. Comparisons of the relative efficacy of mirabegron and solabegron are difficult due to differences in study design, duration, and population [10].

Mirabegron at doses of 50 mg and 100 mg once daily for 12 wk was well tolerated. It is notable that the incidence of dry mouth, reported to be an important factor for

Table 4 – Key and additional secondary efficacy end points

Statistic	Placebo	Mirabegron		Tolterodine ER 4 mg
		50 mg	100 mg	
Change from baseline to final visit in mean volume voided, ml, per micturition (FAS)				
	(*n* = 480)	(*n* = 472)	(*n* = 478)	(*n* = 475)
Adjusted mean change from baseline (SE)*	12.3 (1.99)	24.2 (2.01)	25.6 (2.00)	25.0 (2.00)
95% two-sided CI	(8.4–16.3)	(20.3–28.2)	(21.6–29.5)	(21.1–28.9)
Mean difference vs placebo (SE)	NA	11.9 (2.83)	13.2 (2.82)	12.6 (2.83)
95% two-sided CI	NA	(6.3–17.4)	(7.7–18.7)	(7.1–18.2)
p value‡	NA	<0.001§	<0.001§	<0.001#
Change from baseline to week 4 in mean number of incontinence episodes per 24 h (FAS-I)				
	(*n* = 291)	(*n* = 293)	(*n* = 281)	(*n* = 299)
Adjusted mean change from baseline (SE)*	−0.65 (0.118)	−1.04 (0.118)	−1.03 (0.120)	−1.00 (0.117)
95% two-sided CI	(−0.88 to −0.42)	(−1.27 to −0.81)	(−1.27 to −0.79)	(−1.23 to −0.77)
Mean difference vs placebo (SE)	NA	−0.39 (0.17)	−0.38 (0.17)	−0.35 (0.17)
95% two-sided CI	NA	(−0.71 to −0.06)	(−0.71 to −0.05)	(−0.68 to −0.03)
p value†	NA	0.002§	0.002§	0.019#
Change from baseline to week 4 in mean number of micturitions per 24 h (FAS)				
	(*n* = 479)	(*n* = 471)	(*n* = 477)	(*n* = 474)
Adjusted mean change from baseline (SE)*	−0.77 (0.096)	−1.16 (0.097)	−1.29 (0.096)	−1.10 (0.096)
95% two-sided CI	(−0.96 to −0.58)	(−1.35 to −0.97)	(−1.48 to −1.10)	(−1.29 to −0.091)
Mean difference vs placebo (SE)	NA	−0.40 (0.14)	−0.52 (0.14)	−0.33 (0.14)
95% two-sided CI	NA	(−0.66 to −0.13)	(−0.79 to −0.26)	(−0.60 to −0.06)
p value‡	NA	0.004§	<0.001§	0.016#
Change from baseline to final visit in mean number of urgency episodes, grade 3 or 4, per 24 h (FAS)				
	(*n* = 479)	(*n* = 470)	(*n* = 474)	(*n* = 472)
Adjusted mean change from baseline (SE)*	−1.65 (0.15)	−2.25 (0.15)	−1.96 (0.15)	−2.07 (0.15)
Mean difference vs placebo (SE)	NA	−0.60 (0.21)	−0.31 (0.21)	−0.42 (0.21)
95% two-sided CI	NA	(−1.02 to −0.18)	(−0.73 to 0.11)	(−0.84 to −0.00)
p value‡		0.005#	0.14	0.050#
Responder analysis for reduction in incontinence episodes at final visit (FAS-I)				
	(*n* = 291)	(*n* = 293)	(*n* = 281)	(*n* = 300)
Responders (%)	175 (60.1)	211 (72.0)	190 (67.6)	205 (68.3)
Difference vs placebo	NA	11.9	7.5	8.2
95% two-sided CI¶	NA	(4.3–19.5)	(−0.4 to 15.3)	(0.5–15.9)
Odds ratio vs placebo¶¶	NA	1.75	1.45	1.44
95% two-sided CI	NA	(1.23–2.49)	(1.02–2.05)	(1.02–2.03)
p value¶¶	NA	0.002#	0.037#	0.037#
Responder analysis for zero incontinence episodes at final visit (FAS-I)				
	(*n* = 291)	(*n* = 293)	(*n* = 281)	(*n* = 300)
Responders (%)	118 (40.5)	132 (45.1)	123 (43.8)	142 (47.3)
Difference vs placebo	NA	4.5	3.2	6.8
95% two-sided CI¶	NA	(−3.5 to 12.5)	(−4.9 to 11.3)	(−1.2 to 14.8)
Odds ratio vs placebo¶¶	NA	1.23	1.29	1.35
95% two-sided CI	NA	(0.86–1.76)	(0.90–1.84)	(0.95–1.92)
p value¶¶	NA	0.26	0.17	0.097

ANCOVA = analysis of covariance; CI = confidence interval; ER = extended release; FAS = full analysis set; FAS-I = full analysis set incontinence; NA = not applicable; SE = standard error.

* Adjusted mean change from baseline is calculated from the ANCOVA model that included treatment group, sex, and geographic region as fixed factors and baseline as a covariate.

† Nominal *p* values were from pairwise comparisons versus placebo within the stratified rank ANCOVA, a nonparametric analysis.

‡ Nominal *p* values were from pairwise comparisons versus placebo within the ANCOVA model, a parametric analysis.

§ Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustments.

Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustments.

¶ 95% CI is for the difference of the proportions based on the normal approximation.

¶¶ Odds ratio and *p* values were from the logistic regression model including treatment group, sex, and geographic region as factors and baseline as covariate.

Table 5 – Additional secondary efficacy end points assessing patient perception of quality of life

Statistic	Placebo	Mirabegron		Tolterodine ER 4 mg
		50 mg	100 mg	
Change from baseline to final visit in treatment satisfaction visual analogue scale (FAS)[¶]				
	(*n* = 428)	(*n* = 414)	(*n* = 427)	(*n* = 425)
ANCOVA model[*]				
Adjusted mean change from baseline (SE)	1.89 (0.146)	2.55 (0.149)	2.66 (0.146)	2.44 (0.147)
Mean difference vs placebo (SE)	NA	0.66 (0.208)	0.77 (0.207)	0.55 (0.207)
95% two-sided CI	NA	(0.25–1.07)	(0.36–1.17)	(0.14–0.95)
p value[‡]	NA	0.001[#]	<0.001[#]	0.008[#]
Change from baseline to final visit in Symptom Bother Scale as assessed by the OAB-q (FAS)[¶¶]				
	(*n* = 475)	(*n* = 465)	(*n* = 473)	(*n* = 469)
ANCOVA model[*]				
Adjusted mean change from baseline (SE)	−14.9 (0.84)	−19.6 (0.85)	−19.9 (0.84)	−18.4 (0.85)
Mean difference vs placebo (SE)	NA	−4.7 (1.19)	−5.0 (1.19)	−3.5 (1.19)
95% two-sided CI	NA	(−7.1 to −2.4)	(−7.3 to −2.6)	(−5.9 to −1.2)
p value[‡]	NA	<0.001[#]	<0.001[#]	<0.003[#]
Change from baseline to final visit in Patient Perception of Bladder Condition (FAS)[§]				
	(*n* = 433)	(*n* = 416)	(*n* = 429)	(*n* = 426)
ANCOVA model[*]				
Adjusted mean change from baseline (SE)	−0.8 (0.05)	−1.0 (0.06)	−1.1 (0.05)	−1.0 (0.06)
Mean difference vs placebo (SE)	NA	−0.2 (0.08)	−0.2 (0.08)	−0.2 (0.08)
95% two-sided CI	NA	(−0.3 to −0.0)	(−0.4 to −0.1)	(−0.3 to −0.0)
p value[‡]	NA	0.045[#]	0.001[#]	0.023[#]

ANCOVA = analysis of covariance; CI = confidence interval; ER = extended release; FAS = full analysis set; NA = not applicable; OAB-q = Overactive Bladder Questionnaire; SE = standard error.

[*] The ANCOVA model included treatment group, sex, and geographic region as fixed factors and baseline as a covariate.

[‡] Nominal *p* values were from pairwise comparisons versus placebo within the ANCOVA model.

[#] Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustments.

[¶] Treatment satisfaction was assessed on a visual analogue scale with complete satisfaction indicated by a score of 10. A positive change from baseline indicates improvement.

[¶¶] Scores for the Symptom Bother Scale of the OAB-q ranged from 0 to 100, with a score of 100 indicating the worst severity. A negative change from baseline indicates improvement.

[§] The Patient Perception of Bladder Condition uses a 6-point Likert scale, on which a score of 1 indicates "no problems at all" and a score of 6 indicates "many severe problems." A negative change from baseline indicates improvement.

Table 6 – Common[*] and selected cardiovascular treatment-emergent adverse events[†]

MedDRA (v.9.1) preferred term, *n* (%)	Placebo (*n* = 494)	Mirabegron 50 mg (*n* = 493)	Mirabegron 100 mg (*n* = 496)	Tolterodine ER 4 mg (*n* = 495)
Common TEAEs				
Any AE	214 (43.3)	211 (42.8)	199 (40.1)	231 (46.7)
Hypertension	38 (7.7)	29 (5.9)	27 (5.4)	40 (8.1)
Nasopharyngitis	8 (1.6)	14 (2.8)	14 (2.8)	14 (2.8)
Dry mouth	13 (2.6)	14 (2.8)	14 (2.8)	50 (10.1)
Headache	14 (2.8)	18 (3.7)	9 (1.8)	18 (3.6)
Influenza	8 (1.6)	11 (2.2)	10 (2.0)	7 (1.4)
Urinary tract infection	7 (1.4)	7 (1.4)	9 (1.8)	10 (2.0)
Constipation	7 (1.4)	8 (1.6)	8 (1.6)	10 (2.0)
Cardiovascular TEAEs				
QTc prolongation or its sequelae	0	0	0	2 (0.4)
Atrial fibrillation of medical importance	1 (0.2)	2 (0.4)	2 (0.4)	5 (1.0)
Arrhythmia	5 (1.0)	11 (2.2)	9 (1.8)	16 (3.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[*] ≥2% of patients in any treatment group.

[†] Safety analysis set.

Patients with one or more AEs within a level of a MedDRA term were counted only once in that level. Summarised AEs were reported after the first dose and no more than 30 d after the last dose of the double-blind study drug.

determining persistence with antimuscarinic agents [7,11,12], was similar in the placebo and mirabegron groups. Hence the tolerability profile of mirabegron offers the potential to improve persistence with OAB treatment in clinical practice.

This therapy did not exhibit any significant cardiac AEs. In this study, the overall incidence of hypertension was lower with mirabegron compared with placebo and tolterodine ER. There were more cardiac arrhythmia events in tolterodine-treated patients than in mirabegron- and placebo-treated patients. The overall incidence of adjudicated cardiovascular events was similar in placebo- and mirabegron-treated patients, and slightly higher in tolterodine-treated patients. A dose-dependent increase in pulse rate was observed with mirabegron 50 mg and 100 mg; these changes were small, not clinically meaningful, and comparable with pulse rate changes reported for antimuscarinics [13–15]. The data in this study support the cardiovascular safety of mirabegron in this patient population.

This study has a number of limitations in common with other OAB studies of similar design. First, as for other therapeutic agents assessed in OAB trials of 12-wk duration and similar follow-up periods, the longer term safety, efficacy, and persistence of mirabegron cannot be extrapolated from this study. A longer term (1 yr) safety study has been completed (NCT00688688). Second, the study design did not allow a head-to-head comparison of mirabegron and tolterodine, which was included simply as an active control. Finally, it should be noted that, as seen in other studies of antimuscarinic agents in OAB [16], a high placebo response diminished the treatment effect seen with mirabegron in this study; however, the effects of mirabegron are at least as good as those of tolterodine, the active control. This study population included a significant proportion of patients who had previously discontinued prior antimuscarinic treatment for various reasons, including lack of efficacy, which may have diminished the magnitude of the tolterodine treatment effect.

5. Conclusions

Mirabegron represents a new class of treatment for OAB with proven efficacy and good tolerability. It offers promise as an effective oral agent for the treatment of OAB with a distinct efficacy/tolerability balance.

Author contributions: Vik Khullar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Khullar, Amarenco, Angulo, Cambronero, Høye, Milsom, Chapple, Boerrigter, Drogendijk, Wooning.
Acquisition of data: Khullar, Amarenco, Angulo, Cambronero, Høye, Milsom, Radzisewski, Rechberger, Chapple, Boerrigter, Drogendijk, Wooning.
Analysis and interpretation of data: Khullar, Amarenco, Angulo, Cambronero, Høye, Milsom, Radziszewski, Rechberger, Boerrigter, Drogendijk, Wooning, Chapple.
Drafting of the manuscript: Khullar, Amarenco, Angulo, Cambronero, Høye, Milsom, Radziszewski, Rechberger, Boerrigter, Drogendijk, Wooning, Chapple.
Critical revision of the manuscript for important intellectual content: Khullar, Amarenco, Angulo, Cambronero, Høye, Milsom, Radziszewski, Rechberger, Boerrigter, Drogendijk, Wooning, Chapple.
Statistical analysis: Drogendijk.
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Appendix A

A.1. Inclusion and exclusion criteria

A patient was eligible for enrolment in the study if the following inclusion criteria were met at study screening: male or female $\geq$18 yr of age; institutional review board/independent ethics committee–approved written informed consent and privacy language as per national regulations were obtained from the patient or legally authorised representative; patient was willing and able to complete the micturition diary and questionnaires correctly; and patient had symptoms of OAB (urinary

frequency and urgency with or without incontinence) for ≥3 mo.

A patient was excluded from participation if any of the following criteria applied: if the patient was breastfeeding or pregnant, intended to become pregnant during the study, or was of childbearing potential, sexually active, and not practising a highly reliable method of birth control (in women of childbearing potential, a pregnancy test administered at screening was required to be negative); if the patient had clinically significant bladder outflow obstruction at risk of urinary retention (at the discretion of the investigator), significant stress incontinence or mixed stress/urgency incontinence where stress was the predominant factor as determined by the investigator, an indwelling catheter or practised intermittent self-catheterisation, diabetic neuropathy, severe hypertension (defined as a sitting average systolic blood pressure ≥180 mm Hg and/or average diastolic blood pressure ≥110 mm Hg), evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs, uncontrolled narrow-angle glaucoma, urinary or gastric retention, severe colitis ulcerosa, toxic megacolon, myasthenia gravis, or any other medical condition that in the opinion of the investigator contraindicated the use of anticholinergics; known or suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, other β-ADRrs, or any of the other inactive ingredients; if the patient was receiving nondrug treatment including electrostimulation therapy (although a bladder training program or pelvic floor exercises that had started >30 d prior to entry to the study could be continued); medications intended to treat OAB or prohibited medications (anticholinergics/antispasmodics, CYP2D6 substrates with a narrow therapeutic index [thioridazine, flecainide, and propafenone], strong CYP3A4 inhibitors, antibiotics/antivirals, antifungals, antiarrhythmics, or cisapride, metoclopramide, or nefazodone). The use of CYP3A4 inducers, loop diuretics, α-blockers, and 5α-reductase inhibitors was permitted during the study if the patients had been taking the medication on a long-term basis at one dose and that the dose had not changed in the month prior to entry in the study. In addition, patients were excluded if they had been treated with any investigational drug or device within 30 d (90 d in the United Kingdom) prior to screening; had any clinically significant condition that in the opinion of the investigator made them unsuitable for the study, or were an employee of the Astellas group or third parties associated with the study or the study site.

At baseline, patients were excluded if they had an average total daily urine volume >3000 ml, as recorded in the 3-d micturition diary period; had, in the opinion of the investigator, clinical significant increases in laboratory values as assessed in screening samples (eg, serum creatinine >150 μmol/l, aspartate aminotransferase and/or alanine aminotransferase more than two times the upper limit of normal (ULN), or gamma glutamyl transferase more than three times ULN; severe hypertension (as defined earlier); or an abnormal ECG that in the opinion of the investigator made the patient unsuitable for the study.

A.2. Sample size

There were two co–primary end points: change from baseline to final visit in the mean number of micturitions per 24 h based on a 3-d micturition diary and change from baseline to final visit in the mean number of incontinence episodes per 24 h based on a 3-d micturition diary.

A sample size of 362 evaluable patients per treatment group would provide about 90% power to detect a reduction of 0.7 in the mean number of micturitions per 24 h over placebo in the mirabegron 50-mg group and/or the mirabegron 100-mg group at a two-sided significance level of 0.05. Both mirabegron doses were compared with placebo by means of the Dunnett test, which takes into account multiplicity, and the sample size calculation was based on this test. The standard deviation of the primary efficacy variable was assumed to be 2.7 based on the phase 2 study results.

The sample size calculation for the mean number of incontinence episodes was based on nonparametric methods because the results of the phase 2 study indicated that the assumption of normality might not be valid. The results of this study showed there were a lot of ties for these variables, and therefore the sample size calculation was based on a grouping "change from baseline in mean number of incontinence episodes per 24 h" to seven categories, although the actual analysis did not group the data. The categories for change from baseline in mean number of incontinence episodes per 24 h are listed here together with the percentages occurring in these categories for placebo and mirabegron 50 mg as found in the phase 2 study.

Categories	Placebo, %	Mirabegron 50 mg, %
Less than or equal to −2	20.8	30.6
−1.67	6.6	10.2
−1.33	6.6	4.6
−1	4.7	6.5
−0.67	12.3	15.7
−0.33	13.2	15.7
≥0	35.8	16.7

Only patients who were incontinent at baseline were included in the analysis. From the phase 2 study, it was estimated that this constituted about 65% of the population. This means that about 234 (0.65 × 362) evaluable patients per treatment group would be included in the analysis. A power analysis done for a Wilcoxon rank-sum test based on ordered categories revealed a power of 97% for the categories listed here and for 234 evaluable patients per treatment group with a two-sided significance level of 2.5%. Based on the categories listed here, the probability that a patient on mirabegron would respond better than a patient on placebo was 60.8%. If these data were to be normally distributed, this percentage would correspond to a difference of 0.85 and a standard deviation of 2.2 (obtained from

the phase 2 study). The entries for mirabegron 100 mg are virtually the same as for mirabegron 50 mg in the list of categories.

If "change from baseline in mean number of micturitions per 24 h" and "change from baseline in mean number of incontinence episodes per 24 h" would be independently distributed, the overall power would be 0.9×0.97, which is slightly >87%. However, because the two variables are positively correlated (Spearman rank correlation: 0.31), the overall power is between 87% and 90%.

Assuming that at least 85% of the randomised patients were evaluable, 430 patients were to be randomised to each treatment group. Assuming a dropout rate of 20% during the placebo run-in period, a total of 2160 patients were to be enrolled in the study.

A.3. Multiplicity adjustment for the co–primary efficacy and key secondary efficacy end points

Because there were two primary efficacy end points and three key secondary efficacy end points, multiplicity between the end points was controlled at a type I error rate at the $\alpha = 0.05$ level using a stepwise parallel gatekeeping procedure. Incontinence episodes at the final visit were evaluated at stage 1, and the difference in mean change from baseline between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to stage 2. Micturitions at the final visit were evaluated at stage 2, and the difference in mean change from baseline between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to stage 3. Volume voided per micturition at the final visit was evaluated at stage 3 for the mirabegron dose groups that achieved statistical significance in stages 1 and 2. Incontinence episodes at week 4 were evaluated at stage 4 for the mirabegron dose groups that achieved statistical significance in stages 1, 2, and 3. Micturitions at week 4 were evaluated at stage 5 for the mirabegron dose groups that achieved statistical significance in stages 1, 2, 3, and 4.

Because two mirabegron groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each of the stages just described. If only one of the mirabegron dose groups proceeded to the next stage for any efficacy end point, then the comparison between mirabegron and placebo was assessed at the $\alpha = 0.025$ level. Because the comparison between tolterodine and placebo was a secondary analysis, no adjustment for multiplicity was necessary.

All presented p values were nominal p values; however, their statistical significance was based on the multiplicity adjustment method as previously described.

A.4. Details on the stratified rank analysis of covariance used to analyse incontinence episodes

Change from baseline to week 4 and final visit in mean number of incontinence episodes per 24 h was analysed using a separate stratified rank ANCOVA for each pairwise treatment group differences of interest. The response variable was standardised ranks on change from baseline to final visit value for the stratified rank ANCOVA with baseline standardised ranks and sex as covariates and geographic region as a stratum.

The stratified rank ANCOVA was used for hypothesis testing and calculating the pairwise p values. The least squares mean estimates and two-sided 95% CIs for mean changes from baseline within treatment group, as well as the mean change from baseline in the difference between each mirabegron group and placebo and between tolterodine and placebo, were derived from the corresponding ANCOVA model with all treatment groups in the model as described in Section 2.4, "Statistical analyses."

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