# A strategy utilizing ambulatory monitoring and home and clinic blood pressure measurements to optimize the safety evaluation of noncardiovascular drugs with potential for hemodynamic effects: a report from the SYNERGY trial

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***Objective*** **The aim of this study was to perform a blood pressure (BP) safety evaluation in patients with an overactive bladder receiving solifenacin (an antimuscarinic agent), mirabegron (a $\beta_3$-adrenoceptor agonist), or both compared with placebo in the SYNERGY trial.**

***Patients and methods*** **Patients were randomized to receive solifenacin 5 mg + mirabegron 50 mg (combination 5 + 50 mg); solifenacin 5 mg + mirabegron 25 mg (combination 5 + 25 mg); solifenacin 5 mg; mirabegron 50 mg; mirabegron 25 mg; or placebo for a double-blind 12-week treatment period. Systolic BP, diastolic BP, and heart rate were measured by ambulatory BP monitoring, and in the clinic or home.**

***Results*** **A total of 715 patients were analyzed in an ambulatory BP monitoring substudy. At the end of treatment, ambulatory BP monitoring measurements showed no consistent increases from baseline in the mean 24-h systolic BP or diastolic BP for combination versus monotherapy groups or for monotherapy groups versus placebo. Analysis of 1-h BP averages during the 6 h range that included the $T_{max}$ values of both study drugs showed no significant BP effects. Shift analysis (switch between different normotension/hypertension stages) did not show differences among the active and placebo groups, nor did outlier analysis of major BP changes differ between placebo and active treatment. Similarly, there were no significant signals in the 24-h heart rate. Office and home measurements were consistent with ambulatory BP monitoring findings.**

***Conclusions*** **A paradigm of ambulatory BP monitoring analysis designed to test BP safety of noncardiovascular drugs showed that solifenacin plus mirabegron combination therapy during 12 weeks produced no meaningful changes in BP or heart rate. *Blood Press Monit* 23:153–163 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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## Introduction

Drugs developed for non-cardiovascular (CV) indications can sometimes show off-target effects on blood pressure (BP) or heart rate. For instance, two drugs used for treating the common clinical condition of overactive bladder (OAB), mirabegron (a $\beta_3$-adrenoceptor agonist) and solifenacin (an antimuscarinic agent), can each increase BP and heart rate in a small proportion of patients [1,2]. The recent development of a combination of these two drugs created the need for a rigorous plan to monitor and analyze their hemodynamic effects when used in combination in the treatment of OAB.

OAB has been defined as urinary urgency usually accompanied by daytime frequency and nocturia with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [3,4]. Many patients with OAB have coexisting CV disease [5–7], showing that the

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prevalence of OAB increases with age and affects ~15% of those aged 65 years or older and 40% of those aged 75 years or older [2,8]. Pharmacological treatment with antimuscarinic agents has been used widely in OAB therapy [9–11]. However, CV adverse events with this class of agents include increases in heart rate and prolongation of the corrected QT interval [1]. Furthermore, patient adherence to antimuscarinic treatment is low, mainly because of limited efficacy and side effects, especially dry mouth [12,13], and therefore, it is important to determine that any therapies designed to improve efficacy do not worsen tolerability. The $\beta_3$-adrenoceptor agonist, mirabegron, is an alternative therapy with a distinctly different mechanism of action characterized by $\beta_3$-adrenoceptor activation with low levels of activity at $\beta_1$ and $\beta_2$ adrenoceptors [12,14,15]. Nevertheless, as adrenoceptors are expressed in CV tissues, there is concern that treatment with $\beta_3$-adrenoceptor agonists might impact the CV system and affect heart rate or rhythmicity as well as cause vasoconstriction and elevate BP [2]. These CV effects could interact potentially with, or be additive to, those of an antimuscarinic agent.

The SYNERGY trial (a randomized, double-blind, placebo- and active-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of combinations of solifenacin and mirabegron compared with monotherapy and placebo in the treatment of OAB) [16] was designed to include an accurate assessment of vital signs including BP and heart rate using ambulatory blood pressure monitoring (ABPM). In addition, conventional vital sign measurements were carried out in the clinic or at home following patient training in the use of BP measuring devices [17,18].

Although the 24-h mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) are typically used as measures of treatment effect, we were aware that potentially relevant short-term BP fluctuations could be diluted by being included in the 24-h mean values. We also used the ABPM data to study hour-by-hour averages, with particular focus on the 6-h period surrounding the time after dosing when the study drugs were known to achieve their peak plasma concentrations or maximum effect ($T_{\max 4–10\,h}$). Also, we assessed whether the treatments altered the night-time dipping pattern and whether treatment led to changes in BP categorization versus BP category at baseline. In addition, we assessed the incidence of individual patients with major BP or heart rate increases (outliers) within the treatment groups.

## Methods

### Study design

SYNERGY (NCT01972841, ClinicalTrials.gov.) was a multinational, multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled phase 3 trial of various doses and combinations of mirabegron and solifenacin. The methodology and primary findings of this trial, which was conducted in 3308 patients (full analysis set; 3398 patients in the safety analysis set) at 435 sites in 42 countries, have been reported in detail elsewhere [16].

Briefly, there was a single-blind, 4-week placebo run-in period, and then patients were randomized in a 2 : 2 : 1 : 1 : 1 : 1 ratio to receive solifenacin 5 mg + mirabegron 50 mg (combination 5 + 50 mg); solifenacin 5 mg + mirabegron 25 mg (combination 5 + 25 mg); solifenacin 5 mg alone; mirabegron 50 mg alone; mirabegron 25 mg alone; or placebo for a double-blind 12-week treatment period, followed by a visit 2 weeks after the end of the double-blind treatment (follow-up) (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/BPMJ/A59*). Randomization was stratified by previous OAB treatment (defined as having received any pharmacological OAB treatment at any time in the past), age group (< 65, ≥ 65 years), sex, and geographical region.

Eligibility for the main study included patients aged 18 years or older with symptoms of OAB ('wet': urgency, urinary frequency, and incontinence) for 3 months or more who recorded three or more incontinence episodes, and on average one or more urgency episode/24 h, and eight or more micturition episodes/24 h for 7 days. Exclusion criteria included the following: significant cardiac or cerebrovascular diseases within 6 months of screening; QTcF interval more than 450 ms for men and more than 470 ms for women; severe uncontrolled hypertension (defined as a SBP ≥ 180 mmHg and/or average DBP ≥ 110 mmHg when sitting); clinically significant abnormal 12-lead ECG; moderate-to-severe hepatic impairment; severe renal impairment; known hypersensitivity to mirabegron or solifenacin; or any contraindication for administration of anticholinergic agents.

### Ambulatory blood pressure monitoring substudy

Eligibility for the ABPM substudy included those patients enrolled in the main study who were voluntarily willing and able to undergo the ABPM assessment for 24 h and to make three additional visits to the clinic during the study period. Additional exclusion criteria to the ABPM substudy included the following: seated SBP of at least 160 mmHg or DBP of at least 95 mmHg; a resting heart rate less than 45 bpm or more than 90 bpm; chronic atrial fibrillation (interferes with the ability to obtain precise ambulatory BP recordings); documented venous thrombosis of the upper extremities; or women who had a mastectomy on the side of the nondominant arm.

The ABPM substudy was a per-protocol study where baseline and at least one of week 4/8 or week 12 data were required for inclusion in the analysis. ABPM assessments (24 h mean and maximum 1 h mean at $T_{\max 4–10\,h}$) were completed at baseline, at week 4, and week 12 (end of the trial). Ambulatory BP recorders were worn for at least 24 h, with measurements obtained every 15 min between 8 a.m. and 10 p.m., and then every 30 min between 10 p.m. and 8 a.m. In patients whose baseline ABPM assessment did not fulfill the quality control criteria, the assessment was repeated before the patient took any double-blind study medication. If a second baseline ABPM assessment was not valid, the patient did not continue in the ABPM

substudy. If the week 4 ABPM assessment did not fulfill the quality control criteria, the ABPM was repeated at week 8 and reported as the week 4 assessment. European Society of Hypertension criteria [19] were used to define valid ABPM recordings (having at least 70% of measurements being obtained every 30 min or more frequently throughout the entire 24-h period).

### Home-based measurements

Patients not included in the ABPM substudy undertook self-measurement of vital signs at home. Patients in the ABPM substudy did not perform home-based assessments. During the screening visit, individuals were instructed on how to perform and document self-assessed vital signs and were provided with detailed operating instructions for the home-based devices. Home/self-measured vital signs were recorded by the patient during 5 consecutive days before the clinic visit by those patients not included in the ABPM substudy [17] and assessed at baseline and at 4, 8, and 12 weeks after randomization.

### Blood pressure and heart rate assessments

Seated, resting vital signs (heart rate, SBP, and DBP) were measured using an Ambulo 2400 (Mortara Instrument Inc., Milwaukee, Wisconsin, USA) [20] for ABPM measurements. For home-based measurements, an Omron M5 Blood Pressure Monitor PK-HEM-7200-E2/V/03-06-2012 (Omron Healthcare Inc., Lake Forest, Illinois, USA) [21] was used for those enrolled in the USA and Canada or an Omron M3 Blood Pressure Monitor PK-HEM-7200-E2/V/03-06-2012 (Omron Healthcare Inc.) [22] for patients in other geographical areas. All devices were validated for use in the relevant countries. Vital signs for all patients at each study visit were measured in triplicate at 2-min intervals and the mean was calculated for the second and third measurements. At screening, BPs were measured in both arms and the arm with the highest DBP was used for the rest of the study [23]. The protocol required reporting of the adverse event of hypertension if the following criteria were fulfilled:

(1) The average clinic SBP was at least 140 mmHg and/or the average DBP was at least 90 mmHg at two consecutive visits after the baseline visit in patients who were normotensive at baseline.
(2) The average clinic SBP was increased by at least 20 mmHg and/or the average DBP was increased at least 10 mmHg at two consecutive visits after the baseline visit in patients with hypertension at baseline.
(3) If the dose of previous antihypertensive drugs was increased or if antihypertensive drugs were initiated for the treatment of hypertension.

Patients were classified at baseline into the following BP categories: normal (SBP $< 120$ mmHg); prehypertension (SBP 120–139 mmHg); stage 1 hypertension (SBP 140–159 mmHg); and stage 2 hypertension (SBP $\geq 160$ mmHg) [24].

Adverse events of tachycardia were to be recorded if the average resting heart rate exceeded 100 bpm.

### Statistical analyses

With 608 evaluable patients in the ABPM substudy (152 in each of the combination groups and 76 in each of the monotherapy groups), 80% power was ensured to show that a one-sided 95% confidence interval (CI) for differences in change from baseline in the mean 24-h SBP between active treatment groups and placebo would not exceed 3 mmHg [25]. On the basis of the hypothesis that solifenacin monotherapy and mirabegron monotherapy might each increase SBP by 1 mmHg, a threshold value of more than 3 mmHg was chosen as this would reflect a larger than additive effect and this threshold would require exclusion with sufficient power. On the basis of previous pharmacodynamics modeling results, an expected difference of 0.5 mmHg between active treatment and placebo groups and an SD of 7.1 mmHg were assumed (data on file; Astellas Pharma Europe B.V., Leiden, the Netherlands) [26]. It was expected that 70% of patients would have evaluable data (both baseline and at least one postrandomization ambulatory BP value); hence, 860 patients were required for randomization.

For continuous variables, descriptive statistics included number of patients, mean, SD, minimum, and maximum. Number and percentages were calculated for categorical analyses. Percentages by categories were based on no missing data. Changes from baseline to the end of treatment (EoT) in vital sign variables and in ABPM-based vital sign variables were analyzed using an analysis of covariance (ANCOVA) model with treatment group, sex, age group, previous OAB medication, and geographic region as fixed factors and baseline value as a covariate. The ANCOVA provided the least square means and two-sided 95% CIs for mean changes from baseline within each treatment group and for differences between combination groups and monotherapies as well as between active groups and placebo.

### Study approval

Local ethics committees or institutional review boards approved the protocol and all amendments. For all sites, approval of the protocol was obtained from the relevant government authorities. The study was carried out in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

## Results

### Ambulatory blood pressure and heart rate findings

A total of 953 patients were randomized in the ABPM substudy, but of these, 238 patients were excluded because of insufficient data (lack of baseline and/or postrandomization

evaluable measurements). Therefore, assessments were available for 715 patients. Characteristics at baseline were similar in the various randomized treatment groups (Table 1). The demographics, comorbid disorders, antihypertensive therapies, and clinic and ambulatory BPs were similar among the randomized treatment groups. Demographics and baseline characteristics were also similar between the included and excluded patients, except for a slightly higher incidence of hypertension in the excluded patients (Supplementary Table 1, Supplemental digital content 2, *http://links.lww.com/BPMJ/A60*).

There were no consistent changes from baseline in 24-h mean SBP or DBP for the combination groups compared with monotherapy groups or for monotherapy groups compared with placebo at week 4 and at the EoT at week 12 (Fig. 1). Differences between treatment groups and placebo for the mean 24-h DBP were small and similar across treatment groups ranging from − 0.5 mmHg for mirabegron 25 mg to 1.2 mmHg for the combination 5 + 50 mg group. The differences between treatment groups and placebo for the 24-h heart rate measured by ABPM ranged from − 0.4 bpm for solifenacin 5 mg to 1.3 bpm for mirabegron 50 mg. No clinically meaningful changes in the 24-h profile of BP were observed across treatment groups for hourly mean change from time-matched baseline ABPM (Fig. 2). Similarly, there were no clinically meaningful differences between treatment groups in the mean daytime and mean night-time change from baseline in SBP, DBP, or heart rate (Supplementary Fig. 2, Supplemental digital content 3, *http://links.lww.com/BPMJ/A61*, *http://links.lww.com/BPMJ/A62*, *http://links.lww.com/BPMJ/A63*). Differences in change from baseline in the mean daytime SBP between treatment groups and placebo ranged from − 1.3 mmHg for mirabegron 25 mg to 1.3 mmHg for the combination 5 + 25 mg group, whereas for change from baseline in the mean night-time SBP, the range was − 2.5 mmHg for mirabegron 25 mg to 2.4 mmHg for solifenacin 5 mg. For the mean change from baseline in daytime DBP, differences between treatment groups and placebo ranged from 0.2 mmHg for mirabegron 25 mg to 1.0 mmHg for the combination 5 + 25 mg group, whereas night-time differences ranged from − 1.6 mmHg for mirabegron 25 mg to 1.1 mmHg for solifenacin 5 mg. Differences in change from baseline in the daytime heart rate between treatment groups and placebo ranged from − 0.5 bpm for solifenacin 5 mg to 2.2 bpm for mirabegron 50 mg; night-time differences ranged from 0.1 bpm for solifenacin 5 mg to 1.3 bpm for combination 5 + 50 mg.

The difference versus placebo in change from baseline in the maximum 1-h mean at $T_{\max 4\text{–}10\ h}$ was –2.6 mmHg (95% CI: –9.1 to 4.0 mmHg) for SBP and –2.1 bpm (95% CI: –6.6 to 2.3 bpm) for heart rate for mirabegron 50 mg at week 12 (Table 2). In the 5 + 50 mg combination group, a higher value for SBP, 1.9 mmHg (95% CI: –4.2 to 7.9 mmHg), and a lower mean value for heart rate, –1.3 bpm (95% CI: –4.9 to 2.2 bpm), were observed at week 12 compared with placebo. Thus, there was no evidence for a pressor effect from mirabegron and overall no drug-related effect (compared with placebo) could be identified around $T_{\max}$ for any active treatment group (Table 2).

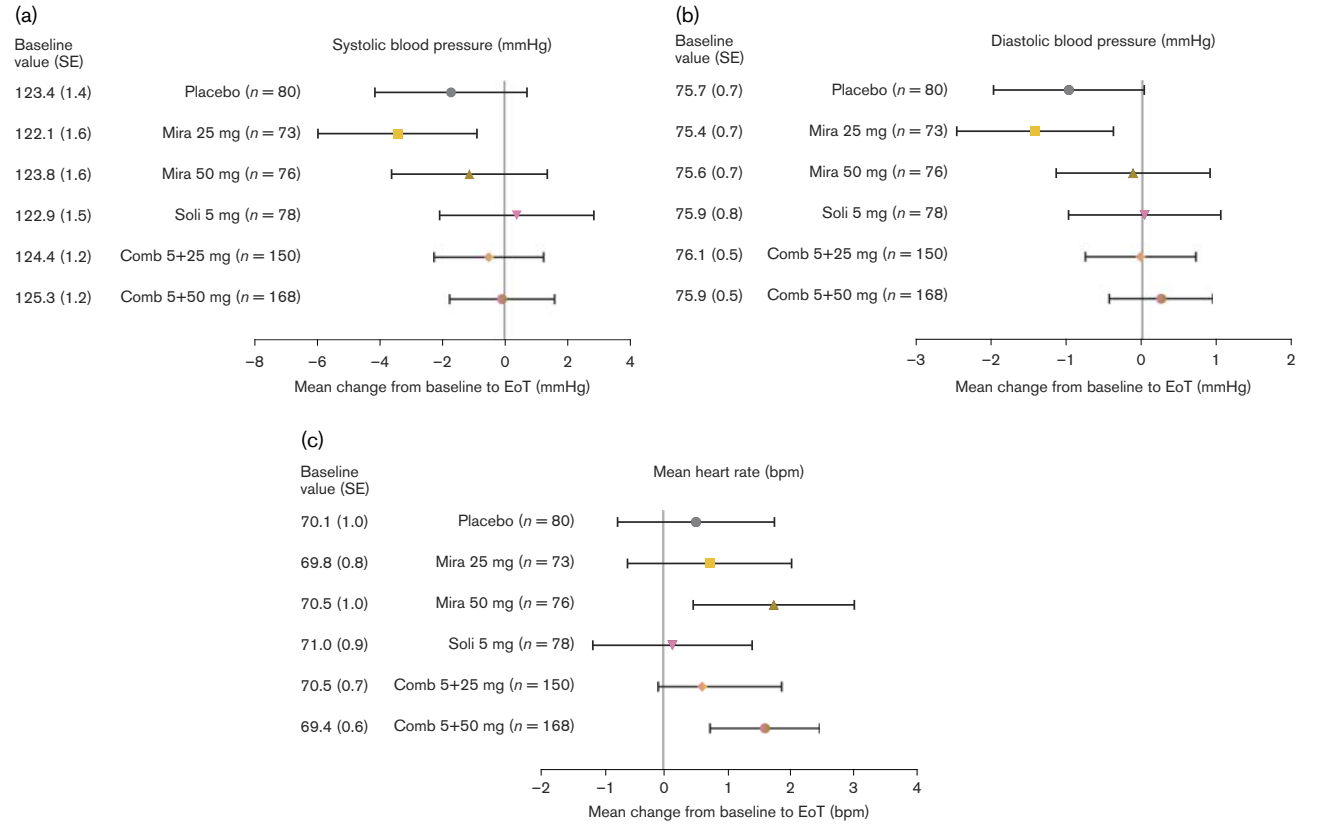
In analyses of ABPM outliers on the basis of 24-h mean values, the frequency of patients with increases from baseline to EoT in SBP (≥15 mmHg), DBP (≥10 mmHg), or heart rate (≥10 bpm) was similar among the treatment groups (Table 3). There were five patients who experienced clinically significant increases in SBP (≥160 and ≥ 20 mmHg increase): one patient (1/76, 1.3% mirabegron 50 mg and 1/73, 1.4% mirabegron 25 mg) in each mirabegron monotherapy group, 2/76 (2.6%) patients in the solifenacin 5 mg group, and 1/150 (0.7%) patient in the combination 5 + 25 mg group. Two patients experienced clinically significant increases in DBP (≥95 and ≥ 15 mmHg increase): 1/80 (1.3%) patient in the placebo group and 1/78 (1.3%) patient in the solifenacin 5 mg group. For heart rate,

**Table 1 Demographic and baseline characteristics (ambulatory blood pressure monitoring analysis set)**

| Parameters | Placebo ($n = 92$) [$n$ (%)] | Mirabegron (25 mg) ($n = 85$) [$n$ (%)] | Mirabegron (50 mg) ($n = 87$) [$n$ (%)] | Solifenacin (5 mg) ($n = 86$) [$n$ (%)] | Comb (5 + 25 mg) ($n = 176$) [$n$ (%)] | Comb (5 + 50 mg) ($n = 189$) [$n$ (%)] |
|---|---|---|---|---|---|---|
| Age (mean) (years) | 55.7 | 56.3 | 56.4 | 58.9 | 56.2 | 57.4 |
| Sex: female | 71 (77.2) | 65 (76.5) | 66 (75.9) | 71 (82.6) | 137 (77.8) | 148 (78.3) |
| Weight (mean ± SD) (kg) | 80.4 ± 17.6 | 74.7 ± 17.0 | 78.1 ± 16.1 | 78.2 ± 17.6 | 78.6 ± 16.0 | 78.8 ± 15.8 |
| BMI (mean ± SD) (kg/m$^2$) | 29.1 ± 5.9 | 27.2 ± 5.5 | 28.2 ± 5.1 | 28.6 ± 5.4 | 28.8 ± 5.6 | 28.9 ± 5.4 |
| Obesity | 6 (6.5) | 2 (2.4) | 5 (5.7) | 7 (8.1) | 7 (4.0) | 12 (6.3) |
| Vascular disorders | 38 (41.3) | 34 (40.0) | 28 (32.2) | 42 (48.8) | 89 (50.6) | 83 (43.9) |
| Hypertension | 37 (40.2) | 34 (40.0) | 26 (29.9) | 40 (46.5) | 85 (48.3) | 77 (40.7) |
| Cardiac disorders | 8 (8.7) | 8 (9.4) | 5 (5.7) | 9 (10.5) | 19 (10.8) | 16 (8.5) |
| Myocardial ischemia | 3 (3.3) | 3 (3.5) | 1 (1.1) | 6 (7.0) | 6 (3.4) | 4 (2.1) |
| Angina pectoris | 0 | 1 (1.2) | 0 | 1 (1.2) | 2 (1.1) | 3 (1.6) |
| Palpitations | 1 (1.1) | 1 (1.2) | 0 | 1 (1.2) | 0 | 1 (0.5) |
| Coronary artery disease | 0 | 2 (2.4) | 0 | 1 (1.2) | 1 (0.6) | 2 (1.1) |
| Hypercholesterolemia | 13 (14.1) | 8 (9.4) | 15 (17.2) | 17 (19.8) | 36 (20.5) | 37 (19.6) |
| Diabetes mellitus | 6 (6.5) | 2 (2.4) | 4 (4.6) | 3 (3.5) | 7 (4.0) | 5 (2.6) |
| ACE inhibitors | 14 (15.2) | 13 (15.3) | 10 (11.5) | 15 (17.4) | 31 (17.6) | 32 (16.9) |
| Angiotensin II antagonists | 7 (7.6) | 6 (7.1) | 4 (4.6) | 9 (10.5) | 14 (8.0) | 12 (6.3) |

ACE, angiotensin-converting enzyme; Comb, combination of solifenacin + mirabegron.

**Fig. 1**




Adjusted 24-h mean change from baseline at EoT for vital signs measured by ambulatory blood pressure monitoring (ambulatory blood pressure monitoring analysis set): (a) systolic blood pressure; (b) diastolic blood pressure; (c) heart rate. Adjusted change from baseline (mean, 95% confidence interval) generated from an analysis of covariance model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no), and geographic region as fixed factors and baseline value as a covariate. Comb, combination of solifenacin + mirabegron; EoT, end of treatment; Mira, mirabegron; Soli, solifenacin.

1/76 (1.3%) patient in the mirabegron 50 mg monotherapy group experienced a potentially clinically significant increase (≥90 and ≥ 15 bpm increase).

### Clinic versus home blood pressure and heart rate

At baseline and EoT, there were 3398 and 3306 patients, respectively, evaluable for clinic-based assessments and 2431 and 2371 patients, respectively, evaluable for home-based assessments. The changes from baseline in clinic-monitored and home-monitored BP and heart rates are shown in Fig. 3. No significant differences were observed for changes from baseline in clinic or self-measured BP on heart rates between monotherapy or combination therapies and placebo. Sensitivity analyses including a different factor for age group and including a factor for use of antihypertensive medication at screening (including those on β-adrenergic blocking drugs) in the ANCOVA model did not show any relevant differences between treatment groups and placebo for the clinic BP and heart rates. Subgroup analyses by sex and by previous OAB medication did not show evidence of effect modification by these two factors.

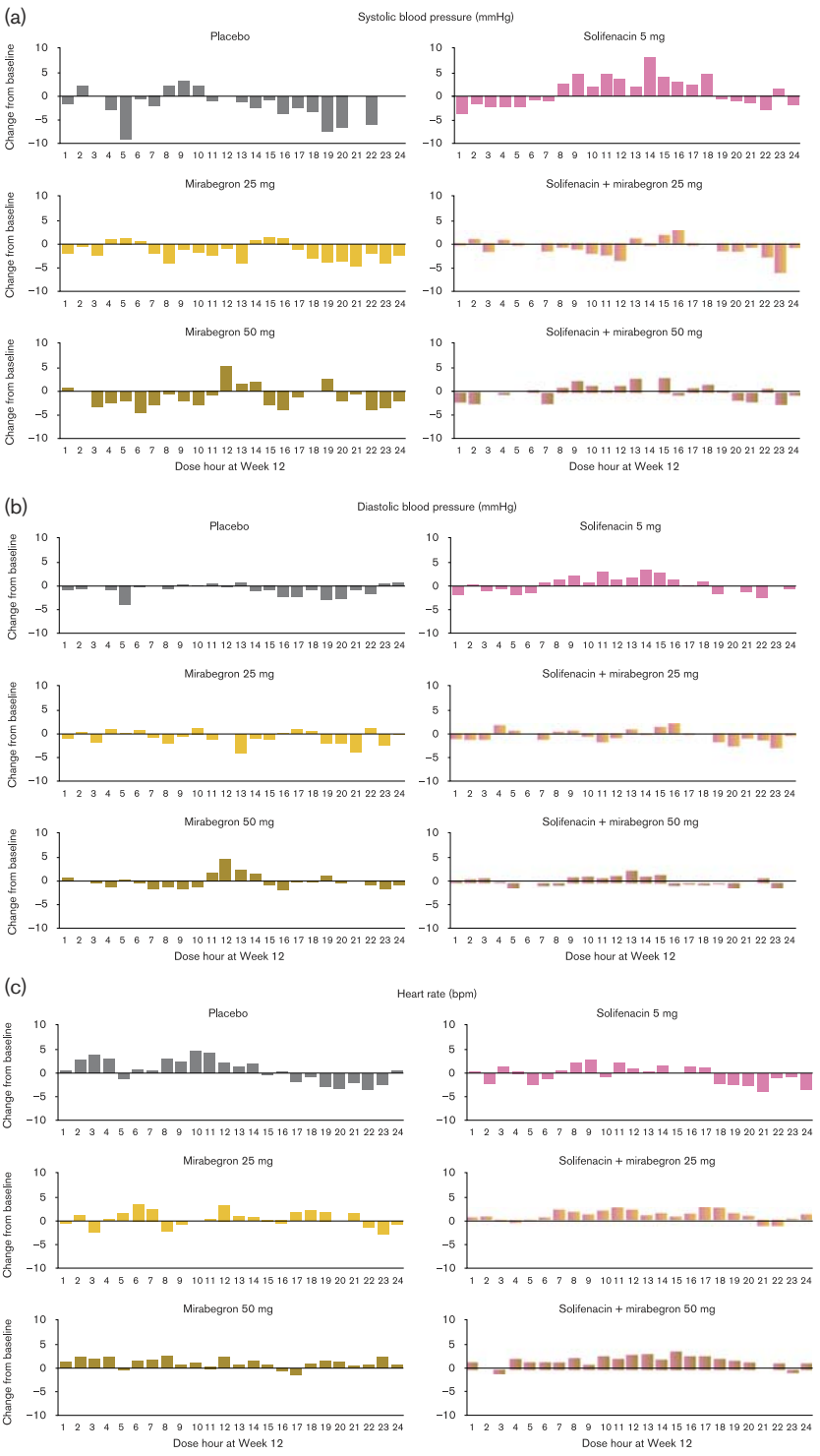
### Categorical analyses

Patients were classified at baseline into the following BP categories: normal (SBP < 120 mmHg); prehypertension (SBP 120–139 mmHg); stage 1 hypertension (SBP 140–159 mmHg); and stage 2 hypertension (SBP ≥160 mmHg). We reclassified each patient using the worst value during the double-blind treatment period and carried out a shift analysis (Supplementary Table 2, Supplemental digital content 4, *http://links.lww.com/BPMJ/A64*). For the placebo group, 55% of patients remained in their original categories; 31% moved to a higher (more hypertensive) category; and 14% moved to a lower (less hypertensive) category. These results were generally similar for the active treatment groups combined (60% remaining in the same category, 27% moving to a higher category; and 13% moving to a lower category) and the combination groups (60, 27, and 13%, respectively, for the three shift categories).

## Discussion

This study evaluated the effects on BP and heart rate of solifenacin and mirabegron, administered individually and in combination for the treatment of OAB using three

**Fig. 2**




Hourly mean change from time-matched baseline ambulatory blood pressure monitoring (ambulatory blood pressure monitoring analysis set): (a) systolic blood pressure; (b) diastolic blood pressure; (c) heart rate.

modalities of BP measurement: ABPM, automated office readings, and home readings. The key observations in this safety report were based on ABPM. For the overall mean 24-h BPs and heart rate, the differences between placebo and the treatment groups, including the drug combination groups, were small and nonsignificant. When the highest 1-h BP and heart rate values across the 6-h time period of maximum plasma drug concentrations

**Table 2** **Mean changes from baseline to week 12 in the maximal 1 h mean during $T_{max}$ (4–10 h postdose; ambulatory blood pressure monitoring analysis set)**

| | Placebo ($n=68$) | Mirabegron (25 mg) ($n=60$) | Mirabegron (50 mg) ($n=59$) | Solifenacin (5 mg) ($n=57$) | Comb (5 + 25 mg) ($n=121$) | Comb (5 + 50 mg) ($n=131$) |
|---|---|---|---|---|---|---|
| Systolic blood pressure | | | | | | |
| Baseline (mean ± SE) (mmHg) | 138.2 ± 1.9 | 137.7 ± 2.1 | 140.6 ± 2.4 | 136.6 ± 2.0 | 139.3 ± 1.7 | 142.5 ± 1.7 |
| Change from baseline to week 12 (mean ± SE) (mmHg) | −1.1 ± 2.2 | −2.2 ± 1.8 | −3.6 ± 2.5 | 2.0 ± 2.3 | 0.3 ± 1.8 | 0.8 ± 1.9 |
| Difference vs. placebo at week 12 [mean (95% CI)] (mmHg) | – | −1.1 (−6.9–4.7) | −2.6 (−9.1–4.0) | 3.1 (−3.4–9.5) | 1.4 (−4.4–7.2) | 1.9 (−4.2–7.9) |
| Patients fulfilling change from baseline criteria [*n*/*N* (%)][a] | 13/68 (19.1) | 6/60 (10.0) | 8/59 (13.6) | 11/57 (19.3) | 26/121 (21.5) | 32/131 (24.4) |
| Diastolic blood pressure | | | | | | |
| Baseline (mean ± SE) (mmHg) | 84.3 ± 0.9 | 84.6 ± 1.3 | 84.9 ± 1.3 | 84.8 ± 1.2 | 85.8 ± 0.9 | 86.8 ± 1.0 |
| Change from baseline to week 12 (mean ± SE) (mmHg) | 0.3 ± 1.0 | 0.0 ± 1.4 | −1.6 ± 1.2 | 0.6 ± 1.2 | 0.3 ± 1.0 | 0.0 ± 1.1 |
| Difference vs. placebo at week 12 [mean (95% CI)] | – | −0.3 (−3.6–3.0) | −1.9 (−5.0–1.2) | 0.3 (−2.8–3.3) | −0.1 (−3.0–2.9) | −0.3 (−3.6–3.0) |
| Patients fulfilling change from baseline criteria [*n*/*N* (%)][a] | 8/68 (11.8) | 9/60 (15.0) | 4/59 (6.8) | 6/57 (10.5) | 11/121 (9.1) | 23/131 (17.6) |
| Heart rate (bpm) | | | | | | |
| Baseline (mean ± SE) (mmHg) | 78.7 ± 1.4 | 82.5 ± 1.5 | 82.1 ± 1.6 | 83.2 ± 1.5 | 81.3 ± 1.1 | 81.5 ± 1.1 |
| Change from baseline to week 12 (mean ± SE) (mmHg) | 3.6 ± 1.6 | −0.4 ± 1.5 | 1.5 ± 1.7 | 0.1 ± 1.5 | 1.5 ± 0.9 | 2.3 ± 1.0 |
| Difference vs. placebo at week 12 [mean (95% CI)] | – | −4.0 (−8.3–0.3) | −2.1 (−6.6–2.3) | −3.5 (−7.8–0.8) | −2.1 (−5.4–1.2) | −1.3 (−4.9–2.2) |
| Patients fulfilling change from baseline criteria [*n*/*N* (%)][a] | 17/68 (25.0) | 12/60 (20.0) | 13/59 (22.0) | 9/57 (15.8) | 21/121 (17.4) | 30/131 (22.9) |

CI, confidence interval; Comb, combination of solifenacin + mirabegron.

[a]Change from baseline to week 12 criteria defined as increase in systolic blood pressure of at least 15 mmHg; increase in diastolic blood pressure of at least 10 mmHg and increase in heart rate of at least 10 bpm, respectively.

**Table 3 Patients fulfilling change from baseline criteria to end of treatment in ambulatory blood pressure monitoring-based mean 24-h vital signs**

| | Placebo [*n* (%)] | Mirabegron (25 mg) [*n* (%)] | Mirabegron (50 mg) [*n* (%)] | Solifenacin (5 mg) [*n* (%)] | Comb (5 + 25 mg) [*n* (%)] | Comb (5 + 50 mg) [*n* (%)] |
|---|---|---|---|---|---|---|
| SBP ≥ 15 mmHg | 9/80 (11.3) | 1/73 (1.4) | 11/76 (14.5) | 7/78 (9.0) | 10/150 (6.7) | 16/168 (9.5) |
| DBP ≥ 10 mmHg | 4/80 (5.0) | 0/73 (0) | 4/76 (5.3) | 4/78 (5.1) | 3/150 (2.0) | 6/168 (3.6) |
| Heart rate ≥ 10 bpm | 8/80 (10.0) | 6/73 (8.2) | 6/76 (7.9) | 3/78 (3.8) | 8/150 (5.3) | 13/168 (7.7) |

Comb, combination of solifenacin + mirabegron; DBP, diastolic blood pressure; SBP, systolic blood pressure.

and effect ($T_{\max 4–10\,h}$) of the therapeutic agents were evaluated, again, there was no evidence for a significant BP difference between placebo and any of the active treatments. Heart rate was slightly higher in the combination groups. A survey of the hour-by-hour mean BP values across the full 24-h monitoring period confirmed that only minimal changes in BP occurred in the treatment groups during this 12-week trial. There were no clinically meaningful differences between treatment groups in the mean daytime and mean night-time vital signs.

By conventional office readings, performed using an automated oscillometric device, there were no significant effects on SBP in any of the active treatment groups compared with placebo; DBP (< 0.7 mmHg) and heart rate (< 1.1 bpm) were nominally higher in the combination groups compared with placebo, but these differences were not significant and were comparable with the results from the mirabegron monotherapy groups. Similar results were observed with patient-measured home BP readings, confirming the findings of the clinic measurements and further indicating that home measurements were performed responsibly and thus can be considered clinically reliable when there are concerns over BP and heart rate issues during therapy.

Using ABPM, we searched for additional evidence for hidden safety signals by identifying individual 'outlier' patients whose mean 24-h SBPs increased by at least 15 mmHg, or DBPs by at least 10 mmHg, or heart rates by at least 10 bpm. There were no differences in the rates of outliers between placebo and any of the monotherapy or combination treatment groups. In an alternative approach to outliers – using a clinically relevant value for ABPM-based mean 24-h BP – only five patients receiving active treatment during the study reached the SBP threshold of 160 mmHg with an increase of at least 20 mmHg; of these, four were receiving monotherapy and one patient was receiving combination treatment.

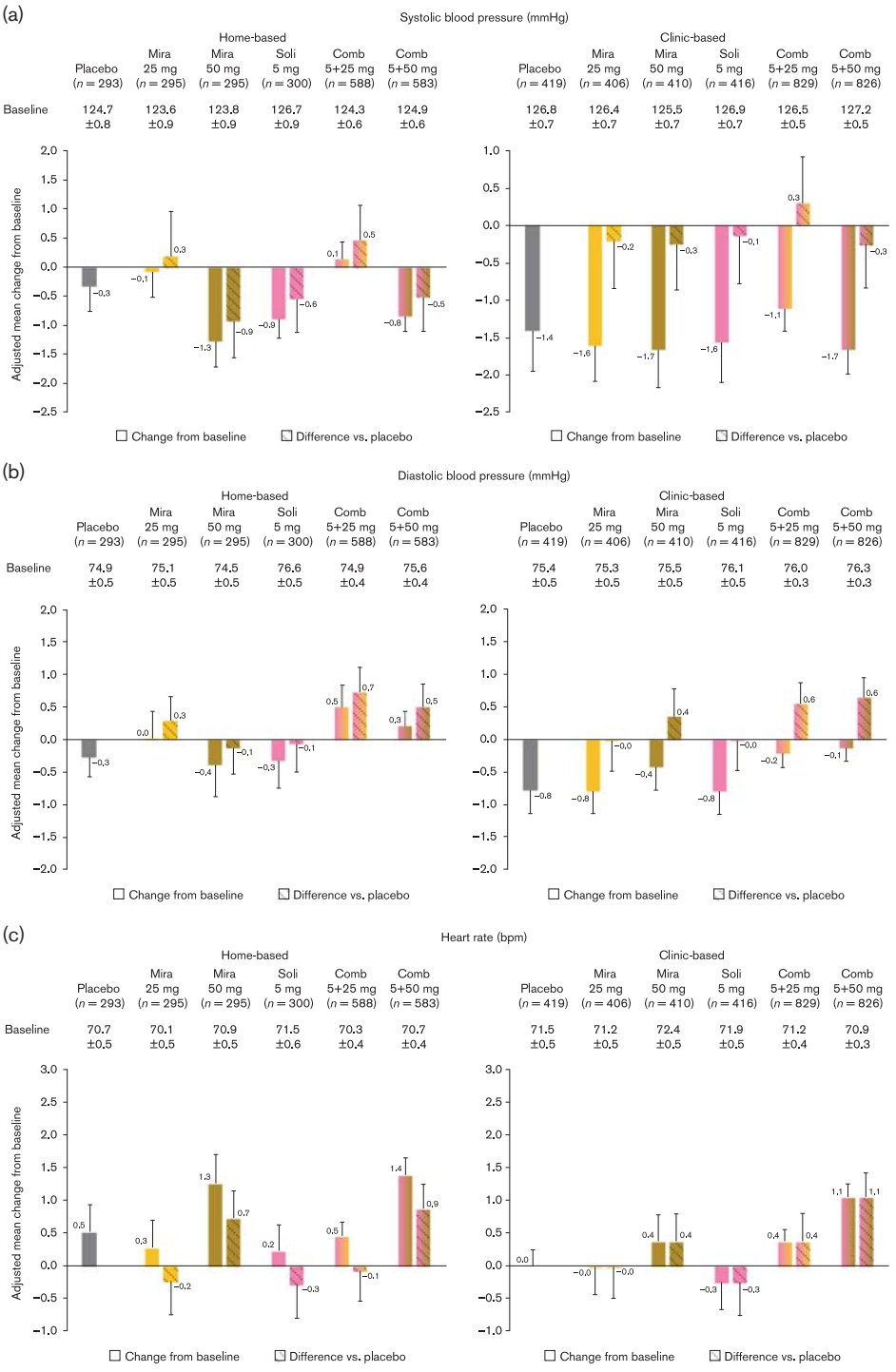
Shift analyses on the basis of the patient BP categories of normal, prehypertension, and stage 1 or 2 hypertension, on the basis of hypertension guideline recommendations, were carried out [27]. During treatment, the proportion of patients remaining at their baseline category, or moving either to a more hypertensive or a less hypertensive category, were nearly identical in the placebo and the monotherapy and combination therapy groups. These data provide reassurance that there is no meaningful effect of these drugs on BP or heart rate for the 12 weeks of therapy.

All three methods of testing the BP and heart rate treatment effects – clinical measurements, home-based self-measurements, and ABPM – yielded similar conclusions, although ABPM provided insights at times of day not usually accessible by clinic or self-measured readings. Two other important observations have emerged from our analyses of these OAB drugs. First, our study confirms that ABPM may be a superior methodology to self-measurement for the evaluation of the hemodynamic effects of non-CV drugs [28]; this trial was not conducted in the clinical practices of hypertension or CV experts, but predominantly in the clinics of urologists, and our findings could potentially lead to the development of a standardized protocol that would be generally applicable to the evaluation on the off-target BP effects of non-CV drugs. The completion rate of the relatively demanding ABPM procedure – which mandated successful 24-h data acquisition both at baseline and during treatment – was 75%, which is a generally acceptable outcome in clinical trial research of this nature. Obtaining evaluable data in 715 patients in this trial exceeded the number required to provide 80% power for excluding a more than 3 mmHg difference between placebo and the active treatment groups. However, the SDs observed in this study were larger than expected so that CIs generally included both 0 and 3 mmHg.

We also have shown that patients were willing and able to perform home BP measurements and follow a detailed 5-day measurement and documentation protocol. For clinicians and research groups concerned about the off-target BP effects of non-CV therapies – for any medical condition – our findings support engaging their patients in systematic home BP measurements.

The findings in this study are consistent with BP and heart rate findings in previous studies of mirabegron and solifenacin [29–33], and establish that the combination of these agents does not produce meaningful effects on BP and heart rate. It should be acknowledged, however, that small changes in BP and possibly heart rate could translate into CV risk, particularly in large populations of patients requiring long-term drug therapy for chronic conditions. Understandably, regulatory bodies engaged in drug approvals and, at the same time, being aware of the importance of public health outcomes, will find it important to define and understand off-target effects on BP of non-CV drugs so that the benefits and risks can be carefully weighed [25]. We believe that the

**Fig. 3**




Adjusted mean change from baseline at end of treatment for vital signs measured by home-based self-monitoring or clinic-based monitoring (safety analysis set): (a) systolic blood pressure; (b) diastolic blood pressure; (c) heart rate. Adjusted change from baseline (mean, SE) generated from an analysis of covariance model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no), and geographic region as fixed factors and baseline value as a covariate. Comb, combination of solifenacin + mirabegron; Mira, mirabegron; Soli, solifenacin.

approaches used in this study provide a practical and effective paradigm that can be utilized for obtaining this critical information.

## Conclusion

The SYNERGY study provides a comprehensive analysis of the effects on BP and heart rate of the $\beta_3$-adrenoceptor

agonist mirabegron alone and in combination with solifenacin therapy across doses. Clinic, home, and ABPM data were congruent and did not show any clinically important drug effects on BP or heart rate for monotherapies versus placebo or for combination versus monotherapy treatments. In summary, there were no meaningful changes in BP or heart rate on the combination of solifenacin plus mirabegron once daily for up to 12 weeks.

## Acknowledgements

Professor White is the editor of the journal and has requested acknowledgment of the guest editor Dr O'Brien to show that Professor White did not serve as an editor of a paper that he is an author on.

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Combination treatment with solifenacin and mirabegron in the treatment of OAB is currently in clinical development and is not registered.

### Conflicts of interest

M.W. has received personal fees from Astellas, Daiichi Sankyo, Allergan, Johnson and Johnson, Novartis, and Menarini. C.R.C. is a consultant, researcher, and speaker for Astellas, Allergan, Pfizer, and Medtronic, and has received personal fees and nonfinancial support from Allergan and Pfizer, and grants, personal fees, and nonfinancial support from Astellas. C.G. has received personal fees from Astellas, Bayer, GSK, Lilly Pharma, Pfizer, Recordati, Steba, Ipsen, Allergan, and Janssen. S.H. has received grants and personal fees from Astellas, Allergan, and Ipsen, and personal fees from Pfizer and Duchesnay. D.R. is a consultant for Astellas, Pfizer, Allergan, and Ferring, and a speaker for Astellas, Pfizer, and Allergan. J.M.F. has received research support and is an advisor and speaker for Astellas, an investigator for Janssen, a consultant and investigator for Ferring, and a speaker for Pfizer. W.B.W. served as chair of the cardiovascular adjudication committee for the mirabegron development program and has received personal fees from Astellas. A.M.R., M.S., A.P., and R.v.M. are employees of Astellas Pharma Global Development Inc.

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