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ORIGINAL RESEARCH ARTICLE

Safety and Tolerability Results from the PILLAR Study: A Phase IV, Double-Blind, Randomized, Placebo-Controlled Study of Mirabegron in Patients ≥ 65 years with Overactive Bladder-Wet

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Abstract

Background In older patients with overactive bladder (OAB), mirabegron, a β_3-adrenoreceptor agonist, represents an alternative treatment that may have a favorable risk–benefit profile.

Objectives Our objective was to further examine the safety and tolerability of mirabegron versus placebo treatment in patients aged ≥ 65 years with OAB-wet.

Methods We conducted a 12-week, double-blind, randomized, placebo-controlled phase IV study to compare mirabegron with placebo. Community-dwelling patients aged ≥ 65 years with OAB-wet (one or more incontinence episode and three or more urgency episodes, and an average of eight or more micturitions/24 h over a 3-day diary) were randomized to receive placebo or mirabegron 25 mg/day (optional dose escalation to 50 mg/day at week 4 or 8). Safety analyses were performed for adverse events (AEs) and vital signs on all randomized patients who received one or more dose of study drug.

Results Treatment-emergent AEs (TEAEs), the majority mild or moderate in severity, were reported in 39.4% of placebo patients and 44.2 and 49.8% of those who received mirabegron 25 mg or 50 mg, respectively. The most common TEAEs in mirabegron-treated patients were urinary tract infection, headache, and diarrhea. The incidence of TEAEs was slightly higher in mirabegron patients aged ≥ 75 years than in those aged < 75 years. There were no clinically meaningful differences in changes in vital signs from baseline to end of treatment for any treatment group, and no differences were observed between mirabegron and placebo treatment groups. TEAEs tended to occur early post exposure and were not dose related.

Conclusions Mirabegron treatment was well-tolerated in older adults with OAB-wet. Safety and tolerability were consistent with the known mirabegron safety profile.

Trial Registration This study is registered at ClinicalTrials.gov: NCT02216214.

1 Introduction

The prevalence of overactive bladder (OAB)—a symptom complex of storage lower urinary tract symptoms characterized by the presence of urinary urgency—increases with age, with a prevalence rate in those aged ≥ 65 years double that in those aged ≤ 45 years [1–4]. Patients with OAB are often treated with antimuscarinics, but these are commonly associated with adverse events (AEs) that limit adherence, such as dry mouth and constipation [5]. The incidence of AEs tends to increase with older age, and AEs experienced with antimuscarinics may be more pronounced in older patients [6, 7]. In older patients receiving multiple medications, use of antimuscarinics may result in considerable anticholinergic burden [5, 8–11].

Mirabegron, a β_3-adrenoreceptor agonist, represents an alternative treatment for OAB and potentially has a more

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Key Points

Mirabegron treatment was well-tolerated in older adults with overactive bladder (OAB)-wet; few serious adverse events (SAEs) were reported, and only two (both in the placebo group) were considered to be drug related by the investigator; there were no mirabegron-related SAEs.

Treatment-emergent adverse effects did not appear to be either dose or age related, and no new safety signal was seen in this exclusively older population.

There were no clinically meaningful differences in changes in vital signs from baseline to end of treatment for any treatment group, and no differences were observed between the mirabegron and placebo treatment groups.

The findings reported provide further evidence for the overall safety and tolerability profile for mirabegron in patients aged ≥ 65 years with OAB-wet.

favorable benefit-to-risk profile than antimuscarinics in older patients [8, 12–14]. In phase III trials of mirabegron, the incidence of dry mouth and constipation was similar to that seen with placebo [15, 16]. Mirabegron and antimuscarinics are both recommended as first-line pharmacotherapy in EU and US guidelines [17, 18].

PILLAR was the first study of mirabegron specifically designed to assess efficacy and safety in patients aged ≥ 65 years with OAB-wet. In the primary analysis, improvements in bladder diary parameters were observed for mirabegron versus placebo; safety and tolerability were in line with the mirabegron safety profile [19].

As older patients with OAB tend to have high levels of comorbidities [6], it is particularly important to understand the in-depth safety profile of medications in this population. Cardiovascular risks are of particular concern because they increase with age, and people with OAB are more likely to have cardiovascular comorbidities than are those without OAB [20].

Consequently, this paper aims to provide an in-depth examination of the safety and tolerability of mirabegron versus placebo in the PILLAR study, beyond that explored in the primary paper.

2 Methods

PILLAR was a double-blind, randomized, placebo-controlled, parallel group, multicenter, 12-week phase IV study (NCT02216214) designed to evaluate mirabegron in a flexible dosing regimen compared with placebo. The study was conducted between October 2014 and December 2017 at 103 sites in the USA and Canada and was powered to detect a difference between placebo and mirabegron on incontinence and micturition frequency.

2.1 Patients

The primary paper was published recently and includes detailed methods for the study [19]. Community-dwelling patients aged ≥ 65 years with OAB-wet (one or more incontinence episode and three or more urgency episodes, and an average of eight or more micturitions/24 h over a 3-day diary) were randomized 1:1 to receive placebo or mirabegron. The mirabegron/placebo dose was started at 25 mg/day, the recommended starting dose in Canada and the USA, but the dose could be increased to 50 mg/day at week 4 or 8 based on individual efficacy/tolerability and investigator discretion. Full inclusion/exclusion criteria are shown in Table 1 in the Electronic Supplementary Material (ESM). Institutional review board/independent ethics committee-approved written informed consent was obtained from all participants or their legally authorized representatives before any study-related procedures were carried out.

2.2 Safety Analyses

Safety evaluations included vital signs, AE recording, clinical laboratory assessments, and physical examinations. Vital signs were measured at all in-office study visits and by home blood pressure monitoring prior to each visit, and electrocardiograms (ECG) were conducted at each study visit.

An AE of hypertension was recorded if one of the following criteria was met on two or more consecutive visits:

1. If the average systolic blood pressure (SBP) was > 140 mmHg and/or the average diastolic blood pressure (DBP) was > 90 mmHg at two consecutive visits after baseline in patients who were normotensive (average SBP < 140 mmHg and average DBP < 90 mmHg) at baseline.
2. If the average SBP was increased > 20 mmHg and/or the average DBP was increased > 10 mmHg at two consecutive visits as compared with baseline (visit 3) in patients with hypertension at baseline (visit 3).
3. If treatment with antihypertensive drugs was initiated for treatment of hypertension or if the dose of prior antihypertensive drugs was increased due to an increase in blood pressure.

The investigator could report an AE of "increased" blood pressure if the above conditions were not met but a high blood pressure was recorded. An AE of tachycardia was considered if resting heart rate (pulse rate) was > 100 bpm.

For home blood pressure monitoring, validated devices and detailed operating instructions for measuring blood pressure and pulse rate were provided to patients. Patients measured their blood pressure and pulse rate three times, each about 2 min apart for 3 days prior to each study visit. Measurements were recorded in the morning before breakfast prior to taking study drug, and again in the evening, and were documented in electronic diaries. Patients were instructed to have a 30-min rest after exercise or smoking or intake of caffeine or alcohol, prior to taking a measurement. An AE of tachycardia should have been considered if the mean morning or afternoon pulse rate in the resting state from patient-reported measurements at home over the last 3 diary days was > 100 bpm. For home-based monitoring, any extreme values outside of normal ranges for the vital sign (SBP 60–220 mmHg; DBP 30–140 mmHg; pulse rate 30–250 bpm) were excluded for vital sign parameter calculations.

AEs were collected throughout the study to week 16 (30 days after the end of treatment [EoT]), at which time patients received a follow-up phone call. Patients reported AEs in response to open-ended questioning. A treatment-emergent AE (TEAE) was defined as one that started or worsened from first study medication dose until 30 days after EoT. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v20.1 [21]. The severity and likely causal relationship to the study drug were determined by the study investigator. An AE was considered a serious AE (SAE) if it resulted in death, was life-threatening, required inpatient hospitalization, or led to prolongation of existing hospitalization.

Physical examinations were conducted, laboratory parameters obtained, and post-void residual (PVR) volume assessed (by ultrasonography/bladder scan) at screening and EoT. Events relating to urinary retention were aggregated for the safety analysis.

An overview of the main TEAEs is presented in the primary paper [19]. TEAEs were assessed overall and in each age subgroup (< 75 and ≥ 75 years). TEAEs of special interest included cardiovascular events, blood pressure, myocardial infarction, stroke, serious arrhythmias, urinary tract infection (UTI), acute urinary retention, benign prostatic obstruction (BPO) requiring surgery, and cognitive impairment as determined by the Montreal Cognitive Assessment score (results presented in a separate manuscript [22]). Cardiovascular events were assessed by an independent adjudication committee.

Safety analyses were performed for AEs and vital signs on the safety analysis set, which included all randomized patients who received one or more dose of study drug. No inferential comparison between treatment groups was performed.

3 Results

3.1 Participants

Of 2380 patients screened, 443 were randomized to placebo and 445 to mirabegron; one patient in the placebo group did not receive treatment (Table 1; Fig. 1). Of patients who discontinued treatment, ten (2.3%) in the placebo arm, six (2.7%) in the mirabegron 25 mg arm, and two (0.9%) in the mirabegron 50 mg arm discontinued because of an AE.

Of the 887 randomized patients who received one or more dose of study drug, 72.3% were female, 79.5% were White, and 28.1% were aged ≥ 75 years. Nearly half of patients who were randomly assigned to mirabegron increased their dose to 50 mg (219 [49.2%] patients). There were no notable differences between the mirabegron group and the placebo group in demographic characteristics at baseline. At baseline, patients had a mean ± standard deviation 8.2 ± 5.7 comorbid conditions and 94.5% were receiving one or more concomitant medication. The mean number of concomitant medications taken by patients was 6.5 ± 4.7. The most frequently reported comorbid conditions were hypertension (56.6%) and osteoarthritis (36.2%).

3.2 Safety

Overall, 327 TEAEs were reported by 174 (39.4%) patients receiving placebo, 169 TEAEs were reported by 100 (44.2%) patients receiving mirabegron 25 mg, and 206 TEAEs were reported by 109 (49.8%) patients receiving mirabegron 50 mg. In total, 57 (12.9%), 47 (20.8%), and 37 (16.9%) TEAEs were deemed possibly or probably related to study drug, respectively (Table 2). The majority of TEAEs in all treatment groups were mild or moderate in severity, and no TEAEs resulted in death. The most common TEAEs in mirabegron-treated patients were UTI, headache, and diarrhea. Serious TEAEs were reported in 12 (2.7%), 7 (3.1%), and 8 (3.7%) patients receiving placebo, mirabegron 25 mg, and mirabegron 50 mg, respectively. Two placebo-treated patients experienced serious TEAEs (cerebrovascular accident and transient ischemic attack) that were considered drug related as assessed by the investigator at the time; there were no mirabegron-related SAEs. Overall, TEAEs that led to study discontinuation were reported in 28 patients (14 [3.2%], 8 [3.5%], and 6 [2.7%] receiving placebo, mirabegron 25 mg, and mirabegron 50 mg, respectively).

The incidence of TEAEs was higher in mirabegron patients aged ≥ 75 years than in those aged < 75 years (Table 2). For TEAEs that occurred in ≥ 2% of patients, UTI, vomiting, fatigue, fall, hypertension, dysuria, and hyperglycemia occurred more frequently in patients aged ≥ 75 years than in those aged < 75 years. The incidence

Table 1 Baseline characteristics (safety analysis set)

Characteristics	Placebo ($n=442$)	Mirabegron		
		25 mg ($n=226$)	50 mg ($n=219$)	Total ($n=445$)
Female sex	324 (73.3)	168 (74.3)	149 (68.0)	317 (71.2)
Age (years)	71.9 ± 6.0	71.6 ± 5.8	71.7 ± 5.2	71.7 ± 5.5
Age ≥ 75 years	124 (28.1)	66 (29.2)	59 (26.9)	125 (28.1)
BMI (kg/m^2)	30.2 ± 6.4	29.2 ± 6.0	30.1 ± 6.6	29.7 ± 6.3
Category				
< 25	91 (20.6)	60 (26.5)	48 (21.9)	108 (24.3)
≥ 25 to < 30	150 (33.9)	84 (37.2)	73 (33.3)	157 (35.3)
≥ 30	201 (45.5)	82 (36.3)	98 (44.7)	180 (40.4)
Race				
White	357 (80.8)	151 (66.8)	197 (90.0)	348 (78.2)
Black or African American	25 (5.7)	16 (7.1)	17 (7.8)	33 (7.4)
Asian	54 (12.2)	58 (25.7)	1 (0.5)	59 (13.3)
Other	6 (1.4)	1 (0.4)	4 (1.8)	5 (1.1)
Country				
USA	389 (88.0)	215 (95.1)	170 (77.6)	385 (86.5)
Canada	53 (12.0)	11 (4.9)	49 (22.4)	60 (13.5)
Medical history, most frequent conditions[a]				
Hypertension	243 (55.0)	134 (59.3)	125 (57.1)	259 (58.2)
Osteoarthritis	173 (39.1)	60 (26.5)	87 (39.7)	147 (33.0)
Hypertonic bladder[b]	145 (32.8)	86 (38.1)	72 (32.9)	158 (35.5)
Gastroesophageal reflux disease	135 (30.5)	54 (23.9)	77 (35.2)	131 (29.4)
Concomitant non-OAB medications, most frequent				
Vitamins	208 (47.1)	95 (42.0)	114 (52.1)	209 (47.0)
Analgesics	201 (45.5)	100 (44.2)	110 (50.2)	210 (47.2)
Lipid-modifying agents	190 (43.0)	93 (41.2)	99 (45.2)	192 (43.1)

Data are presented as mean ± standard deviation or *N* (%) unless otherwise indicated. Safety analysis set: all randomized subjects who received one or more dose of study medication. Reprinted from Wagg et al. [19] with permission from Elsevier

BMI body mass index, *OAB* overactive bladder

[a]By preferred term

[b]Worsening OAB

of dizziness was higher in patients aged < 75 years than in those aged ≥ 75 years.

TEAEs by titration occurring in ≥ 5% of patients in any dose group are shown in Table 3. TEAEs tended to occur early and were not dose related. TEAEs were reported in 44.2% of the mirabegron 25 mg group and, in the mirabegron 50 mg group prior to titration, in 23.4% at week 4 and 33.3% at week 8. Post-titration, in the mirabegron 50 mg group, TEAEs were reported in 35.9% at week 4 and 14.8% at week 8.

3.2.1 Treatment-Emergent Adverse Events of Special Interest

According to the independent cardiovascular event adjudication committee, four patients experienced an Antiplatelet Trialists' Collaboration (APTC)/major adverse cardiovascular event (MACE). Of the four APTC/MACE patients, a nonfatal myocardial infarction was reported for one patient in the mirabegron 50 mg group and nonfatal stroke was reported in three patients (two receiving placebo and one receiving mirabegron 50 mg). Non-APTC/MACE was reported in two patients, both in the placebo group: one transient ischemic attack (mentioned previously) and one arrhythmia (no evidence of ischemia and not considered serious).

A TEAE of increased blood pressure was reported for two patients in the placebo group and five patients in the mirabegron total group (two receiving mirabegron 25 mg, three receiving mirabegron 50 mg). A TEAE of increased heart rate was reported for two patients in the mirabegron total group (one receiving mirabegron 25 mg, one receiving mirabegron 50 mg).

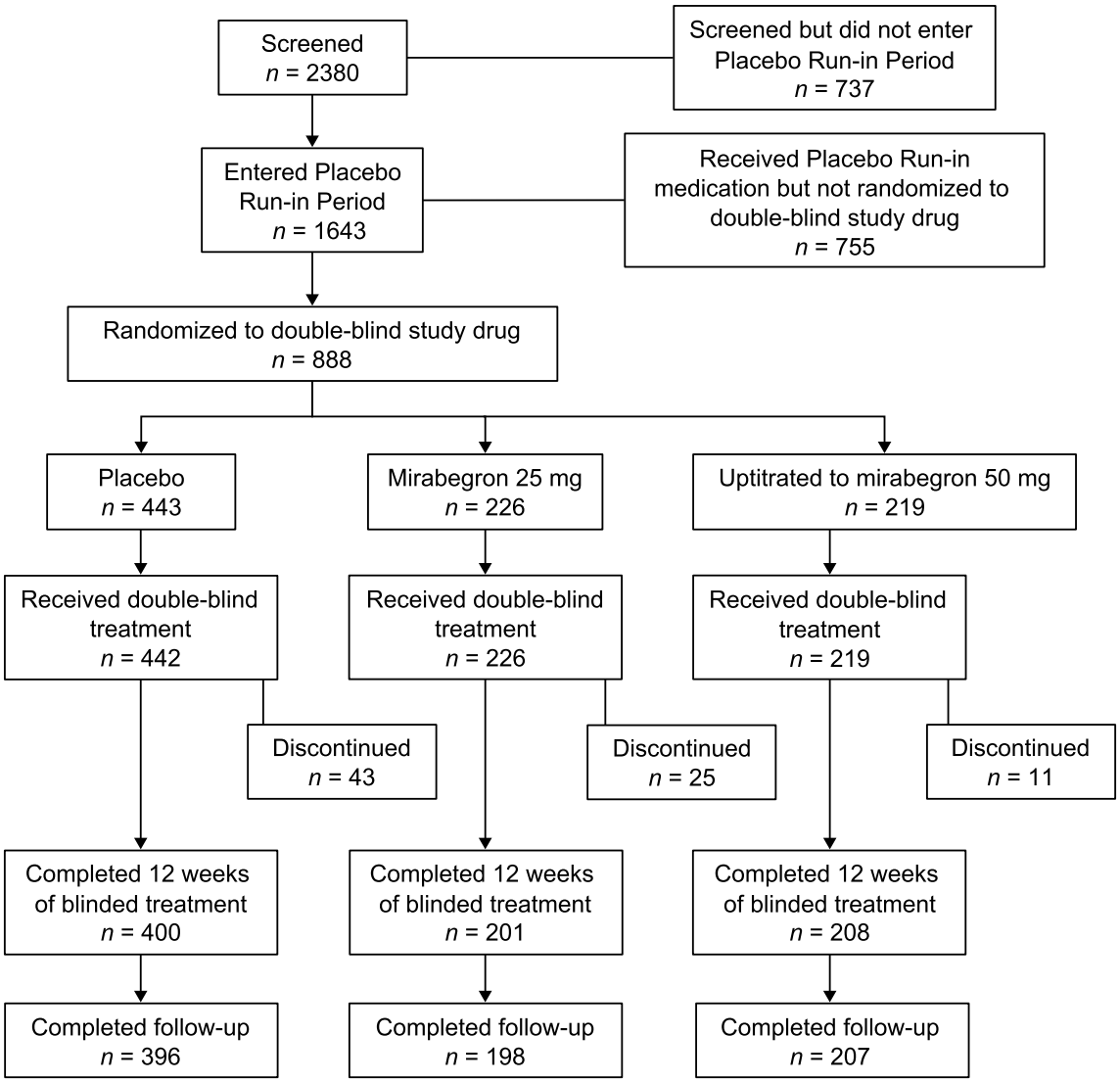

Fig. 1 Study flow chart

In terms of UTI, the proportion of patients experiencing a TEAE belonging to the composite UTI category (UTI, *Escherichia* UTI, UTI bacterial, and streptococcal UTI) was similar across treatment groups: 7.0% with placebo, 7.1% with mirabegron 25 mg, and 4.1% with mirabegron 50 mg. A TEAE in the category of urinary retention was reported for a similar proportion of patients (two receiving placebo and two receiving mirabegron). No cases required catheterization. No patients in any treatment group reported a TEAE of BPO.

3.2.2 Vital Signs—Central Tendency over Time

Adjusted mean change from baseline to EoT in SBP recorded during office visits was greatest in the placebo group (0.80 mmHg; 95% confidence interval [CI] − 0.78 to 2.37) and lowest in the mirabegron 25 mg group (0.25 mmHg; 95% CI − 1.76 to 2.26). From home-based monitoring, excluding extreme values, adjusted mean change from baseline to EoT in overall SBP (morning and afternoon measurements) was − 2.95 mmHg (95% CI − 4.33 to − 1.58) in the mirabegron 50 mg group and − 1.76 mmHg (95% CI − 2.94 to − 0.58) in the placebo group.

For DBP, adjusted mean change from baseline to EoT from office visits was − 0.98 mmHg (95% CI − 2.24 to 0.27) in the mirabegron 25 mg group and − 0.05 mmHg (95% CI − 1.18 to 1.09) in the mirabegron 50 mg group. From home-based monitoring, excluding extreme values, adjusted mean change in overall DBP (morning and afternoon measurements) was − 1.71 mmHg (95% CI − 2.62 to − 0.80) in the mirabegron 50 mg group and − 1.03 mmHg (95% CI − 1.81 to − 0.25) in the placebo group.

Table 2 Treatment-emergent adverse events by age group (< 75, ≥ 75 years)—safety analysis set

TEAEs[a]	Placebo ($n=442$)		Mirabegron 25 mg ($n=226$)		Mirabegron 50 mg ($n=219$)		Mirabegron total ($n=445$)	
	< 75 years ($n=318$)	≥ 75 years ($n=124$)	< 75 years ($n=160$)	≥ 75 years ($n=66$)	< 75 years ($n=160$)	≥ 75 years ($n=59$)	< 75 years ($n=320$)	≥ 75 years ($n=125$)
One or more TEAE	125 (39.3)	49 (39.5)	65 (40.6)	35 (53.0)	80 (50.0)	29 (49.2)	145 (45.3)	64 (51.2)
Drug-related TEAEs[b]	43 (13.5)	14 (11.3)	30 (18.8)	17 (25.8)	29 (18.1)	8 (13.6)	59 (18.4)	25 (20.0)
Serious TEAEs	9 (2.8)	3 (2.4)	5 (3.1)	2 (3.0)	7 (4.4)	1 (1.7)	12 (3.8)	3 (2.4)
Serious drug-related TEAEs[b]	2 (0.6)	0	0	0	0	0	0	0
TEAEs leading to discontinuation	6 (1.9)	8 (6.5)	6 (3.8)	2 (3.0)	4 (2.5)	2 (3.4)	10 (3.1)	4 (3.2)
Drug-related TEAEs leading to discontinuation[b]	5 (1.6)	2 (1.6)	4 (2.5)	2 (3.0)	2 (1.3)	2 (3.4)	6 (1.9)	4 (3.2)
Cardiac disorders	3 (0.9)	2 (1.6)	2 (1.3)	0	7 (4.4)	0	9 (2.8)	0
Most frequent TEAEs[c]								
Urinary tract infection[d]	21 (6.6)	10 (8.1)	11 (6.9)	5 (7.6)	5 (3.1)	4 (6.8)	16 (5.0)	9 (7.2)
Headache	8 (2.5)	4 (3.2)	12 (7.5)	3 (4.5)	4 (2.5)	4 (6.8)	16 (5.0)	7 (5.6)
Diarrhea	2 (0.6)	4 (3.2)	8 (5.0)	3 (4.5)	2 (1.3)	0	10 (3.1)	3 (2.4)
Fatigue	8 (2.5)	6 (4.8)	3 (1.9)	3 (4.5)	3 (1.9)	1 (1.7)	6 (1.9)	4 (3.2)
Upper respiratory tract infection	6 (1.9)	4 (3.2)	3 (1.9)	0	5 (3.1)	2 (3.4)	8 (2.5)	2 (1.6)
Nausea	5 (1.6)	1 (0.8)	4 (2.5)	3 (4.5)	1 (0.6)	0	5 (1.6)	3 (2.4)
Dizziness	7 (2.2)	0	1 (0.6)	0	5 (3.1)	0	6 (1.9)	0
Nasopharyngitis	7 (2.2)	3 (2.4)	2 (1.3)	1 (1.5)	2 (1.3)	0	4 (1.3)	1 (0.8)

Data are presented as *N* (%) unless otherwise indicated. MedDRA version 20.1. Safety analysis set: all randomized subjects who received one or more dose of study medication

TEAE treatment-emergent adverse event

[a]TEAEs are defined as adverse events that started or worsened in the period from first double-blind medication intake until 30 days after the last double-blind medication intake. The number of patients reporting an event are presented

[b]Possible or probable, as assessed by the investigator, or where relationship was missing

[c]Preferred term; affecting ≥ 2% of any treatment group

[d]*Escherichia* urinary tract infection, streptococcal urinary tract infection, urinary tract infection, or urinary tract infection bacterial

For pulse rate, adjusted mean change from baseline to EoT from office visits was greatest in the mirabegron 25 mg group (− 1.46 bpm; 95% CI − 2.79 to − 0.14) and lowest in the mirabegron 50 mg group (− 0.84 bpm; 95% CI − 2.04 to 0.36). From home-based monitoring, excluding extreme values, adjusted mean change from baseline to EoT in overall pulse rate (morning and afternoon measurements) was greatest in the mirabegron 25 mg group (− 1.43 bpm; 95% CI − 2.42 to − 0.44) and lowest in the mirabegron 50 mg group (− 0.81 bpm; 95% CI − 1.70 to 0.08).

The incidence of potentially clinically significant (PCS) changes in vital signs from office visits was higher than from home-based monitoring (Table 4). No shifts from a baseline normal SBP or DBP to worst result (hypertension stage 2) during the double-blind treatment period were noted in patients in any treatment group for office visits or for home-based monitoring at any time point (Table 5). Shifts from a baseline normal DBP to worst result (hypertension stage 2) during the double-blind treatment period for home-based monitoring were noted in one patient in the placebo group and two in the mirabegron 25 mg group for morning measurements, and for one patient in the mirabegron 50 mg group who uptitrated at week 4 for afternoon measurements. Overall, shifts from baseline normal DBP to worst result during the double-blind treatment period were noted in two (0.6%) and two (1.2%) patients in the placebo and mirabegron 25 mg groups, respectively. Shifts from a baseline pulse rate ≤ 100 to > 100 bpm during the double-blind treatment period for office visits were noted in three (0.7%), two (0.9%), and two (0.9%) patients receiving placebo, mirabegron 25 mg, and mirabegron 50 mg, respectively; the shifts

Table 3 Treatment-emergent adverse events (occurring in ≥ 5% in any treatment group) by titration

System organ class	Placebo 25 mg ($n=187$)	Mirabegron 25 mg ($n=226$)	Prior to titration				Post titration			
			Placebo 50 mg, week 4 ($n=215$)	Placebo 50 mg, week 8 ($n=40$)	Mirabegron 50 mg, week 4 ($n=192$)	Mirabegron 50 mg week 8 ($n=27$)	Placebo 50 mg, week 4 ($n=215$)	Placebo 50 mg, week 8 ($n=40$)	Mirabegron 50 mg, week 4 ($n=192$)	Mirabegron 50 mg, week 8 ($n=27$)
Overall	73 (39.0)	100 (44.2)	31 (14.4)	12 (30.0)	45 (23.4)	9 (33.3)	69 (32.1)	6 (15.0)	69 (35.9)	4 (14.8)
Infections and infestations	32 (17.1)	31 (13.7)	10 (4.7)	6 (15.0)	11 (5.7)	2 (7.4)	30 (14.0)	3 (7.5)	24 (12.5)	1 (3.7)
Gastrointestinal disorders	11 (5.9)	27 (11.9)	7 (3.3)	1 (2.5)	9 (4.7)	3 (11.1)	13 (6.0)	2 (5.0)	7 (3.6)	0
Nervous system disorders	13 (7.0)	20 (8.8)	3 (1.4)	2 (5.0)	6 (3.1)	2 (7.4)	6 (2.8)	0	12 (6.3)	1 (3.7)
General disorders and administration site conditions	14 (7.5)	9 (4.0)	5 (2.3)	1 (2.5)	3 (1.6)	0	4 (1.9)	1 (2.5)	8 (4.2)	0
Musculoskeletal and connective tissue disorders	9 (4.8)	5 (2.2)	4 (1.9)	1 (2.5)	7 (3.6)	4 (14.8)	10 (4.7)	0	1 (0.5)	2 (7.4)
Metabolism and nutrition disorders	3 (1.6)	3 (1.3)	0	3 (7.5)	0	1 (3.7)	2 (0.9)	0	4 (2.1)	0
Cardiac disorders	2 (1.1)	2 (0.9)	1 (0.5)	2 (5.0)	1 (0.5)	0	0	0	7 (3.6)	0

Data are presented as *N* (%) unless otherwise indicated. Prior to titration: TEAE experienced between first double-blind medication intake and prior to titration up to 50 mg. Post titration: TEAE event started or worsened after titration up to 50 mg until 14 days after the last double-blind medication intake. Placebo 50 mg at week 4 or week 8: Uptitrated from 25 to 50 mg matched placebo at week 4 or 8 post baseline, once-daily oral administration. Mirabegron 50 mg at week 4 or week 8: Uptitrated from mirabegron 25 to 50 mg at week 4 or 8 post baseline, once-daily, oral administration. Treatment group: Placebo 25 mg: Patients remained on matched placebo 25 mg. Mirabegron 25 mg: Patients remained on mirabegron 25 mg throughout the study

Table 4 Potentially clinically significant vital signs by age group (< 75, ≥ 75 years) – Home-based and office visit measurements

Vital sign	Increase criteria	Placebo ($n=442$)		Mirabegron 25 mg ($n=226$)		Mirabegron 50 mg ($n=219$)		Mirabegron total ($n=445$)	
		< 75 years ($n=318$)	≥ 75 years ($n=124$)	< 75 years ($n=160$)	≥ 75 years ($n=66$)	< 75 years ($n=160$)	≥ 75 years ($n=59$)	< 75 years ($n=320$)	≥ 75 years ($n=125$)
Home-based (excluding extreme values)									
SBP (mmHg)	> 10	6/238 (2.5)	3/87 (3.4)	3/126 (2.4)	0	8/116 (6.9)	1/43 (2.3)	11/242 (4.5)	1/92 (1.1)
	> 15	0	2/87 (2.3)	2/126 (1.6)	0	1/116 (0.9)	0	3/242 (1.2)	0
	> 20	0	0	0	0	0	0	0	0
DBP (mmHg)	> 5	17/238 (7.1)	5/87 (5.7)	9/126 (7.1)	4/49 (8.2)	5/116 (4.3)	4/43 (9.3)	14/242 (5.8)	8/92 (8.7)
	> 10	4/238 (1.7)	2/87 (2.3)	1/126 (0.8)	2/49 (4.1)	1/116 (0.9)	1/43 (2.3)	2/242 (0.8)	3/92 (3.3)
	> 15	0	0	0	0	0	0	0	0
Pulse rate (bpm)	> 5	17/237 (7.2)	9/86 (10.5)	15/125 (12.0)	6/49 (12.2)	9/115 (7.8)	2/43 (4.7)	24/240 (10.0)	8/92 (8.7)
	> 10	0	1/86 (1.2)	0	0	1/115 (0.9)	0	1/240 (0.4)	0
	> 15	0	0	0	0	1/115 (0.9)	0	1/240 (0.4)	0
Office visits									
SBP (mmHg)	> 10	31/312 (9.9)	18/121 (14.9)	9/158 (5.7)	9/66 (13.6)	20/160 (12.5)	11/59 (18.6)	29/318 (9.1)	20/125 (16.0)
	> 15	12/312 (3.8)	14/121 (11.6)	7/158 (4.4)	7/66 (10.6)	16/160 (10.0)	7/59 (11.9)	23/318 (7.2)	14/125 (11.2)
	> 20	4/312 (1.3)	8/121 (6.6)	5/158 (3.2)	5/66 (7.6)	9/160 (5.6)	4/59 (6.8)	14/318 (4.4)	9/125 (7.2)
DBP (mmHg)	> 5	37/312 (11.9)	18/121 (14.9)	24/158 (15.2)	7/66 (10.6)	32/160 (20.0)	11/59 (18.6)	56/318 (4.1)	18/125 (14.4)
	> 10	11/312 (3.5)	7/121 (5.8)	6/158 (3.8)	5/66 (7.6)	7/160 (4.4)	3/59 (5.1)	13/318 (4.1)	8/125 (6.4)
	> 15	3/312 (1.0)	4/121 (3.3)	2/158 (1.3)	3/66 (4.5)	1/160 (0.6)	0	3/318 (0.9)	3/125 (2.4)
Pulse rate (bpm)	> 5	47/312 (15.1)	20/121 (16.5)	20/158 (12.7)	8/66 (12.1)	29/160 (18.1)	9/59 (15.3)	49/318 (15.4)	17/125 (13.6)
	> 10	13/312 (4.2)	2/121 (1.7)	5/158 (3.2)	4/66 (6.1)	10/160 (6.3)	5/59 (8.5)	15/318 (4.7)	9/125 (7.2)
	> 15	6/312 (1.9)	1/121 (0.8)	1/158 (0.6)	1/66 (1.5)	5/160 (3.1)	0	6/318 (1.9)	1/125 (0.8)

DBP diastolic blood pressure, *SBP* systolic blood pressure

Data are presented as n/N (%)

N = number of patients with at least one non-missing value during treatment. Number and percentage of patients meeting each criteria on 2 consecutive post-baseline visits are summarized

were observed in patients who titrated up to mirabegron 50 mg after week 4.

3.2.3 Other Safety Parameters

Two patients in the placebo group had a clinically significant abnormal ECG at week 8 (right bundle branch block, inferior epicardial injury), and two patients in the mirabegron 50 mg group had a clinically significant abnormal ECG at EoT (left bundle branch block, atrial fibrillation). Mean change from baseline to EoT in PVR volume was comparable for all treatments. Eight patients (2.1%) in the placebo group and four in the mirabegron total group shifted from a PVR volume < 150 mL at baseline to ≥ 150 mL and < 300 mL at EoT. Two patients in the mirabegron group shifted from a PVR volume of < 150 mL at baseline to ≥ 300 mL at EoT.

4 Discussion

Mirabegron treatment was well-tolerated in older adults with OAB-wet. Safety and tolerability in this study of patients aged ≥ 65 years were consistent with the known mirabegron safety profile [23]. Despite a mean of eight comorbid conditions and 6.5 concomitant medications at baseline, few SAEs were reported and only two (both in the placebo group) were considered drug related by the investigator; there were no mirabegron-related SAEs. The majority of TEAEs in all treatment groups were mild or moderate in severity.

The overall frequency of mirabegron TEAEs in this study (47.0%) was similar to that previously reported in patients aged ≥ 65 years enrolled in phase III studies (mirabegron 25 mg, 54.5%; mirabegron 50 mg, 50.2%) [13]. Additionally, the most frequently reported TEAEs (UTI, headache, and diarrhea) were consistent with the known safety profile of mirabegron [23].

In PILLAR, TEAEs did not appear to be either dose or age related, and the majority were reported early following medication exposure. An increase in dose did not appear to precipitate an increase in AE reporting (Table 3). Interestingly, the people who titrated up to 50 mg appeared fundamentally different: prior to titration, the incidence of TEAEs for these patients was higher in both the placebo and the mirabegron 50 mg groups. In addition, there were also baseline differences in weight, body mass index category, race, and OAB severity that may have been associated with the choice of uptitration. Reporting of TEAEs may be related to

Table 5 Shift table for systolic and diastolic blood pressure during the double-blind treatment period (measured during office visits)

Systolic and diastolic blood pressure and study drug	Post-baseline	Baseline				
		Normal	Prehypertension	Hypertension stage 1	Hypertension stage 2	Total
Systolic blood pressure						
Placebo	Normal	36 (8.4)	13 (3.0)	0	0	49
	Prehypertension	66 (15.3)	149 (34.6)	18 (4.2)	2 (0.5)	235
	Hypertension stage 1	11 (2.6)	65 (15.1)	50 (11.6)	5 (1.2)	131
	Hypertension stage 2	0	4 (0.9)	10 (2.3)	2 (0.5)	16
	Total	113	231	78	9	431
	No data	2	5	3	1	11
Mirabegron 25 mg	Normal	11 (4.9)	6 (2.7)	0	0	17
	Prehypertension	33 (14.7)	92 (41.1)	11 (4.9)	0	136
	Hypertension stage 1	8 (3.6)	31 (13.8)	21 (9.4)	2 (0.9)	62
	Hypertension stage 2	0	3 (1.3)	3 (1.3)	3 (1.3)	9
	Total	52	132	35	5	224
	No data	1	1	0	0	2
Mirabegron 50 mg titration at week 4	Normal	22 (11.5)	6 (3.1)	0	0	28
	Prehypertension	24 (12.5)	38 (19.8)	18 (9.4)	0	80
	Hypertension stage 1	13 (6.8)	32 (16.7)	27 (14.1)	1 (0.5)	73
	Hypertension stage 2	0	2 (1.0)	9 (4.7)	0	11
	Total	59	78	54	1	192
	No data	0	0	0	0	0
Mirabegron 50 mg titration at week 8	Normal	2 (7.4)	1 (3.7)	0	0	3
	Prehypertension	3 (11.1)	9 (33.3)	1 (3.7)	0	13
	Hypertension stage 1	1 (3.7)	2 (7.4)	3 (11.1)	2 (7.4)	8
	Hypertension stage 2	0	0	1 (3.7)	2 (7.4)	3
	Total	6	12	5	4	27
	No data	0	0	0	0	0
Mirabegron 50 mg	Normal	24 (11.0)	7 (3.2)	0	0	31
	Prehypertension	27 (12.3)	47 (21.5)	19 (8.7)	0	93
	Hypertension stage 1	14 (6.4)	34 (15.5)	30 (13.7)	3 (1.4)	81
	Hypertension stage 2	0	2 (0.9)	10 (4.6)	2 (0.9)	14
	Total	65	90	59	5	219
	No data	0	0	0	0	0
Diastolic blood pressure						
Placebo	Normal	217 (50.2)	25 (5.8)	2 (0.5)	0	244
	Prehypertension	78 (18.1)	57 (13.2)	7 (1.6)	1 (0.2)	143
	Hypertension stage 1	18 (4.2)	21 (4.9)	5 (1.2)	1 (0.2)	45
	Hypertension stage 2	0	0	0	0	0
	Total	313	103	14	2	432
	No data	8	2	0	0	10
Mirabegron 25 mg	Normal	118 (52.7)	20 (8.9)	1 (0.4)	0	139
	Prehypertension	41 (18.3)	20 (8.9)	2 (0.9)	1 (0.4)	64
	Hypertension stage 1	8 (3.6)	8 (3.6)	3 (1.3)	0	19
	Hypertension stage 2	0	1 (0.4)	0	1 (0.4)	2
	Total	167	49	6	2	224
	No data	1	1	0	0	2

Table 5 (continued)

Systolic and diastolic blood pressure and study drug	Post-baseline	Baseline				
		Normal	Prehypertension	Hypertension stage 1	Hypertension stage 2	Total
Mirabegron 50 mg titration at week 4	Normal	75 (39.1)	11 (5.7)	0	0	86
	Prehypertension	41 (21.4)	35 (18.2)	6 (3.1)	1 (0.5)	83
	Hypertension stage 1	7 (3.6)	10 (5.2)	5 (2.6)	0	22
	Hypertension stage 2	0	0	1 (0.5)	0	1
	Total	123	56	12	1	192
	No data	0	0	0	0	0
Mirabegron 50 mg titration at week 8	Normal	10 (37.0)	2 (7.4)	0	0	12
	Prehypertension	6 (22.2)	7 (25.9)	0	0	13
	Hypertension stage 1	1 (3.7)	1 (3.7)	0	0	2
	Hypertension stage 2	0	0	0	0	0
	Total	17	10	0	0	27
	No data	0	0	0	0	0
Mirabegron 50 mg	Normal	85 (38.8)	13 (5.9)	0	0	98
	Prehypertension	47 (21.5)	42 (19.2)	6 (2.7)	1 (0.5)	96
	Hypertension stage 1	8 (3.7)	11 (5.0)	5 (2.3)	0	24
	Hypertension stage 2	0	0	1 (0.5)	0	1
	Total	140	66	12	1	219
	No data	0	0	0	0	0

Data are presented as *N* (%)

inefficacy; studies of fesoterodine have shown that patients experiencing greater efficacy are less likely to report TEAEs than those experiencing less efficacy [24].

Few patients met the criteria for PCS laboratory values, with no relevant differences across treatment groups. There were no clinically meaningful differences in changes in vital signs from baseline to EoT for any treatment group, and no differences were observed between the mirabegron and placebo treatment groups.

As shown in Table 4, for home-based monitoring, the incidence of PCS increases of SBP (> 10 mmHg), excluding extreme values, was slightly higher in the mirabegron 50 mg group than in the placebo and mirabegron 25 mg groups, and the incidence of PCS increases of DBP (> 5 mmHg) was slightly higher in the mirabegron 25 mg group than in the other groups. Incidences of increases of > 15 mmHg for SBP and of > 10 mmHg for DBP were low and similar in all treatment groups. PCS increases of > 5 bpm in pulse rate were slightly more frequent only in the mirabegron 25 mg group versus the other groups, suggesting that these observations may not be due to any true effect.

For office-based monitoring, the incidence of PCS increases of SBP (> 10 and > 15 mmHg) was slightly higher in the mirabegron 50 mg group than in the other groups. The incidence of PCS increases of DBP (> 5 mmHg) was slightly higher in the mirabegron 50 mg group than in the other groups. The incidence of increases of > 10 mmHg for DBP was low and similar in all treatment groups. Increases of > 5 bpm in pulse rate were slightly less frequent in the mirabegron 25 mg group than in the other groups.

Overall, the incidence of PCS vital signs from office visits was slightly higher than from home-based monitoring, possibly due to white coat hypertension.

The mirabegron pivotal studies used the same definition for recording an AE of hypertension as was used in this study and similarly reported only small differences versus the placebo arms [16]. When the safety set for the pooled population from these pivotal studies ($n = 4611$ patients) was examined, mirabegron 50 mg/day was associated with a mean increase of ≤ 1 mmHg in blood pressure versus placebo, and the incidence of hypertension was similar between the total mirabegron, placebo, and tolterodine extended release 4 mg groups [16]. In addition, the change in mean pulse rate for mirabegron was approximately 1 bpm (clinically insignificant) compared with placebo and was reversible upon treatment discontinuation. The incidence of urinary retention was greater in the placebo and tolterodine groups than in mirabegron-treated patients, and ECG, PVR volume, and laboratory data were unremarkable across each treatment group [16].

Strengths of the current study include its randomized controlled design and that there were few exclusion criteria,

with the aim of including as wide a range of older people as possible. Since patients aged ≥ 65 years are often under-represented in clinical trials, results from this older population, including a significant number of patients aged ≥ 75 years, are clinically relevant. Despite this, a relatively high number of patients failed to meet trial criteria after the placebo run-in period. From the diary variables, the majority failed on the urgency episode criterion. Other limitations of this study are that the study duration was only 12 weeks, and the characteristics of the sample may not be representative of all older patients with OAB, although, as previously noted, the overall frequency of mirabegron TEAEs in this study was similar to that in patients aged ≥ 65 years enrolled in phase III studies [13]. In addition, because knowledge about prior treatment exposure was lacking, there may have been a systematic reduction in TEAE reporting, although it should be noted that there was a treatment-free run-in period and that the rates of TEAE were roughly equivalent to those in previous trials including older patients [8, 25, 26]. Although the incidence of TEAEs in older patients was numerically higher than in younger patients, this was not associated with an increased number of withdrawals.

5 Conclusions

Mirabegron treatment was well-tolerated in older adults with OAB. Safety and tolerability were consistent with the known mirabegron safety profile.

The findings reported here provide further evidence for the overall safety and tolerability profile for mirabegron in patients aged ≥ 65 years with OAB-wet. PILLAR provides data from a dedicated study in a population that is often under-represented in clinical trials despite the increasing prevalence of both the condition and the risk of AEs with older age.

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Compliance with Ethical Standards

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Conflict of interest Sender Herschorn has received grants from Astellas, Urovant, and Allergan and personal fees from Astellas and Pfizer. David Staskin has received grants and personal fees for services as an investigator, consultant, and speaker for Astellas. Carol R. Schermer and Rita M. Kristy are employees of Astellas Pharma Global Development, Inc. Adrian Wagg has received grants, personal fees, and other non-financial support from Astellas, Essity, Pfizer, and Pierre Fabre.

Ethical Approval Institutional review board/independent ethics committee-approved written informed consent was obtained from all participants or their legally authorized representative before any study-related procedures were carried out.

Data Sharing Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at http://www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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