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Platinum Priority – Incontinence

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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

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Abstract

Background: Despite several antimuscarinic treatment options for overactive bladder (OAB), there is still a need for distinct treatment approaches to manage this condition. Mirabegron, a β_3-adrenoceptor agonist, has demonstrated efficacy and tolerability for up to 12 wk in phase 3 trials.
Objective: To assess the 12-mo safety and efficacy of mirabegron.
Design, setting, and participants: Patients ≥18 yr of age with OAB symptoms for ≥3 mo.
Interventions: After a 2-wk single-blind placebo run-in, patients with eight or more micturitions per 24 h and three or more urgency episodes in a 3-d micturition diary were randomized 1:1:1 to once-daily mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release (ER) 4 mg for 12 mo.
Outcome measurements and statistical analysis: Primary variable: incidence and severity of treatment-emergent AEs (TEAEs). Secondary variables: change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms.
Results and limitations: A total of 812, 820, and 812 patients received mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively. Baseline demographic and OAB characteristics were similar across groups. TEAEs were reported in 59.7%, 61.3%, and 62.6% of patients, respectively; most were mild or moderate. Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, respectively. The most common TEAEs were similar across groups. Dry mouth was reported by 2.8%, 2.3%, and 8.6% of patients, respectively. Adjusted mean changes from baseline to final visit in morning systolic blood pressure were 0.2, 0.4, and −0.5 mm Hg for mirabegron 50 mg, 100 mg, and tolterodine ER 4 mg, respectively. Mirabegron and the active control, tolterodine, improved key OAB symptoms from the first measured time point of 4 wk, and efficacy was maintained throughout the 12-mo treatment period. The study was not placebo controlled, which was a limitation.
Conclusions: The safety and tolerability of mirabegron was established over 1 yr, with sustained efficacy observed over this treatment period.
Trial registration: ClinicalTrials.gov identifier: NCT00688688.

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1. Introduction

For several decades, oral antimuscarinic agents have represented the current mainstay of pharmacotherapy for improving overactive bladder (OAB) symptoms; however, they may elicit inadequate response in some patients, and/or their use may be associated with adverse events (AEs) (eg, dry mouth, constipation, and blurred vision) [1,2].

In the bladder, β_3-adrenoceptors are predominantly located in detrusor muscle and facilitate urine storage by inducing detrusor relaxation [3]. β_3-adrenoceptor agonists represent a new class of agents with a distinct mechanism of action [4–6]. Mirabegron is the first in class to have completed phase 3 registrational trials, and following approval in Japan and the United States, it represents a new oral agent for OAB treatment. Recent phase 3 trials have demonstrated the efficacy and safety of mirabegron for up to 12 wk of therapy (NCT00689104 and NCT00662909) [7,8]. The primary objective of the present study was to assess the safety and tolerability of 12-mo treatment with once-daily mirabegron (50 mg and 100 mg) in a randomized double-blind parallel group, active controlled trial. Secondary objectives were to assess the efficacy of 12-mo mirabegron treatment and the 12-mo safety and efficacy of mirabegron in parallel with tolterodine.

2. Methods

This study was conducted at 306 sites in Europe, the United States, Canada, South Africa, Australia, and New Zealand between April 2008 and May 2010, consisting of a 2-wk single-blind placebo run-in period followed by a 12-mo randomized treatment (Fig. 1). The study was conducted in accordance with ethical principles derived from the Declaration of Helsinki, Good Clinical Practice, and International Conference of Harmonization Guidelines. All patients provided written informed consent.

2.1. Patients and study design

Patients ≥18 yr of age with symptoms of OAB (urinary frequency and urgency with or without urgency incontinence) ≥3 mo were eligible for the placebo run-in. Approximately 2500 patients were planned for enrollment, based on estimates of numbers enrolling after completing studies NCT00689104 and NCT00662909. No formal sample size calculation was performed. Patients who had completed recent phase 3 mirabegron studies in Europe, the United States, Canada, and Australia had the option to enroll but required ≥30 d of drug washout. Antihypertensive drugs were permitted.

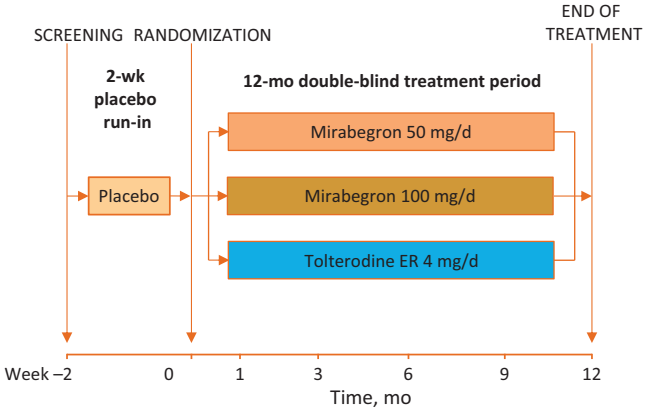

Fig. 1 – Study flow chart. ER = extended release.

During the placebo run-in, patients were eligible for randomization if they met the following criteria during the 3-d micturition diary period: average micturition frequency eight or more times per 24 h and three or more episodes of urgency (grade 3 or 4 using the Patient Perception of Intensity of Urgency Scale) with or without incontinence. Appendix 1 shows the inclusion and exclusion criteria.

Eligible patients were randomized 1:1:1 using a computer-generated randomization scheme, prepared by Pierrel Research Europe (Essen, Germany), to receive oral mirabegron 50 mg or 100 mg, or tolterodine extended release (ER) 4 mg once daily for 12 mo. The investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials). Demographics and other baseline characteristics were recorded at the start of the placebo run-in period. Patients completed a 3-d micturition diary just before the randomization visit and before visits at months 1, 3, 6, 9, and 12. In addition, patients recorded morning and afternoon blood pressure (BP) and pulse rate (PR) during the 5 d preceding randomization and at months 1, 3, 6, 9, and 12. Compliance was monitored by counting the medication dispensed to and returned by the patient at each visit. Patients were considered compliant if compliance was between 80% and 120% of the medication required to be taken in the interval since the previous visit.

2.2. Assessments and end points

2.2.1. Safety assessments

The primary safety variable was the incidence and severity of treatment-emergent adverse events (TEAEs). A TEAE was an AE starting or worsening in the period from the first double-blind study drug intake until 30 d after the last double-blind study drug intake. Safety was also assessed by evaluating vital signs (AM and PM sitting systolic and diastolic BP [SBP/DBP] and PR) and by laboratory tests (hematology, biochemistry, urinalysis), physical examination, and electrocardiographic (ECG) parameters (Appendix 2). An ambulatory blood pressure monitoring (ABPM) substudy conducted in a subset of patients at selected investigational sites in the United States measured SBP/DBP and heart rate every 15 min during a 24-h period at baseline and at months 6 and 12.

The protocol prespecified definition for recording a hypertension event was if the average SBP was ≥140 mm Hg and/or the average DBP was ≥90 mm Hg at two consecutive visits postbaseline in normotensive patients, average SBP increased ≥20 mm Hg and/or average DBP increased ≥10 mm Hg at two consecutive visits versus baseline in patients with hypertension at baseline, antihypertensive drugs were initiated, or if the dose of prior antihypertensive medication was increased due to BP increase. An independent data safety monitoring board (DSMB) reviewed safety data quarterly (or as needed).

2.2.2. Efficacy end points

Efficacy end points were secondary and included change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms recorded in the 3-d micturition diary. Patient-reported outcomes were assessed using the overactive bladder questionnaire (OAB-q; at baseline and months 1, 3, 6, 9, and 12), Patient Perception of Bladder Condition (PPBC) scale (baseline and month 12), and the Treatment Satisfaction Visual Analog Scale (TS-VAS; baseline and month 12). In addition, two responder analyses based on incontinence episodes were performed at months 1, 3, 6, 9, and 12. Responders were defined as those with ≥50% decrease from baseline in the mean number of incontinence episodes per 24 h or those with zero incontinence episodes postbaseline at final visit (dry rate). The study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups.

2.3. Statistical analysis

Safety analyses were performed for patients in the safety analysis set: all randomized patients receiving one or more dose of the double-blind study drug. Efficacy analyses were performed for patients in the full analysis set (FAS): all patients receiving one or more dose of the double-blind study drug with baseline and one or more postbaseline visit micturition measurements, with the exception of incontinence-related variables, which were performed in the FAS incontinence set (all FAS patients who had one or more incontinence episode at baseline). For safety and efficacy data, analysis based on final visit included patients who withdrew before month 12 and therefore did not have safety or efficacy measurements available for that month. The final visit analysis used a last observation carried forward approach.

Two models were used to analyze efficacy and vital sign variables (except ABPM). A repeated-measures model analyzed change from baseline to study visits (time) for efficacy and vital sign variables to obtain adjusted means by treatment group and time. Factors in the repeated-measures model included previous study history, sex, geographic region, treatment group, time, treatment by time interaction, and sex by time interaction with baseline and baseline by time interaction as covariates. Change from baseline to final visit was analyzed using an analysis of covariance (ANCOVA) model to obtain adjusted means for each treatment group. Factors in the ANCOVA model included previous study history, sex, geographic region, and treatment group with baseline as a covariate. All other safety variables were analyzed descriptively. All data processing, summarization, and analyses were performed by Astellas, using SAS v.9.1.

3. Results

3.1. Baseline characteristics

A total of 2444 randomized patients received the study drug (mirabegron 50 mg [*n* = 812], mirabegron 100 mg [*n* = 820],

Table 1 – Demographic and overactive bladder–related characteristics

Demographics, SAF*	Mirabegron 50 mg *n* = 812	Mirabegron 100 mg *n* = 820	Tolterodine ER 4 mg *n* = 812
Sex, *n* (%)			
Male	210 (25.9)	212 (25.9)	212 (26.1)
Female	602 (74.1)	608 (74.1)	600 (73.9)
Race, *n* (%)			
White	778 (95.8)	774 (94.4)	780 (96.1)
Age, yr, mean ± SD	59.2 ± 12.56	60.1 ± 11.92	59.6 ± 12.47
<65	523 (64.4)	504 (61.5)	509 (62.7)
<75	737 (90.8)	739 (90.1)	729 (89.8)
Type of incontinence, *n* (%)			
Urgency incontinence	296 (36.5)	305 (37.2)	317 (39.0)
Mixed stress/Urgency incontinence	232 (28.6)	228 (27.8)	210 (25.9)
Frequency	284 (35.0)	287 (35.0)	285 (35.1)
Used prior OAB drug, *n* (%)	446 (54.9)	419 (51.1)	447 (55.0)
OAB mean duration, mo	87.4 ± 96.28	87.9 ± 91.52	83.8 ± 87.34
Previous treatment in phase 3 studies, *n* (%)			
Placebo	190 (23.4)	174 (21.2)	180 (22.2)
Mirabegron 50 mg	170 (20.9)	180 (22.0)	171 (21.1)
Mirabegron 100 mg	183 (22.5)	198 (24.1)	197 (24.3)
Tolterodine ER 4 mg	130 (16.0)	107 (13.0)	108 (13.3)
Naive	139 (17.1)	161 (19.6)	156 (19.2)
OAB parameters, FAS†	***n* = 789**	***n* = 802**	***n* = 791**
Number of micturitions per 24 h, mean ± SE	11.13 ± 0.10	11.16 ± 0.10	10.94 ± 0.09
Volume voided/micturition, mean ± SE	160.1 ± 2.09	164.9 ± 2.06	160.1 ± 2.01
Nocturia episodes per 24 h, mean ± SE	2.08 ± 0.05	2.11 ± 0.05	2.02 ± 0.05
OAB-q score, mean ± SE			
Symptom bother score	44.6 ± 0.75	44.3 ± 0.72	44.2 ± 0.74
HRQoL total score	66.5 ± 0.77	66.6 ± 0.77	67.3 ± 0.76
Coping	60.8 ± 0.93	60.6 ± 0.94	61.1 ± 0.94
Concern	65.8 ± 0.88	65.7 ± 0.90	66.6 ± 0.87
Sleep	62.1 ± 0.89	62.4 ± 0.89	63.0 ± 0.90
Social	81.0 ± 0.76	81.6 ± 0.73	82.5 ± 0.74
PPBC score, mean ± SE	3.9 ± 0.04	3.9 ± 0.04	3.8 ± 0.04
TS-VAS, mean ± SE	4.87 ± 0.14	4.88 ± 0.13	5.01 ± 0.13
OAB parameters, FAS-I‡	***n* = 479**	***n* = 483**	***n* = 488**
No. of incontinence episodes per 24 h, ml, mean ± SE	2.66 ± 0.12	2.49 ± 0.11	2.42 ± 0.11

ER = extended release; FAS = full analysis set; HRQoL = health-related quality of life; OAB = overactive bladder; OAB-q = overactive bladder questionnaire; PPBC = Patient Perception of Bladder Condition; SAF = safety analysis set; SD = standard deviation; SE = standard error; TS-VAS = Treatment Satisfaction Visual Analog Scale.

* All randomized patients who took one or more doses of the double-blind study drug (SAF).

† All patients who took one or more doses of the double-blind study drug and had baseline and one or more postbaseline micturition measurements (FAS).

‡ FAS patients who had one or more incontinence episodes at baseline (FAS-I).

and tolterodine ER 4 mg [$n = 812$]). In total, 81.3% of patients had participated in previous mirabegron phase 3 trials; similar proportions (21–24%) had previously received placebo, mirabegron 50 mg, or mirabegron 100 mg; a total of 14.1% of patients had previously received tolterodine. Demographic and OAB-related baseline characteristics were similar across all groups (Table 1). Comorbidities and concomitant medications are shown in Appendix 3 and 4.

3.2. *Safety assessments*

The incidence of TEAEs was similar across the mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%), and tolterodine ER 4 mg (62.6%) groups. Most TEAEs were mild or moderate in severity. The most frequent TEAEs included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group (8.6%) versus mirabegron 50 mg (2.8%) and 100 mg (2.3%) (Table 2).

Discontinuations due to AEs were comparable across treatment groups, occurring in only 6.4%, 5.9%, and 6.0% of patients on mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively (Fig. 2). Five deaths were reported (three in the mirabegron 50 mg and two in the tolterodine ER 4 mg group); four were considered treatment emergent, and all five were considered unrelated to the study drug.

Incidence of treatment-emergent serious adverse events (SAEs) was similar across the mirabegron 50 mg (5.2%), mirabegron 100 mg (6.2%), and tolterodine ER 4 mg (5.4%) groups. Most SAEs were not considered related to the study drug; no SAEs of urinary retention (UR) were reported.

UR was reported for one patient in the mirabegron 50 mg group (0.1%), one patient in the mirabegron 100 mg group (0.1%; confounded by a prior lumbar stenosis procedure not considered treatment related), and three patients (0.4%) in the tolterodine ER 4 mg group. There was no acute urinary retention (AUR) in the mirabegron 50 mg group. AUR requiring catheterization was reported by one patient each in the mirabegron 100 mg group and the tolterodine ER 4 mg group.

Incidence of cardiac arrhythmias was higher in the tolterodine ER 4 mg group (6.0%) versus mirabegron 50 mg (3.9%) and 100 mg (4.1%; Table 2).

The overall incidence of TEAEs adjudicated by an independent cardiovascular adjudication committee (Antiplatelet Trialists' Collaboration [APTC]) as major adverse cardiovascular events (MACEs) was 0.7% in the mirabegron 50 mg group, 0% in the mirabegron 100 mg group, and 0.5% in the tolterodine ER 4 mg group.

Adjusted mean changes from baseline to final visit for SBP in mirabegron 50 and 100 mg and tolterodine were 0.2, 0.4, and −0.5 mm Hg for AM measurements and −0.3, 0.1, and −0.0 mm Hg for PM measurements. Adjusted mean changes for DBP were −0.3, 0.4, and 0.1 mm Hg for AM measurements and −0.0, 0.1, and 0.6 mm Hg for PM measurements (Appendix 5). Data for the ABPM subgroup are not shown because they concerned only 73 patients and were similar to patient diary data.

Across the 12-mo period, adjusted mean change from baseline PR showed a small increase in each group; this was similar in the tolterodine ER 4 mg and mirabegron 100 mg

Table 2 – Most frequent (≥2% in any treatment group) treatment-emergent adverse events* and adverse events of interest

MedDRA (v.9.1) preferred term, *n* (%)	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
Any AE	485 (59.7)	503 (61.3)	508 (62.6)
Hypertension	75 (9.2)	80 (9.8)	78 (9.6)
Urinary tract infection	48 (5.9)	45 (5.5)	52 (6.4)
Dry mouth	23 (2.8)	19 (2.3)	70 (8.6)
Nasopharyngitis	32 (3.9)	35 (4.3)	25 (3.1)
Headache	33 (4.1)	26 (3.2)	20 (2.5)
Influenza	21 (2.6)	25 (3.0)	28 (3.4)
Constipation	23 (2.8)	25 (3.0)	22 (2.7)
Back pain	23 (2.8)	29 (3.5)	13 (1.6)
Dizziness	22 (2.7)	13 (1.6)	21 (2.6)
Diarrhea	15 (1.8)	24 (2.9)	16 (2.0)
Sinusitis	22 (2.7)	18 (2.2)	12 (1.5)
Arthralgia	17 (2.1)	19 (2.3)	16 (2.0)
Tachycardia	8 (1.0)	19 (2.3)	25 (3.1)
Cystitis	17 (2.1)	11 (1.3)	19 (2.3)
Adverse events of interest, *n* (%)			
Corrected QT interval prolongation†	3 (0.4)	2 (0.2)	3 (0.4)
Hypertension†	89 (11.0)	83 (10.1)	86 (10.6)
Cardiac arrhythmia†	32 (3.9)	34 (4.1)	49 (6.0)
Urinary retention	1 (0.1)	1 (0.1)	3 (0.4)
Acute urinary retention	0	1 (0.1)	1 (0.1)
Hypersensitivity	45 (5.5)	44 (5.4)	42 (5.2)
Syncope/seizure	1 (0.1)	0	1 (0.1)
Hepatotoxicity†	17 (2.1)	19 (2.3)	15 (1.8)

AE = adverse event; ER = extended release; MedDRA = Medical Dictionary for Regulatory Activities.

* In the safety analysis set.

† Definition based on standardized MedDRA query. Adverse events not based on standardized MedDRA queries were predefined.

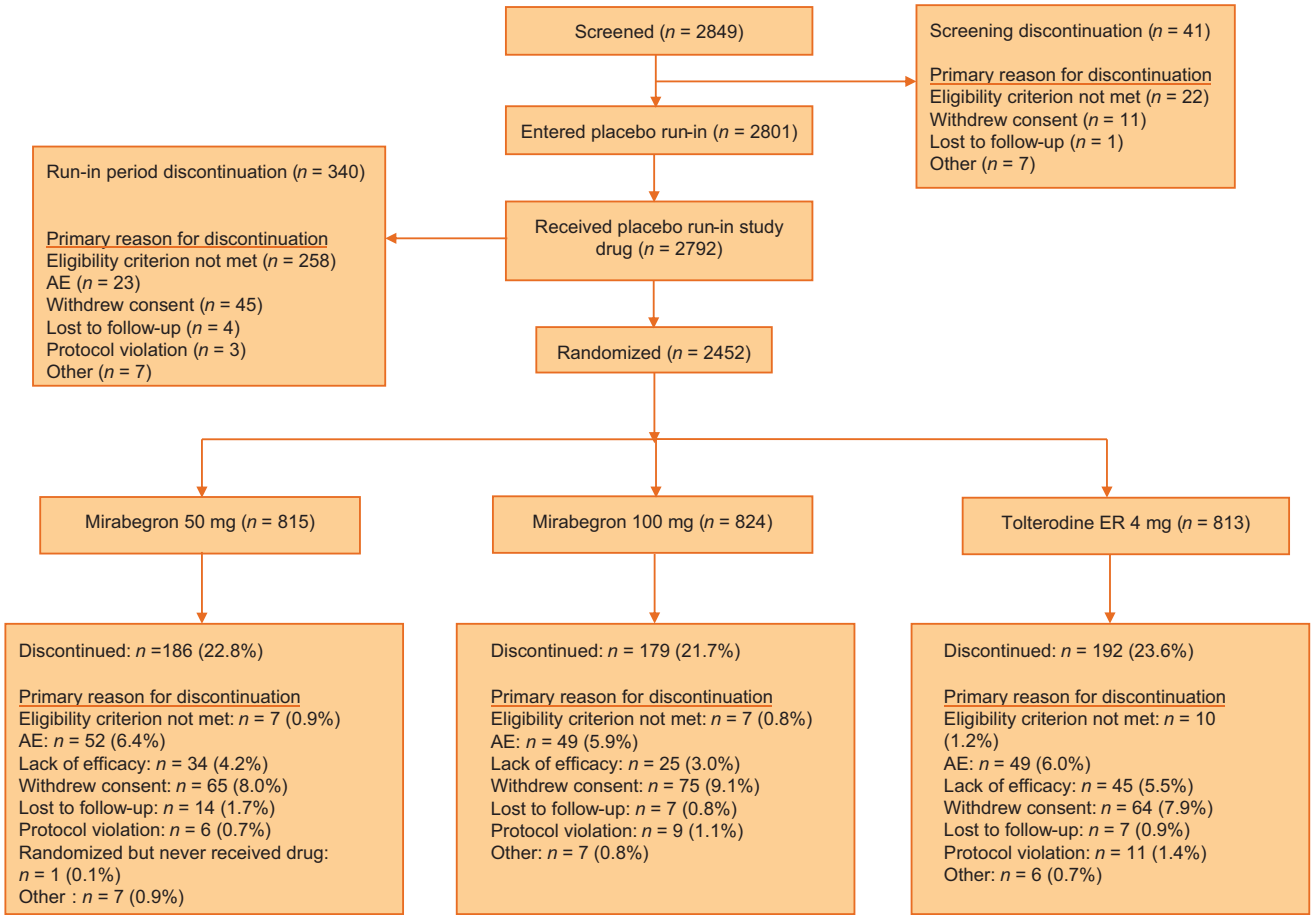

Fig. 2 – Patient disposition. AE = adverse event; ER = extended release.

groups, and less in the mirabegron 50 mg group (0.9, 1.6, and 1.5 beats per minute [bpm] for AM measurements for the mirabegron 50 mg, 100 mg, and tolterodine groups, respectively, and 0.4, 1.3, and 1.9 bpm for PM measurements). The change from baseline to final visit for PR in patients with OAB randomized to 50 mg mirabegron was approximately 1 bpm.

No consistent trends in ECG changes were identified, and categorical outliers for QTc interval assessments were unremarkable across treatment groups (Appendix 6).

A blinded independent DSMB inspection of SAEs, discontinuation rates, overall AEs and TEAEs, clinical laboratory assessments, vital signs, and ECG readings concluded there were no relevant safety concerns during or at the end of the study across the treatment groups.

A higher incidence of neoplasms (benign, malignant, and unspecified including cysts and polyps) was observed in the mirabegron 100 mg group (1.3%) compared with mirabegron 50 mg (0.1%) or tolterodine ER 4 mg (0.5%). These were heterogeneous in tissue of origin and were not considered to be treatment related.

3.3. *Efficacy assessments*

Numerical improvements in efficacy variables were evident from the first measured time point (month 1) and were maintained throughout 12 mo in each treatment group. These included similar reductions in the adjusted mean change from baseline for the mean number of micturitions per 24 h (−1.27 for mirabegron 50 mg, −1.41 for mirabegron 100 mg, and −1.39 for tolterodine ER 4 mg), mean number of incontinence episodes per 24 h (−1.01 for mirabegron 50 mg, −1.24 for mirabegron 100 mg, and −1.26 for tolterodine ER 4 mg), and improvements in mean volume voided/micturition (17.5 ml for mirabegron 50 mg, 21.5 ml for mirabegron 100 mg, and 18.1 ml for tolterodine ER 4 mg; Fig. 3). Similar findings were evident for responder analyses based on incontinence episodes. At the final visit, the percentage of responders with ≥50% decrease from baseline in the mean number of incontinence episodes per 24 h was 63.7%, 66.3%, and 66.8% in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg groups, respectively, and the percentage of responders for zero incontinence episodes was 43.4%, 45.8%, and 45.1%, respectively. Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and health-related quality of life, treatment satisfaction, number of nocturia episodes, and PPBC (Table 3).

4. Discussion

This study demonstrates the 12-mo safety and tolerability of mirabegron at doses of 50 and 100 mg. The safety

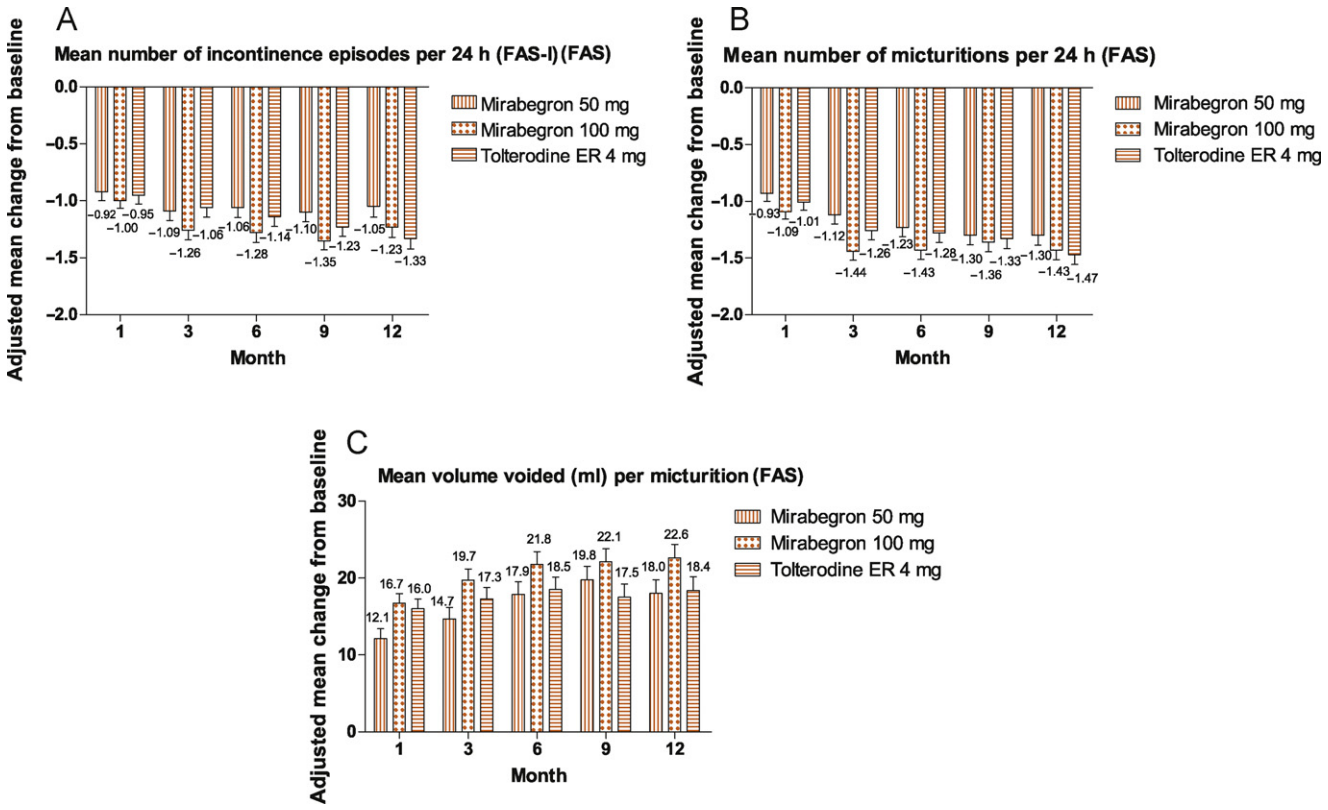

Fig. 3 – Efficacy variables—adjusted mean change from baseline at each visit: (A) mean number of incontinence episodes per 24 h (full analysis set [FAS]-I); (B) mean number of micturitions per 24 h (FAS); (C) mean volume voided per micturition (FAS). ER = extended release.

Table 3 – Adjusted mean change from baseline to final visit in other secondary variables

	Mirabegron 50 mg *n* = 789	Mirabegron 100 mg *n* = 802	Tolterodine ER 4 mg *n* = 791
OAB-q			
Symptom bother score	−13.1 ± 0.65	−14.8 ± 0.65	−14.3 ± 0.65
95% CI	−14.4 to −11.8	−16.1 to −13.5	−15.6 to −13.1
HRQoL total score	10.7 ± 0.58	11.7 ± 0.57	11.4 ± 0.58
95% CI	9.5–11.8	10.5–12.8	10.3–12.6
Coping	12.2 ± 0.69	13.6 ± 0.68	13.3 ± 0.69
95% CI	10.8, 13.5	12.3, 15.0	12.0, 14.7
Concern	11.8 ± 0.66	13.3 ± 0.65	12.5 ± 0.65
95% CI	10.8–13.5	12.3–15.0	12.0–14.7
Sleep	10.7 ± 0.68	10.8 ± 0.67	11.2 ± 0.68
95% CI	9.4–12.0	9.5–12.1	9.9–12.6
Social	6.5 ± 0.49	7.2 ± 0.49	7.2 ± 0.49
95% CI	5.5–7.5	6.2–8.1	6.2–8.1
PPBC score	−0.8 ± 0.04	−0.9 ± 0.04	−0.8 ± 0.04
95% CI	−0.9 to −0.7	−1.0 to −0.8	−0.9 to −0.8
TS-VAS	2.08 ± 0.17	2.11 ± 0.16	2.27 ± 0.16
95% CI	1.75–2.41	1.79–2.43	1.94–2.59
No. of nocturia episodes*	−0.46 ± 0.04	−0.39 ± 0.04	−0.43 ± 0.04
95% CI	−0.53 to −0.38	−0.47 to −0.32	−0.50 to −0.35

CI = confidence interval; ER = extended release; HRQoL = health-related quality of life; OAB-q = overactive bladder questionnaire; PPBC = Patient Perception of Bladder Condition; TS-VAS = Treatment Satisfaction-Visual Analog Scale.
Data are for the full analysis set. All data are adjusted mean changes plus or minus standard error from baseline unless otherwise indicated. Analysis of covariance model included treatment group, previous study history, sex, and geographic regions as fixed factors and baseline as a covariate.
* Only subjects who had one or more nocturia episodes at baseline are included.

profile of mirabegron following 12-mo exposure is consistent with that seen in 12-wk phase 3 studies [7,8]. Although small increases in PR and BP were seen with mirabegron in the current study, small changes in vital signs, predominantly PR, are not unprecedented for OAB therapies and did not result in more cardiovascular AEs and APTC/MACE events in mirabegron groups versus tolterodine. Overall, the data support the acceptable

safety and tolerability profile of mirabegron in the treatment of OAB at a dose of 50 mg.

Although no formal statistical analyses were conducted to compare the efficacy of mirabegron with tolterodine in this study, 3.6% of mirabegron patients discontinued due to lack of efficacy versus 5.5% of tolterodine ER 4 mg patients. Incidence of dry mouth, a common side effect associated with the use of antimuscarinics, was more than three-fold higher in the tolterodine ER 4 mg group than in the mirabegron 50 mg or 100 mg groups. In the 12-wk phase 3 studies, the incidence of dry mouth with mirabegron was similar to placebo [7,8], which may potentially translate into better adherence to OAB treatment, given that dry mouth is the sentinel AE of the current mainstay of therapy that limits adherence [1,9].

Improvements with mirabegron in incontinence, micturitions, and mean volume voided per micturition was demonstrable at the first measurable time point (month 1) and sustained throughout 12 mo. In addition, data from the OAB-q, PPBC, and TS-VAS together with responder analyses showed that 12-mo treatment with mirabegron results in clinically meaningful benefits, similar to those seen using a well-established antimuscarinic treatment for OAB. Although most of the patients were recruited from previous phase 3 studies, approximately 20% were direct enrollers into this study.

Data from this active-controlled 12-mo safety study provide evidence demonstrating the persistence of efficacy for mirabegron. Efficacy analyses were secondary, and there were no statistical comparisons of efficacy between treatment groups. Supportive nonclinical data have demonstrated the absence of potential tachyphylaxis or tolerance to mirabegron in vivo in rats, and current literature supports that the β_3-adrenoceptor, unlike other β-adrenoceptor subtypes, is not prone to desensitization [10]. Taken together, the clinical data over a 12-mo treatment period and supportive nonclinical characterization demonstrate the durability of effect for mirabegron in the treatment of OAB.

4.1. Study limitations

This was not a placebo-controlled study; however, placebo inclusion would be problematic in 12-mo treatment of this symptomatic condition where ethical considerations and a likely differential dropout rate would potentially unblind the study. Additionally, 81.3% of patients had been treated in prior phase 3 studies with mirabegron, tolterodine, or placebo, so they were not treatment naive. Adherence/persistence generally differs between real-world clinical practice and clinical trials; however, further information will be gained from the clinical practice of mirabegron.

5. Conclusions

This is the first randomized active-controlled drug trial in patients with OAB to assess the 12-mo safety and tolerability of once-daily mirabegron 50 and 100 mg in patients with OAB relative to that of tolterodine ER 4 mg. In this study, mirabegron demonstrated an acceptable safety and tolerability profile with improvements in OAB symptoms at the first measurable time point of month 1, with sustained improvement throughout 12 mo. The effect size was within the range of a representative antimuscarinic agent without evidence of tolerance to mirabegron. Incidence of dry mouth was more than three-fold higher in the tolterodine ER 4 mg group than observed in mirabegron-treated patients, and small increases in PR and BP were seen with mirabegron; however, no formal comparison was made between groups. Mirabegron, a β_3-adrenoreceptor agonist, has demonstrated 12-mo safety, tolerability, and persistence of effect in patients with OAB.

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

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Acquisition of data: Chapple, Drogendijk, Cummings, Martin.
Analysis and interpretation of data: Chapple, Kaplan, Mitcheson, Klecka, Drogendijk, Cummings, Dorrepaal, Martin.
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Appendix 1 – Inclusion and exclusion criteria for NCT00688688

Inclusion criteria		
	Screening	Baseline
Symptoms of OAB (urinary frequency and urgency with/without incontinence) for ≥3 mo	√	√
Frequency of micturition on average eight or more times per 24 h during the 3-d micturition diary period		√
Three or more episodes of urgency (grade 3 or 4) with/without incontinence during the 3-d micturition diary period		√
Exclusion criteria		
	Screening	Baseline
Breastfeeding; pregnant; intending to become pregnant during the study; or of childbearing potential, sexually active, and not practicing a highly reliable method of birth control. A pregnancy test (β-human chorionic gonadotropin in serum) at screening visit had to be negative in women of childbearing potential	√	
Clinically significant bladder outflow obstruction at risk of urinary retention[a]	√	
Significant stress incontinence or mixed stress/urge incontinence where stress was the predominant factor[a]	√	
An indwelling catheter or practiced intermittent self-catheterization	√	
Diabetic neuropathy	√	
Evidence of a symptomatic UTI, 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 contraindicated the use of anticholinergics[b]	√	
Current nondrug treatment including electrostimulation therapy (a bladder training program or pelvic floor exercises that started >30 d prior to study entry was allowed to be continued)	√	
Use of medications intended to treat OAB	√	
Known/suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, other β-AR agonists, or any of the other inactive ingredients	√	
Any clinically significant condition that made the patient unsuitable for the study[b]	√	
Treatment with any investigational drug within 30 d (90 d in the United Kingdom for all clinical studies except NCT00689104) prior to visit 1/screening	√	
Average total daily urine volume >3000 ml as recorded in the 3-d micturition diary		√
Serum creatinine >150 μmol/l, or AST or ALT more than two-fold the ULN range or GGT more than three-fold the ULN, as assessed in screening samples and considered clinically significant in laboratory values[b]		√
Severe hypertension (defined as a sitting average SBP ≥180 mm Hg and/or average DBP ≥110 mm Hg)	√	√
An abnormal ECG, which made the patient unsuitable for the study[b]		√

ALT = alanine aminotransferase; AR = adrenergic receptor; AST = aspartate aminotransferase; DBP = diastolic blood pressure; ECG = electrocardiogram; GGT = γ-glutamyltransferase; OAB = overactive bladder; SBP = systolic blood pressure; ULN = upper limit of normal; UTI = urinary tract infection.
[a] As determined by the investigator.
[b] In the opinion of the investigator.
Antihypertensive drugs were permitted, but dose increase was not permitted for loop diuretics.

Appendix 2 – Schedule of assessments/procedures

	Week −2	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12
Safety							
Physical examination	√						√
Hematology and biochemistry[a]	√		√		√		√
Urinalysis[b]	√		√		√		√
Pregnancy test[c]	√		√	(√)	√	(√)	√
Vital signs[a]	√	√[e]	√[e]	√[e]	√[e]	√[e]	√[e]
ECG[a]	√				√		√
Adverse events	√	√	√	√	√	√	√
24-hour ABPM[d]		√			√		√
Efficacy							
3-d patient diary		√	√	√	√	√	√
OAB-q		√	√	√	√	√	√
PPBC, TS-VAS		√					√

ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; ECG = electrocardiogram; OAB-q = overactive bladder questionnaire; PPBC = Patient Perception of Bladder Condition; SBP = systolic blood pressure; TS-VAS = Treatment-Satisfaction-Visual Analog Scale.
[a] Hematology, biochemistry, and vital signs were performed at unscheduled visits. ECG was performed if deemed necessary by the investigator. Blood pressure measurements were taken in triplicate (2-min intervals) after subjects had been resting in sitting position for 5 min. Vital sign measurements for pulse rate, SBP, and DBP were collected by the patient during the AM (after waking up in the morning) and PM (between 2 and 6 PM) in a 5-d vital sign diary using a self-measurement device. The AM vital sign measurements were to be collected before taking the study drug. Vital sign data were captured for 5 d preceding study visits at baseline and at months 1, 3, 6, 9, and 12.
[b] Urine culture if urinalysis was symptomatic for urinary tract infection.
[c] Pregnancy test in women of childbearing potential. For countries outside the United States: at screening and end of treatment in serum samples. For United States only: at screening, months 1 and 6, and end of treatment in serum samples and at months 3 and 9 in urine samples. (√) = pregnancy test in urine samples.
[d] Applicable to select US sites only.
[e] Vital signs measurements were recorded by patients during the 5 d preceding the visit. At the visit, vital signs were measured on site with the device the patient was using for the self-measurement and the sites' standard office measuring device.

Appendix 3 – The five most frequently reported occurrences of medical history and comorbidities

MedDRA (v.9.1) preferred term, *n* (%)	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
Hypertension	348 (42.9)	351 (42.8)	372 (45.8)
Hysterectomy	145 (17.9)	156 (19.0)	184 (22.7)
Menopausal symptoms	167 (20.6)	155 (18.9)	156 (19.2)
Drug hypersensitivity	106 (13.1)	128 (15.6)	118 (14.5)
Depression	130 (16.0)	101 (12.3)	106 (13.1)

ER = extended release; MedDRA = Medical Dictionary for Regulatory Activities.
Data are for the safety analysis set.

Appendix 4 – The five most commonly reported medication classes prior to study entry

n (%)	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
Urinary antispasmodics	446 (54.9)	419 (51.1)	448 (55.2)
Other urologics	208 (25.6)	203 (24.8)	211 (26.0)
Stomatologic preparations for local oral treatment	156 (19.2)	134 (16.3)	149 (18.3)
HMG-CoA reductase inhibitors	157 (19.3)	130 (15.9)	142 (17.5)
Platelet aggregation inhibitors (excluding heparin)	147 (18.1)	129 (15.7)	132 (16.3)

ER = extended release; HMG-CoA reductase inhibitors = statins.
Data are for the safety analysis set. Concomitant medications were those taken prior to screening.

Appendix 5 – Adjusted mean change from baseline to final visit in vital signs measured by patient's diary

	Mirabegron 50 mg (*n* = 812)		Mirabegron 100 mg (*n* = 820)		Tolterodine ER 4 mg (*n* = 812)	
Pulse rate, bpm						
AM	0.9 ± 0.23		1.6 ± 0.22		1.5 ± 0.22	
95% CI	0.5–1.4		1.2–2.1		1.1–2.0	
PM	0.4 ± 0.24		1.3 ± 0.24		1.9 ± 0.24	
95% CI	−0.1 to 0.8		0.8–1.7		1.4–2.4	
Blood pressure, mm Hg	SBP	DBP	SBP	DBP	SBP	DBP
AM	0.2 ± 0.33	−0.3 ± 0.21	0.4 ± 0.33	0.4 ± 0.20	−0.5 ± 0.33	0.1 ± 0.21
95% CI	−0.4 to 0.9	−0.7 to 0.1	−0.2 to 1.1	−0.0 to 0.8	−1.1 to 0.2	−0.3 to 0.5
PM	−0.3 ± 0.33	−0.0 ± 0.21	0.1 ± 0.32	0.1 ± 0.21	−0.0 ± 0.33	0.6 ± 0.21
95% CI	−0.9 to 0.3	−0.4 to 0.4	−0.5 to 0.8	−0.3 to 0.5	−0.7 to 0.6	0.2 to 1.0

DBP = diastolic blood pressure; ER = extended release; SBP = systolic blood pressure.
Data are for the Safety Analysis Set. All data are adjusted mean changes plus or minus standard error from baseline unless otherwise indicated.

Appendix 6 – Number of patients with extreme QTcF values and changes from baseline

QTcF category	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
n	736	747	733
>450 ms, *n* (%)	36 (4.9)	29 (3.9)	32 (4.4)
>480 ms, *n* (%)	5 (0.7)	2 (0.3)	6 (0.8)
>500 ms, *n* (%)	2 (0.3)	1 (0.1)	1 (0.1)
n	729	741	724
≥30 s to <60 ms increase, *n* (%)	89 (12.2)	79 (10.7)	95 (13.1)
≥60 ms increase, *n* (%)	3 (0.4)	3 (0.4)	4 (0.6)
Total (≥30 ms) increase, *n* (%)	92 (12.6)	82 (11.1)	99 (13.7)

ER = extended release; QTcF = QTc interval measured using the Fridericia correction method.

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