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Cardiovascular safety of mirabegron add-on therapy to tamsulosin for the treatment of overactive bladder in men with lower urinary tract symptoms: A post hoc analysis from the MATCH study

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Abstract

Objectives: To investigate the cardiovascular safety of mirabegron add-on treatment to tamsulosin in male patients with residual overactive bladder symptoms.

Methods: This was a post hoc analysis of MATCH, the first double-blind, placebo-controlled study comparing mirabegron and placebo as add-on therapy to tamsulosin for treatment of overactive bladder in men with lower urinary tract symptoms. The analysis focused on treatment-emergent adverse events relating to the cardiovascular system or blood pressure, and changes in vital signs during 12 weeks of follow-up.

Results: Cardiovascular-related treatment-emergent adverse events were reported by 6/566 patients, although only one serious treatment-emergent adverse event was related to treatment (unstable angina in the tamsulosin + placebo group). Hypertension (two patients) and increased blood pressure (one patient) were reported in the tamsulosin + placebo group, but there were no blood pressure-related treatment-emergent adverse events among tamsulosin + mirabegron patients. There were no clinically meaningful changes from baseline in blood pressure, and changes in pulse rate were small (+1.2 bpm in the tamsulosin + mirabegron group). Increased pulse rate was more frequent with tamsulosin + mirabegron than with tamsulosin + placebo in older patients, although within the normal range.

Conclusions: Cardiovascular-related adverse events were uncommon in both treatment groups. Mirabegron is a well-tolerated add-on therapy to tamsulosin in Japanese and Korean males with residual overactive bladder symptoms.

KEYWORDS

benign prostatic hyperplasia, cardiovascular, mirabegron, overactive bladder, tamsulosin

Abbreviations: ADR, adverse drug reaction; AE, adverse event; BMI, body mass index; BPH, benign prostatic hyperplasia; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; EOT, end of treatment; FGID, functional gastrointestinal disorders; LUTS, lower urinary tract symptoms; OAB, overactive bladder; PSA, prostate-specific antigen; Q_{max}, maximum urinary flow rate; SAS, safety analysis set; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; WHO, World Health Organization.

1 | INTRODUCTION

Overactive bladder (OAB) is a highly prevalent syndrome, with an estimated 12.4% of the Japanese population ≥40 years of age experiencing symptoms.[1] The prevalence of OAB is 23.9%, 19.7%, and 15.8% in China, South Korea, and Taiwan, respectively.[2] Cardiovascular comorbidities are more prevalent in patients with OAB than in age- and gender-matched controls,[3,4] so the cardiovascular safety of OAB pharmacotherapies is particularly important.

Treatments for OAB symptoms include antimuscarinic agents and the β_3-adrenoceptor agonist mirabegron. Mirabegron stimulates bladder relaxation by activating β_3-adrenoceptors on the bladder detrusor muscle, facilitating bladder filling and urine storage.[5,6] Preclinical studies have demonstrated that β-adrenoceptors are also expressed in the cardiovascular system.[7-10]

Despite involvement of β_3-adrenoceptors in the cardiovascular system and in the mechanism of action of mirabegron, previous studies have not detected cardiovascular safety signals in patients treated with mirabegron. In a Japanese phase III study, pulse rate, blood pressure, and the incidence of cardiovascular-related adverse events (AEs) in patients receiving mirabegron were similar to those in patients receiving placebo.[11] In postmarketing studies, the incidence of cardiovascular adverse drug reactions (ADRs) was 0.48% in patients with OAB[12] and 5.51% in patients with OAB and existing cardiovascular disease (CVD).[13] An integrated clinical trial database analysis conducted specifically to assess the cardiovascular safety of mirabegron concluded there was no evidence of an increased risk for cardiovascular events for mirabegron, compared with placebo.[14]

Based on current clinical guidelines for lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH),[15] α_1-blockers are often used first line for male LUTS. However, the α_1-adrenoceptor is also involved in regulating blood pressure, regional vascular resistance, and venous capacitance. α_1b-adrenoceptors have a key role in mediation of the vascular response to adrenergic stimulation and occur in relatively high densities in the human heart.[16] The α_1-blocker tamsulosin was developed for the treatment of LUTS associated with BPH and selectively antagonizes α_1a- and α_1d-adrenoceptors while demonstrating little affinity for the α_1b subtype.[17,18] A recent meta-analysis concluded that tamsulosin is associated with fewer AEs than other α_1-blockers.[19]

TABLE 1 Baseline patient demographics

Parameter	Tamsulosin + placebo (n = 284)	Tamsulosin + mirabegron (n = 282)	*P* value
Age in years, mean (SD)	65.5 (9.0)	65.3 (8.5)	.696[a]
Age group, n (%)			
<65 yr	128 (45.1)	118 (41.8)	.447[b]
≥65 yr	156 (54.9)	164 (58.2)	
<75 yr	236 (83.1)	247 (87.6)	.116[b]
≥75 yr	48 (16.9)	35 (12.4)	
Ethnicity, n (%)			
Japanese	268 (94.4)	268 (95.0)	.852[b]
Korean	16 (5.6)	14 (5.0)	
BMI in kg/m^2, mean (SD)	23.56 (2.99)	23.91 (3.00)	.163[a]
Prostate volume in mL, mean (SD)	31.10 (10.20)	30.86 (12.55)	.809[a]
Q_{max} in mL/s, mean (SD)	14.17 (7.15)	14.28 (7.46)	.855[a]
OAB duration in months, mean (SD)[c]	52.9 (59.5)	44.6 (44.4)	.076[a]
OAB duration by group[c], n (%)			
<12 mo	60 (21.1)	64 (22.7)	.601[b]
≥12 mo	197 (69.4)	185 (65.6)	
Status of urinary incontinence, n (%)			
Absent	120 (42.3)	103 (36.5)	.281[b]
Urgency urinary incontinence	156 (54.9)	167 (59.2)	
Mixed urinary incontinence	8 (2.8)	12 (4.3)	

Abbreviations: BMI, body mass index; OAB, overactive bladder; Q_{max}, maximum urinary flow rate.
[a]Two sample *t* test.
[b]Fisher exact test.
[c]Duration of primary diagnosis not known in 60 patients (27 placebo, 33 mirabegron). n = 257 for tamsulosin + placebo; n = 249 for tamsulosin + mirabegron.

TABLE 2 Baseline vital signs by age group

Parameter	Tamsulosin + placebo					Tamsulosin + mirabegron				
	Total (n = 284)	<65 yr (n = 128)	≥65 yr (n = 156)	<75 yr (n = 236)	≥75 yr (n = 48)	Total (n = 282)	<65 yr (n = 118)	≥65 yr (n = 164)	<75 yr (n = 247)	≥75 yr (n = 35)
Mean SBP, mmHg (SD)	**125.9 (13.0)**	122.8 (13.1)	128.5 (12.4)	124.7 (12.8)	132.0 (12.4)	**127.2 (12.6)**	124.3 (12.5)	129.3 (12.3)	126.6 (12.7)	132.0 (11.2)
Mean DBP, mmHg (SD)	**79.0 (7.8)**	80.2 (8.3)	78.0 (7.3)	79.4 (7.8)	77.1 (7.8)	**79.9 (8.6)**	80.9 (9.0)	79.1 (8.2)	80.2 (8.6)	77.7 (7.9)
Mean pulse rate, bpm (SD)	**68.0 (9.0)**	70.2 (9.6)	66.2 (8.0)	68.5 (9.1)	65.2 (8.0)	**68.9 (9.4)**	70.4 (9.3)	67.9 (9.5)	69.0 (9.5)	68.2 (9.3)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Potential pharmacokinetic and cardiovascular interactions between mirabegron and tamsulosin have been evaluated previously. In 48 healthy men aged 44 to 72 years, tamsulosin + mirabegron co-therapy did not cause clinically relevant changes in cardiovascular parameters up to 12 hours after dose.[20] However, the doses of mirabegron and tamsulosin used were higher than approved doses in Japan, so the results are not directly applicable to the Japanese population. Two additional studies have shown that mirabegron add-on treatment to tamsulosin was well tolerated in Japanese patients,[21,22] although neither was double blinded nor placebo controlled. Consequently, there still is a theoretical concern that combining mirabegron with α_1-blockers may result in additive and/or synergistic effects on the cardiovascular system, particularly in Japanese patients.

MATCH was a randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of mirabegron add-on treatment to tamsulosin in patients with residual OAB symptoms.[23] The present post hoc analysis investigated cardiovascular safety outcomes from the MATCH study, specifically any increases in blood pressure or pulse rate. Given the relationship between age and cardiac disorders,[24] the impact of age was also analyzed, using cutoffs of 65 and 75 years.

2 | METHODS

2.1 | Study design and participants

MATCH (NCT02656173) was conducted in Japan (53 sites) and Korea (5 sites) between January 2016 and July 2017, in accordance with International Council for Harmonization guidelines and ethical principles that have their origin in the Declaration of Helsinki. The local institutional review board/independent ethics committee reviewed and approved the protocol and all patients provided written informed consent prior to enrollment, in accordance with Japanese and Korean guidelines.

The study enrolled male outpatients aged ≥40 years who had received tamsulosin 0.2 mg for ≥4 weeks prior to screening and experienced an average of ≥2 episodes of urgency/24 h and ≥8 micturitions/24 h during the 3 days prior to screening. Patients with a postvoid residual volume >100 mL, Q_{max} < 5 mL/s, or prostate-specific antigen ≥4 ng/mL were excluded, as described previously.[23] Eligible patients received tamsulosin 0.2 mg + placebo orally once daily for 4 weeks. Patients who remained eligible at the end of screening continued with tamsulosin 0.2 mg once daily and were randomized 1:1 to receive add-on treatment with mirabegron 50 mg or placebo for 12 weeks. Efficacy endpoints and patient-reported outcomes have been reported previously, along with an overview of treatment-emergent adverse events (TEAEs).[23]

2.2 | Cardiovascular safety assessment

The present post hoc analysis focuses on TEAEs of special interest (cardiovascular events or increased blood pressure with onset during treatment or prevalent at screening that worsened during double-blind treatment), along with changes in vital signs (systolic blood

TABLE 3 Concurrent cardiovascular disease reported by ≥1% of patients in at least one treatment group at screening

System organ class code/preferred term	Tamsulosin + placebo					Tamsulosin + mirabegron				
	Total (*n* = 284)	<65 yr (*n* = 128)	≥65 yr (*n* = 156)	<75 yr (*n* = 236)	≥75 yr (*n* = 48)	Total (*n* = 282)	<65 yr (*n* = 118)	≥65 yr (*n* = 164)	<75 yr (*n* = 247)	≥75 yr (*n* = 35)
Overall	111 (39.1)	31 (24.2)	80 (51.3)	77 (32.6)	34 (70.8)	126 (44.7)	29 (24.6)	97 (59.1)	108 (43.7)	18 (51.4)
Cardiac disorders	14 (4.9)	3 (2.3)	11 (7.1)	7 (3.0)	7 (14.6)	18 (6.4)	4 (3.4)	14 (8.5)	15 (6.1)	3 (8.6)
Atrioventricular block first degree	2 (0.7)	0	2 (1.3)	0	2 (4.2)	4 (1.4)	0	4 (2.4)	3 (1.2)	1 (2.9)
Arrhythmia	2 (0.7)	0	2 (1.3)	1 (0.4)	1 (2.1)	3 (1.1)	0	3 (1.8)	2 (0.8)	1 (2.9)
Atrial fibrillation	0	0	0	0	0	3 (1.1)	1 (0.8)	2 (1.2)	2 (0.8)	1 (2.9)
Bundle branch block right	1 (0.4)	0	1 (0.6)	0	1 (2.1)	3 (1.1)	1 (0.8)	2 (1.2)	3 (1.2)	0
Angina pectoris	3 (1.1)	1 (0.8)	2 (1.3)	2 (0.8)	1 (2.1)	1 (0.4)	0	1 (0.6)	1 (0.4)	0
Vascular disorders	108 (38.0)	29 (22.7)	79 (50.6)	74 (31.4)	34 (70.8)	119 (42.2)	28 (23.7)	91 (55.5)	102 (41.3)	17 (48.6)
Hypertension	108 (38.0)	29 (22.7)	79 (50.6)	74 (31.4)	34 (70.8)	117 (41.5)	28 (23.7)	89 (54.3)	100 (40.5)	17 (48.6)

Note: Assume that patients could report >1 cardiovascular disorder.

TABLE 4 Cardiovascular-related concomitant medications

	Tamsulosin + placebo					Tamsulosin + mirabegron				
	Total (*n* = 284)	<65 yr (*n* = 128)	≥65 yr (*n* = 156)	<75 yr (*n* = 236)	≥75 yr (*n* = 48)	Total (*n* = 282)	<65 yr (*n* = 118)	≥65 yr (*n* = 164)	<75 yr (*n* = 247)	≥75 yr (*n* = 35)
Overall	36 (12.7%)	9 (7.0%)	27 (17.3%)	23 (9.7%)	13 (27.1%)	44 (15.6%)	5 (4.2%)	39 (23.8%)	30 (12.1%)	14 (40.0%)
Agents acting on RAS[a]	17 (6.0%)	7 (5.5%)	10 (6.4%)	12 (5.1%)	5 (10.4%)	23 (8.2%)	4 (3.4%)	19 (11.6%)	19 (7.7%)	4 (11.4%)
Antigout preparations	0	0	0	0	0	1 (0.4%)	0	1 (0.6%)	0	1 (2.9%)
Antihypertensives[b]	0	0	0	0	0	1 (0.4%)	0	1 (0.6%)	0	1 (2.9%)
Antithrombotic agents	17 (6.0%)	1 (0.8%)	16 (10.3%)	7 (3.0%)	10 (20.8%)	18 (6.4%)	1 (0.8%)	17 (10.4%)	8 (3.2%)	10 (28.6%)
Beta-blocking agents	1 (0.4%)	1 (0.8%)	0	1 (0.4%)	0	0	0	0	0	0
Calcium channel blockers[a]	7 (2.5%)	1 (0.8%)	6 (3.8%)	4 (1.7%)	3 (6.3%)	7 (2.5%)	1 (0.8%)	6 (3.7%)	6 (2.4%)	1 (2.9%)
Cardiac therapy	2 (0.7%)	0	2 (1.3%)	1 (0.4%)	1 (2.1%)	0	0	0	0	0
Diuretics	3 (1.1%)	0	3 (1.9%)	0	3 (6.3%)	3 (1.1%)	1 (0.8%)	2 (1.2%)	1 (0.4%)	2 (5.7%)
Drugs for FGID	0	0	0	0	0	1 (0.4%)	0	1 (0.6%)	0	1 (2.9%)
Lipid-modifying agents	3 (1.1%)	0	3 (1.9%)	3 (1.3%)	0	4 (1.4%)	0	4 (2.4%)	2 (0.8%)	2 (5.7%)
Peripheral vasodilators	0	0	0	0	0	2 (0.7%)	0	2 (1.2%)	1 (0.4%)	1 (2.9%)
Herbal/traditional medicine	0	0	0	0	0	1 (0.4%)	0	1 (0.6%)	1 (0.4%)	0

Abbreviations: FGID, functional gastrointestinal disorders; RAS, renin-angiotensin system.

[a]Possibly used to treat hypertension.

[b]Concomitant medicines that were prescribed as treatment for cardiovascular-related complications were extracted and categorized in accordance with the Anatomical Therapeutic Chemical Classification System second level.

pressure [SBP], diastolic blood pressure [DBP], and pulse rate) between the baseline visit and end of treatment (EOT).

Vital signs were measured at home for 3 days prior to the baseline visit (week 0), and weeks 4, 8, and 12 of randomized treatment. For each visit, measurements were taken at waking and at bedtime and averaged for statistical analysis. In this post hoc assessment, potentially clinically significant changes in vital signs were examined by comparing the highest values obtained during treatment with those from baseline assessments for each patient. Electrocardiograms (ECGs) were performed at screening (week −4) only.

Cardiovascular-related concomitant medications were classified according to the World Health Organization (WHO) Drug Dictionary, and cardiovascular-related complications and TEAEs were classified according to Medical Dictionary for Regulatory Activities terminology.

2.3 | Statistical analyses

Safety assessments were based on the safety analysis set (SAS), which included all patients who received ≥1 dose of double-blind study drug. The number of TEAEs and the number and percentage of patients with TEAEs were summarized by severity and by relationship to study drug in each treatment group. Vital signs were summarized using descriptive statistics by treatment group and by age group (<65 years vs ≥65 years; <75 years vs ≥75 years) at each visit and at EOT.

3 | RESULTS

3.1 | Patient demographics

As described previously,[23] 730 patients received tamsulosin + placebo after screening, 568 were then randomized to tamsulosin + placebo or tamsulosin + mirabegron, and 544 completed the study (tamsulosin + placebo: 272, tamsulosin + mirabegron: 272). Two patients were excluded from the SAS as they did not take the study drug during the treatment period.

TABLE 5 Cardiovascular-related TEAEs

System organ class code/preferred term	Tamsulosin + placebo (*n* = 284)	Tamsulosin + mirabegron (*n* = 282)
Cardiovascular events	3 (1.1)	3 (1.1)
Tachycardia	0	2 (0.7)
Arrhythmia	1 (0.4)	0
Bradyarrhythmia	1 (0.4)	0
Unstable angina	1 (0.4)	1 (0.4)
Blood pressure	3 (1.1)	0
Blood pressure increased	1 (0.4)	0
Hypertension	2 (0.7)	0

Abbreviation: TEAE, treatment-emergent adverse event.
Note: In all cases, patients experienced a single event of each type.

There were no significant differences between the tamsulosin + placebo (n = 284) and tamsulosin + mirabegron (n = 282) groups in terms of demographics (Table 1) and baseline vital signs (Table 2). SBP tended to be higher and DBP lower in the older vs younger age groups. Mean pulse rates were generally lower in the older age groups and were slightly higher in the ≥75-year age group on tamsulosin + mirabegron than in the corresponding tamsulosin + placebo group (68.2 ± 9.3 vs 65.2 ± 8.0 bpm).

At screening, 237/566 patients (41.9%) reported concurrent CVD (tamsulosin + mirabegron: 44.7%, tamsulosin + placebo: 39.1%; Table 3), with hypertension affecting 225/237 patients (94.9%) with CVD. The prevalence of CVD increased with age, although this was more pronounced in the tamsulosin + placebo group than in the tamsulosin + mirabegron group. For patients ≥75 years, CVD was more prevalent in the tamsulosin + placebo group (70.8%) than in the tamsulosin + mirabegron group (51.4%), although the opposite trend was observed for patients <75 years (32.6% vs 43.7%, respectively).

Concomitant use of cardiovascular medications during the treatment period increased with age and was slightly more common in the tamsulosin + mirabegron group compared with the tamsulosin + placebo group (Table 4). In patients <65 years, only 14/246 patients (5.7%; 5 in the tamsulosin + mirabegron group and 9 in the tamsulosin + placebo group) required cardiovascular medication, while in those ≥75 years of age, 27/83 patients (32.5%; 14 and 13 patients, respectively) required cardiovascular treatment.

3.2 | Adverse events

Cardiovascular-related TEAEs were reported by three patients (1.1%) in both the tamsulosin + placebo (unstable angina, arrhythmia, and bradyarrhythmia) and tamsulosin + mirabegron groups (unstable angina and two patients with tachycardia; Table 5). TEAEs relating to blood pressure were reported by three patients in the tamsulosin + placebo group (blood pressure increased and two patients with hypertension), but no patients in the tamsulosin + mirabegron group. There was no apparent relationship between patient age and the

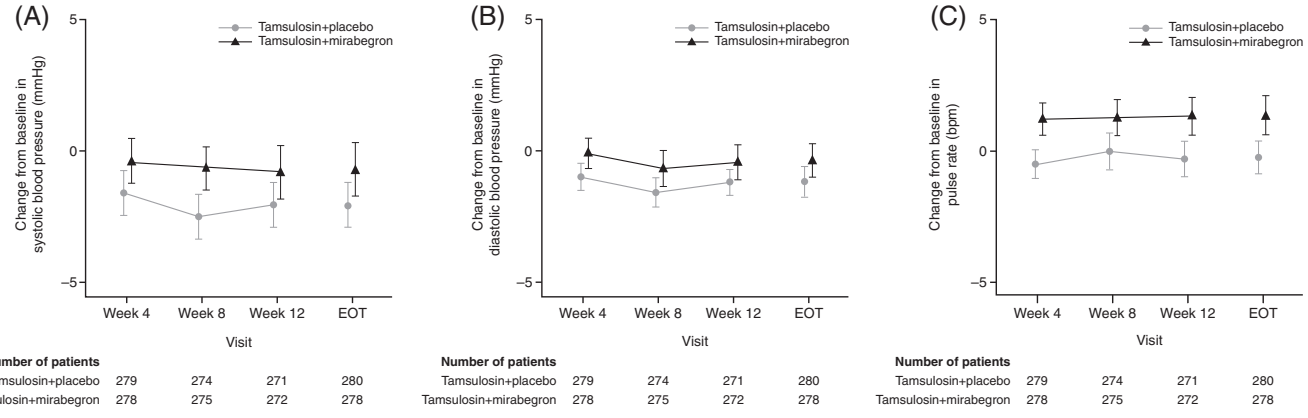

FIGURE 1 Change from baseline in A, systolic blood pressure, B, diastolic blood pressure, and C, pulse rate. EOT, end of treatment

TABLE 6 Changes in vital signs from baseline by age

	Tamsulosin + placebo					Tamsulosin + mirabegron				
	Total (*n* = 271-280)	<65 yr (*n* = 123-126)	≥65 yr (*n* = 148-154)	<75 yr (*n* = 228-234)	≥75 yr (*n* = 43-46)	Total (*n* = 272-278)	<65 yr (*n* = 116)	≥65 yr (*n* = 156-162)	<75 yr (*n* = 238-243)	≥75 yr (*n* = 34-35)
Change in SBP (mmHg), mean (SD)										
4 wk	−1.6 (6.5)	−0.9 (6.0)	−2.2 (6.8)	−1.6 (6.4)	−1.7 (6.7)	−0.4 (6.9)	0.1 (6.7)	−0.7 (7.1)	0 (6.8)	−2.9 (7.3)
8 wk	−2.5 (7.1)	−1.9 (6.6)	−3.1 (7.4)	−2.6 (6.6)	−2.2 (9.1)	−0.7 (7.7)	−0.3 (7.4)	−0.9 (8.0)	−0.3 (7.7)	−2.9 (7.2)
12 wk	−2.0 (7.2)	−2.0 (7.6)	−2.0 (7.0)	−2.0 (7.1)	−2.2 (8.2)	−0.8 (8.5)	−0.1 (8.2)	−1.3 (8.7)	−0.4 (8.5)	−3.9 (7.8)
EOT	−2.0 (7.3)	−1.9 (7.6)	−2.1 (7.1)	−2.0 (7.1)	−1.9 (8.2)	−0.7 (8.4)	−0.1 (8.2)	−1.1 (8.6)	−0.3 (8.4)	−3.7 (7.7)
Change in DBP (mmHg), mean (SD)										
4 wk	−1.1 (4.2)	−0.6 (4.4)	−1.4 (4.1)	−1.0 (4.3)	−1.5 (4.0)	−0.2 (4.6)	0 (4.9)	−0.3 (4.4)	0 (4.6)	−1.4 (4.9)
8 wk	−1.6 (4.6)	−1.1 (5.0)	−2.1 (4.2)	−1.7 (4.7)	−1.2 (3.9)	−0.7 (5.7)	−0.3 (6.2)	−1.0 (5.3)	−0.5 (5.8)	−2.4 (4.6)
12 wk	−1.3 (4.8)	−0.9 (5.3)	−1.6 (4.3)	−1.2 (4.8)	−1.5 (4.8)	−0.5 (5.4)	−0.3 (5.3)	−0.6 (5.5)	−0.3 (5.4)	−2.0 (5.9)
EOT	−1.2 (4.8)	−0.8 (5.3)	−1.6 (4.4)	−1.2 (4.8)	−1.4 (4.8)	−0.4 (5.4)	−0.3 (5.3)	−0.5 (5.5)	−0.2 (5.3)	−1.9 (5.8)
Change in pulse rate (bpm), mean (SD)										
4 wk	−0.6 (4.3)	−0.7 (4.8)	−0.5 (3.8)	−0.6 (4.4)	−0.7 (3.8)	1.1 (5.1)	0.8 (5.0)	1.3 (5.2)	1.0 (4.9)	1.9 (6.3)
8 wk	−0.1 (5.5)	0.3 (6.7)	−0.5 (4.3)	0 (5.7)	−0.6 (4.7)	1.1 (5.2)	1.4 (5.4)	0.9 (5.0)	1.1 (5.2)	1.4 (4.8)
12 wk	−0.4 (5.1)	−0.5 (5.5)	−0.3 (4.7)	−0.3 (5.2)	−1.2 (4.4)	1.2 (5.8)	0.9 (6.2)	1.4 (5.4)	1.0 (5.8)	2.5 (5.4)
EOT	−0.4 (5.1)	−0.4 (5.6)	−0.3 (4.6)	−0.2 (5.2)	−1.2 (4.4)	1.2 (5.7)	0.9 (6.2)	1.5 (5.3)	1.0 (5.8)	2.6 (5.3)

Abbreviations: DBP, diastolic blood pressure; EOT, end of treatment; SBP, systolic blood pressure.
Note: Not all patients provided blood pressure data at every visit, so n values differ between time points.

occurrence of cardiovascular-related TEAEs (3/246 [1.2%] in patients <65 years vs 3/320 [0.9%] in patients ≥65 years; 5/483 [1.0%] in patients <75 years vs 1/83 [1.2%] in those ≥75 years). Blood pressure-related TEAEs only occurred in tamsulosin + placebo patients, and there were too few events to draw any meaningful conclusions relating to age.

Only two cardiovascular-related TEAEs were classified as serious (one case of unstable angina in each treatment group). In the tamsulosin + mirabegron group, the event was regarded as unrelated to study drug and did not resolve despite discontinuation of the study drug. In the tamsulosin + placebo group, the investigator regarded the event as possibly related to treatment, and it resolved after study drug discontinuation (Table S1).

3.3 | Investigations

3.3.1 | Blood pressure

There were no clinically meaningful changes from baseline in either SBP (Figure 1A) or DBP (Figure 1B) in either treatment group. In the tamsulosin + placebo group, the maximum change from a baseline SBP of 125.9 ± 13.0 mmHg (mean ± SD) was −2.5 ± 7.1 mmHg at week 8, compared with a −0.8 ± 8.5 mmHg change at week 12 from a baseline of 127.2 ± 12.6 mmHg in the tamsulosin + mirabegron group. Changes of a similar magnitude (≤2%) were observed in DBP in the two treatment groups.

Changes in blood pressure were also analyzed by age group (Table 6). For patients in the tamsulosin + mirabegron group, decreases in SBP were generally greater in older patients and were most pronounced in the ≥75-year age group (−3.9 mmHg at week 12). In contrast, there was less difference in the change in SBP between age groups in the tamsulosin + placebo group. Similar overall trends were observed in DBP.

Three thresholds were used to identify potentially clinically significant increases in blood pressure (Table 7). For SBP, there were no clear differences between the <65- and ≥65-year age groups in the proportion of patients experiencing these increases in either treatment group. However, increases were typically more prevalent in the tamsulosin + mirabegron group than in the tamsulosin + placebo group (7.9% and 9.1% in the tamsulosin + placebo group for patients <65 years and ≥65 years, respectively, compared with 17.2% and 16.0% in the tamsulosin + mirabegron group). Increases in SBP appeared to be more prevalent in the ≥75-year group among patients treated with tamsulosin + placebo and in the <75-year group for those treated with tamsulosin + mirabegron. Trends in DBP were generally similar to those seen for SBP, with little difference between the <65- and ≥65-year groups but numerically more events in the tamsulosin + mirabegron group than in the tamsulosin + placebo group. Patients ≥75 years only reported changes in DBP at the lowest threshold (≥5 mmHg increase) and at a lower rate than in the <75-year age group.

3.3.2 | Pulse rate

Changes from baseline in pulse rate were minimal in both treatment groups (Figure 1C). In the tamsulosin + placebo group, the maximum change from a baseline pulse rate of 68.0 ± 9.0 bpm (mean ± SD) was −0.6 ± 4.3 bpm at week 4 vs a +1.2 ± 5.8 bpm change at week 12 from a baseline of 68.9 ± 9.4 bpm in the tamsulosin + mirabegron group. When pulse rates were analyzed by age groups (Table 6), small

TABLE 7 Potentially clinically significant changes in BP and pulse from baseline by age

	Tamsulosin + placebo					Tamsulosin + mirabegron				
	Total (*n* = 280)	<65 yr (*n* = 126)	≥65 yr (*n* = 154)	<75 yr (*n* = 234)	≥75 yr (*n* = 46)	Total (*n* = 278)	<65 yr (*n* = 116)	≥65 yr (*n* = 162)	<75 yr (*n* = 243)	≥75 yr (*n* = 35)
SBP increase										
≥10 mmHg	24 (8.6%)	10 (7.9%)	14 (9.1%)	17 (7.3%)	7 (15.2%)	46 (16.5%)	20 (17.2%)	26 (16.0%)	42 (17.3%)	4 (11.4%)
≥15 mmHg	4 (1.4%)	1 (0.8%)	3 (1.9%)	3 (1.3%)	1 (2.2%)	20 (7.2%)	8 (6.9%)	12 (7.4%)	19 (7.8%)	1 (2.9%)
≥20 mmHg	1 (0.4%)	0	1 (0.6%)	0	1 (2.2%)	6 (2.2%)	3 (2.6%)	3 (1.9%)	6 (2.5%)	0
DBP increase										
≥5 mmHg	56 (20.0%)	33 (27.0%)	23 (14.9%)	49 (20.9%)	7 (15.2%)	77 (27.7%)	35 (30.2%)	42 (25.9%)	71 (29.2%)	6 (17.1%)
≥10 mmHg	5 (1.8%)	5 (4.0%)	0	5 (2.1%)	0	18 (6.5%)	8 (6.9%)	10 (6.2%)	18 (7.4%)	0
≥15 mmHg	1 (0.4%)	1 (0.8%)	0	1 (0.4%)	0	2 (0.7%)	0	2 (1.2%)	2 (0.8%)	0
Pulse rate increase										
≥5 bpm	69 (24.6%)	37 (29.4%)	32 (20.8%)	62 (26.5%)	7 (15.2%)	112 (40.3%)	50 (43.1%)	62 (38.3%)	95 (39.1%)	17 (48.6%)
≥10 bpm	14 (5.0%)	10 (7.9%)	4 (2.6%)	12 (5.1%)	2 (4.3%)	31 (11.2%)	15 (12.9%)	16 (9.9%)	26 (10.7%)	5 (14.3%)
≥15 bpm	4 (1.4%)	4 (3.2%)	0	4 (1.7%)	0	7 (2.5%)	2 (1.7%)	5 (3.1%)	5 (2.1%)	2 (5.7%)

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

increases were observed in the tamsulosin + mirabegron group and small decreases in the tamsulosin + placebo group, regardless of age. The magnitude of these changes was broadly similar between the <65- and ≥65-year age groups, although changes were slightly more pronounced in the ≥75-year group than in the <75-year group (+1.4 to +2.6 vs +1.0 to +1.1 for tamsulosin + mirabegron; −0.6 to −1.2 vs 0 to −0.6 bpm for tamsulosin + placebo).

Three thresholds were also used to identify potentially clinically significant increases in pulse rate (Table 7). Broadly similar proportions of patients in the <65- and ≥65-year age groups reported significant increases in pulse rate. Regardless of the threshold used, changes in pulse rate were reported by a higher proportion of patients in the tamsulosin + mirabegron group than the tamsulosin + placebo group. However, in the <65-year age group, the most pronounced threshold (an increase of ≥15 bpm) was reached by 3.2% of patients in the tamsulosin + placebo group vs 1.7% of patients in the tamsulosin + mirabegron group. Patients ≥75 years experienced more increases in pulse rate on tamsulosin + mirabegron but fewer increases on tamsulosin + placebo, compared with the patients <75 years.

4 | DISCUSSION

MATCH was the first double-blind, placebo-controlled study to investigate mirabegron add-on therapy to tamsulosin, enrolling male patients from Japan and Korea with residual OAB symptoms. This post hoc analysis focused specifically on cardiovascular safety. Cardiovascular-related TEAEs were uncommon during the 12-week double-blind treatment period, with three patients (1.1%) reporting events in each group and three patients (1.1%) reporting blood pressure-related TEAEs in the tamsulosin + placebo group. Two cardiovascular-related TEAEs (unstable angina) were classified as serious, and only one of these (in the tamsulosin + placebo group) was regarded as related to treatment. Although the proportion of patients with CVD at baseline (a potential risk factor for cardiovascular TEAEs during the study) was slightly higher in the tamsulosin + mirabegron group than in the tamsulosin + placebo group (44.7% of patients vs 39.1%), the number of cardiovascular-related TEAEs during the study was lower in the tamsulosin + mirabegron group.

This post hoc analysis adds to a considerable volume of data relating to the cardiovascular safety of mirabegron. For example, a low incidence of cardiovascular-related AEs was recorded in phase III trials with mirabegron monotherapy.[25] Although small, statistically significant increases in pulse rate (≈1 bpm) have been observed.[26-28] These were reversed once treatment was discontinued,[28] and were regarded as clinically acceptable. In addition, pooled data from mirabegron clinical trials (≈13 400 patients) showed no evidence of an increased risk for cardiovascular events with mirabegron or antimuscarinics (solifenacin or tolterodine) vs placebo.[14] The authors of the pooled data analysis concluded that cardiovascular-related TEAEs were more likely to be related to a patient's preexisting condition than to OAB treatment.

In the present analysis, SBP and DBP at baseline were slightly higher in the tamsulosin + mirabegron group than in the tamsulosin + placebo group, but no increases from baseline were observed in either treatment group. When analyzed by age, there were small decreases from baseline in SBP and DBP at EOT in all age/treatment groups. For patients in the <65-, ≥65-, and <75-year age groups, these decreases were slightly higher in the tamsulosin + placebo group than in the tamsulosin + mirabegron group, although this trend was reversed in the ≥75-year patient group. The prevalence of clinically significant changes in blood pressure was slightly lower in the oldest patient group (≥75 years) than in younger patients (<75 years), while there was little difference between the <65- and ≥65-year age groups.

Small increases in pulse rate were observed in the tamsulosin + mirabegron group (≤1.2 bpm), while changes in the placebo group were generally limited to small decreases (≥−0.6 bpm). Changes in both groups were slightly more pronounced in patients ≥75 years (≤2.6 bpm and ≥−1.2 bpm, respectively). The increased pulse rate in patients ≥75 years receiving tamsulosin + mirabegron may be associated with the reduction in blood pressure mentioned above, due to relatively elevated sensitivity for autonomic reflex to lowering BP in older people. The overall increase in pulse rate on tamsulosin + mirabegron at EOT (+1.2 bpm) is consistent with data from phase III studies.[27]Although the results from this post hoc analysis of pulse rates in older patients (≥75 years) are thought to be physiological changes within normal ranges, these findings may be of interest to physicians who manage patients with symptoms of OAB in this age group.

One of the justifications for this analysis was to investigate the possibility that combining mirabegron with tamsulosin may result in additive and/or synergistic effects on the cardiovascular system. Our results, showing no increase in blood pressure and only small increases in pulse rate with no associated increase in cardiovascular-related TEAEs, provide no evidence to support this theoretical concern. The effect of tamsulosin and mirabegron on cardiovascular symptoms may have been balanced out.

Although this was a post hoc analysis of a clinical study determining the overall efficacy and safety of mirabegron add-on treatment to tamsulosin in patients with residual OAB symptoms,[23] it does provide much-needed insight into the cardiovascular safety of this treatment regimen. Additional information could have been gathered on cardiac findings (ECG data) and pulse rates following the EOT, had these analyses been planned prospectively. The small number of patients from the Korean centers may also limit the applicability of these findings to patients outside Japan. Additional limitations are the relatively small number of patients that were evaluated for cardiovascular safety and the short observational time period for this evaluation.

In conclusion, as OAB is a chronic condition requiring long-term treatment, pharmacotherapies need to be well tolerated. This post hoc analysis focusing on cardiovascular-related AEs and vital signs indicates that the combination of tamsulosin and add-on mirabegron has an acceptable safety profile. A low prevalence of cardiovascular-related AEs was observed, although increased pulse rates appeared to be more frequent with tamsulosin + mirabegron than with tamsulosin + placebo, especially in patients of ≥75 years of age.

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CONFLICT OF INTEREST

Takao Katoh is a consultant for Astellas Pharma Inc, Kissei, and Sumitomo Dainippon.

Hidehiro Kakizaki is a consultant, lecturer, and advisory board member for Astellas Pharma Inc; consultant and advisory board member for Kyorin; speaker for Kissei, Daiichi Sankyo, Nippon Shinyaku, and Pfizer; and consultant for Taiho.

Kyu-Sung Lee is a consultant for Astellas Pharma Inc.

Kota Ishida, Daisuke Katou, Osamu Yamamoto, and Satoshi Uno are employees of Astellas Pharma Inc, Japan.

Jar Jong was an employee of Astellas Pharma, Singapore, at the time of this analysis.

Budiwan Sumarsono is an employee of Astellas Pharma, Singapore.

Osamu Yamaguchi is a consultant, lecturer, and advisory board member for Astellas Pharma Inc; lecturer for Kyorin and Pfizer; consultant for Taiho; and consultant and lecturer for Hisamitsu and Asahi Kasei.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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