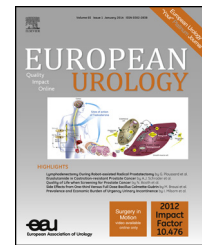


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Platinum Priority – Voiding Dysfunction

Editorial by XXX on pp. x–y of this issue

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)

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Abstract

Background: Combining the β_3 -adrenoceptor agonist mirabegron and the antimuscarinic (AM) agent solifenacin may improve efficacy in the treatment of overactive bladder (OAB) while reducing the AM side effects.

Objective: The primary objective was to evaluate the efficacy of combinations of solifenacin/mirabegron compared with solifenacin 5 mg monotherapy. The secondary objective was to explore the dose–response relationship and the safety/tolerability compared with placebo and monotherapy.

Design, setting, and participants: A phase 2, factorial design, randomised, double-blind, parallel-group, placebo- and monotherapy-controlled trial, conducted at 141 sites in 20 European countries. Male and female patients were aged ≥ 18 yr with symptoms of OAB for ≥ 3 mo.

Intervention: A total of 1306 patients (66.4% female) were randomised to 12 wk of treatment in 1 of 12 groups: 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), 5 monotherapy groups (solifenacin 2.5, 5, or 10 mg, or mirabegron 25 or 50 mg), or placebo.

Outcome measurements and statistical analysis: Change from baseline to end of treatment in mean volume voided per micturition (MVV) (primary end point) and mean numbers of micturitions per 24 h, incontinence episodes per 24 h, and urgency episodes per 24 h were analysed using an analysis of covariance model. Safety assessments included treatment-emergent adverse events (TEAEs), blood pressure, pulse rate, post-void residual (PVR) volume, and laboratory and electrocardiography (ECG) parameters.

Results and limitations: Compared with solifenacin 5 mg monotherapy, all combinations with solifenacin 5 or 10 mg significantly improved MVV, with adjusted differences ranging from 18.0 ml (95% confidence interval [CI], 5.4–30.0) to 26.3 ml (95% CI, 12.0–41.0). Three combination groups significantly reduced micturition frequency compared with solifenacin 5 mg, ranging from -0.80 (95% CI, -1.39 to -0.22) to -0.98 (95% CI, -1.68 to -0.27). Five of six combinations significantly reduced urgency episodes compared with solifenacin 5 mg, ranging from -0.98 (95% CI, -1.78 , to -0.18) to

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–1.37 (95% CI, –2.03 to –0.70). No dose-related trends in TEAEs, blood pressure, pulse rate, PVR volume, or laboratory or ECG parameters were observed between combination and monotherapy groups, although the incidence of constipation was slightly increased with combination therapy.

Conclusions: Combination therapy with solifenacin/mirabegron significantly improved MVV, micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. All combinations were well tolerated, with no important additional safety findings compared with monotherapy or placebo.

Patient summary: To improve treatment of overactive bladder (OAB), mirabegron/solifenacin in combination was compared with each drug alone and placebo. Combination therapy improved OAB symptoms and had similar safety and acceptability.

Trial registration: Clinical trials.gov: NCT01340027.

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1. Introduction

Antimuscarinic (AM) agents are the mainstay of oral pharmacotherapy for overactive bladder (OAB), but persistence with treatment is limited by insufficient efficacy and AM-associated adverse events (AEs) [1]. The approval of the β 3-adrenoceptor agonist mirabegron has added a new class of pharmacotherapy for OAB. In 12-wk trials, mirabegron (25, 50, and 100 mg) demonstrated significant reductions compared with placebo in micturition and incontinence episode frequency, with an incidence of AM-associated AEs similar to placebo [2–4].

As these agents have different mechanisms of action, combining a β 3-adrenoceptor agonist with an AM agent may improve efficacy in OAB treatment; combinations with reduced doses may deliver an improved tolerability profile compared with monotherapy, without compromising efficacy. The potential for modulation of bladder function with combination therapy has been demonstrated in preclinical models [5]. In view of the minimal cardiovascular effects observed with both agents, a key element in understanding the safety of the combination will be to evaluate cardiovascular parameters.

The primary objective of the current study was to evaluate the efficacy of combinations of solifenacin (2.5 and 5 mg) plus mirabegron (25 and 50 mg) compared with solifenacin 5 mg monotherapy (the recommended daily starting dose of solifenacin and the most widely used dose in clinical practice). Secondary objectives included evaluation of the dose–response relationship of combinations of solifenacin (2.5, 5, and 10 mg) and mirabegron (25 and 50 mg) and comparison of the safety/tolerability between combination therapy and placebo and the corresponding monotherapies.

2. Methods

2.1. Study design and patient population

This phase 2, factorial design, multicentre, randomised, double-blind, parallel-group, placebo- and monotherapy-controlled trial enrolled male and female patients aged ≥ 18 yr with symptoms of OAB (urgency, urinary frequency, and/or urgency incontinence) for ≥ 3 mo.

Following a 2-wk, single-blind placebo run-in period and washout of existing OAB medications (prior use of solifenacin or mirabegron was not excluded) and prohibited medications, patients with eight or more

micturitions per 24 h and one urgency episode or more per 24 h (with or without incontinence), based on a 3-d electronic patient micturition diary, were randomised to 12 wk of treatment in 1 of 12 groups (6 combination groups, 5 active-control groups, and 1 placebo arm) in a 2:1 ratio for primary compared with secondary treatment groups (Fig. 1). Using a double-blind, double-dummy technique, all patients received three tablets daily throughout the treatment phase: solifenacin (2.5, 5, or 10 mg) or placebo, mirabegron 25 mg or placebo, and mirabegron 50 mg or placebo.

The study protocol was approved by an institutional review board/independent ethics committee at each site. All subjects gave written informed consent.

2.2. Efficacy assessments

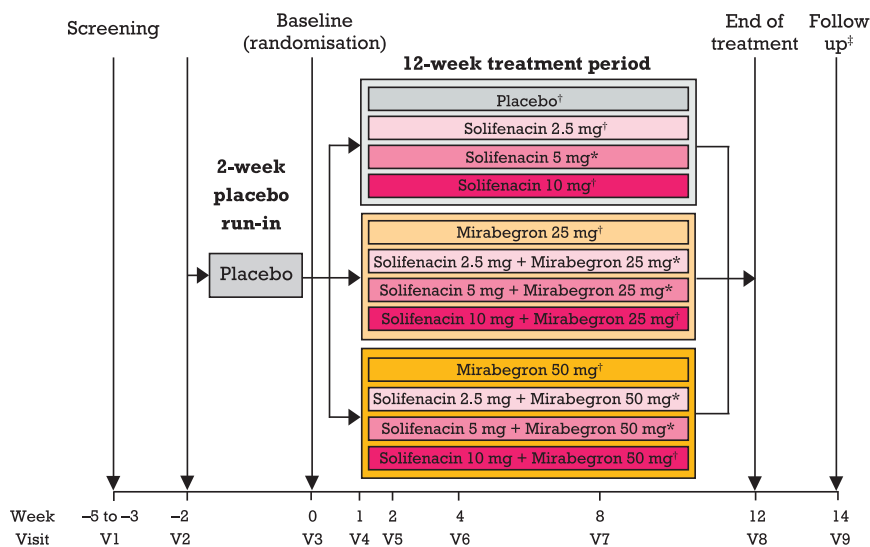
The primary efficacy variable was change from baseline to end of treatment (EOT) in mean volume voided per micturition (MVV). Changes from baseline to EOT were also assessed for mean number of micturitions per 24 h and mean number of incontinence episodes per 24 h (key secondary efficacy variables), as well as mean number of urgency episodes per 24 h (grade 3 or 4, according to the Patient Perception of Intensity of Urgency Scale) [6], an additional secondary efficacy variable.

2.3. Safety assessment

Safety parameters assessed at screening and at each study visit included laboratory assessments, vital signs (blood pressure [BP] and pulse rate), electrocardiography (ECG) parameters, postvoid residual (PVR) volume (determined by bladder scan or ultrasound), and the frequency of treatment-emergent AEs (TEAEs). Using a standard office device, BP and pulse rate were measured in triplicate (each reading approximately 2 min apart) by the investigator and the average calculated using two readings, as well as by patients (results provided in the Supplement and Supplemental Table 2) using an automated device for 5 d consecutively. Standard office device measurements are reported herein.

2.4. Statistical analyses

A sample size of 140 patients in the five primary treatment groups provided 80% power to detect a significant difference of ≥ 17.3 ml in MVV (based on treatment differences from previous studies [2,3,7,8]) between a combination group and solifenacin 5 mg monotherapy, based on a two-sided *t* test with $\alpha = 0.05$ and a standard deviation of 50 ml; a sample size of 70 patients in the remaining treatment arms provided a power of $\geq 80\%$ to detect a difference of ≥ 24 ml compared with placebo. The study was not powered to detect differences in the key secondary efficacy variables. Assuming postrandomisation dropout rates of 10%, 1326 patients were to be randomised.



*5 groups of primary interest; †7 groups of secondary interest; ‡A 2-week follow-up phase was performed 14 to 21 days after the end of treatment

Fig. 1 – Study design.

* Five groups of primary interest.

† Seven groups of secondary interest.

‡ A 2-wk follow-up phase was performed 14–21 d after the end of treatment.

Change from baseline to EOT in MVV and in mean number of micturitions per 24 h were analysed for the full analysis set (FAS; all patients who took one dose or more of double-blind study medication and had primary efficacy data at baseline and one postbaseline visit or more). Change from baseline to EOT in MVV and mean number of micturitions per 24 h was analysed using an analysis of covariance (ANCOVA) model with mirabegron and solifenacin dose as the two main factors; their interaction, sex, age group, and geographic region as fixed factors; and the patient's MVV or mean number of micturitions per 24 h, respectively, at baseline as a covariate. Least squares mean estimates and two-sided 95% confidence intervals (CIs) for mean changes from baseline, within each treatment group and for differences between each combination group, and solifenacin 5 mg or placebo were calculated. The change from baseline in the number of incontinence episodes per 24 h was analysed in the subpopulation of FAS patients who reported one incontinence episode or more in the baseline diary (FAS-I) using a stratified rank ANCOVA for each pairwise comparison of interest. The model included the same factors as described for MVV.

The safety analysis set comprised all randomised patients who received one dose or more of double-blind study medication. Laboratory evaluations, vital signs, ECG parameters, and PVR volume were evaluated for mean change from baseline values using the same ANCOVA model used for the analysis of MVV. No formal statistical testing was performed for these safety parameters.

3. Results

3.1. Demographic and baseline characteristics

In total, 1306 patients were randomised and received one dose or more of study drug. Across all treatment arms, >90% of patients completed the study; the three most frequently cited primary reasons for discontinuation were withdrawal of consent, AEs, and protocol violation (Fig. 2). Patient

demographics and baseline characteristics were comparable across treatment groups in the FAS populations, although incontinence, urgency, and frequency were less severe in the placebo group ($n = 1278$; Table 1). Only 21.5% of the FAS population reported one incontinence episode or more at baseline (FAS-I).

3.2. Efficacy results

Across all combination groups, a clear dose-response relationship was observed for MVV. The observed treatment effect was larger with increasing doses of solifenacin and mirabegron (Table 2, Fig. 3). For all combinations with solifenacin 5 or 10 mg, the mean change from baseline to EOT in MVV was statistically significantly greater than with solifenacin 5 mg monotherapy (Table 2, Fig. 3A). The mean increase in MVV from baseline to EOT was statistically significantly greater in all active treatment groups than with placebo, except mirabegron 25 mg monotherapy (Table 2, Fig. 3B).

For the change from baseline to EOT in mean number of micturitions per 24 h, statistically significant differences compared with solifenacin 5 mg and placebo were observed with combinations at doses of solifenacin 5 mg plus mirabegron 50 mg, solifenacin 10 mg plus mirabegron 25 mg, and solifenacin 10 mg plus mirabegron 50 mg (Fig. 4A and 4B).

All treatment groups, including placebo, demonstrated a reduction in the number of incontinence episodes from baseline to EOT. Only the solifenacin 5 mg plus mirabegron 25 mg combination showed a statistically significant difference compared with solifenacin 5 mg monotherapy

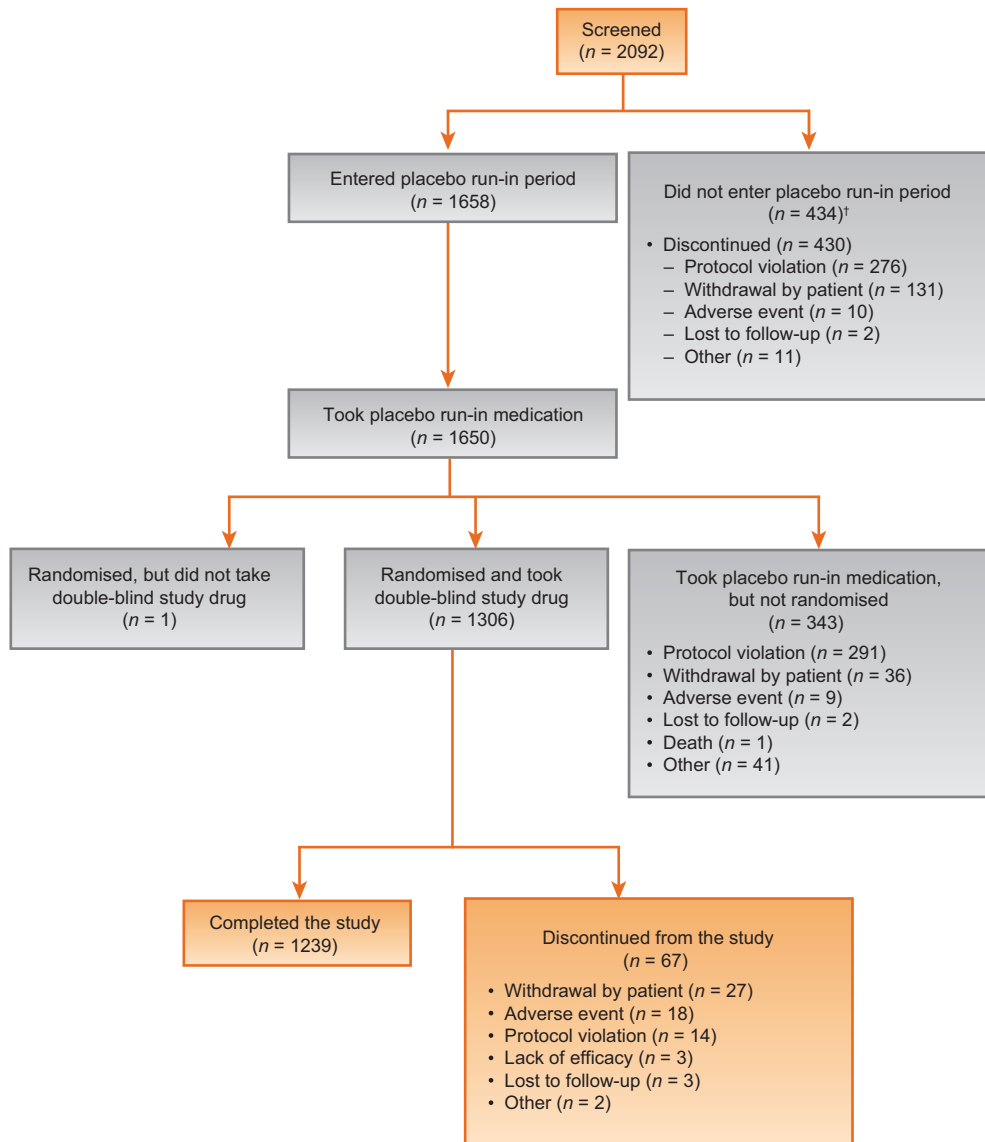


Fig. 2 – Study disposition.

[†] The primary reason for discontinuation was inadvertently not populated in the analysis data sets for four rescreened subjects, which are not included in the counts by reason.

($p < 0.01$); none of the active treatment groups significantly reduced incontinence episodes compared with placebo, and there was no discernible trend towards a dose relationship for this parameter.

Statistically significant improvements with all combinations (except solifenacin 2.5 mg plus mirabegron 25 mg) compared with solifenacin 5 mg were observed in the change from baseline to EOT in urgency episodes (Fig. 5).

3.3. Safety results

A total of 1239 patients (94.8%) completed the study, with 18 patients (1.4%) discontinuing because of an AE (Fig. 2); there were no relevant differences in numbers completing

the study or reasons for discontinuation among treatment groups.

The incidence and type of TEAEs were similar in the active treatment and placebo groups, except for AM-associated AEs (dry mouth, constipation, blurred vision, and dyspepsia) and hypertension. There was no relevant difference in frequency of TEAEs between combination and monotherapy groups, although the incidence of constipation was slightly increased in the combination groups (Table 3). Incidence of drug-related TEAEs ranged from 15.2% (solifenacin 2.5 mg monotherapy) to 44.4% (solifenacin 10 mg plus mirabegron 50 mg combination); the most commonly reported were dry mouth (12.2%), hypertension (5.3%), and constipation (3.1%). There were two serious TEAEs considered to be treatment related:

Table 1 – Demographic and baseline characteristics and overactive bladder characteristics

Parameter	PBO	MIRA 25 mg	MIRA 50 mg	SOLI 2.5 mg	SOLI 5 mg	SOLI 10 mg	SOLI 2.5 mg + MIRA 25 mg	SOLI 2.5 mg + MIRA 50 mg	SOLI 5 mg + MIRA 25 mg	SOLI 5 mg + MIRA 50 mg	SOLI 10 mg + MIRA 25 mg	SOLI 10 mg + MIRA 50 mg
SAF population, no.	81	77	78	79	156	78	149	149	144	153	81	81
Female, no. (%)	54 (66.7)	52 (67.5)	52 (66.7)	51 (64.6)	103 (66.0)	53 (67.9)	100 (67.1)	100 (67.1)	95 (66.0)	101 (66.0)	52 (64.2)	54 (66.7)
White, no. (%)	81 (100)	77 (100)	78 (100)	78 (98.7)	156 (100)	77 (98.7)	149 (100)	148 (99.3)	143 (99.3)	153 (100)	81 (100)	81 (100)
Mean age, yr (SD)	54.6 (13.4)	55.2 (14.5)	53.4 (14.0)	56.1 (11.7)	54.2 (15.5)	55.0 (12.8)	55.8 (13.7)	53.7 (14.6)	55.0 (14.6)	54.1 (14.1)	56.5 (12.3)	55.5 (13.8)
Mean BMI, kg/m ² (SD)	27.1 (13.6)	26.4 (4.0)	26.6 (3.6)	27.3 (4.8)	26.3 (3.9)	27.2 (3.7)	26.6 (4.1)	26.5 (4.0)	26.3 (3.8)	26.5 (3.6)	27.1 (3.2)	26.3 (3.3)
FAS population, no.	80	76	77	77	150	76	146	147	141	150	78	80
Type of OAB, no. (%) [*]												
Urgency incontinence	14 (17.9)	27 (36.0)	18 (23.7)	17 (22.4)	38 (25.5)	19 (25.0)	40 (27.6)	33 (22.6)	35 (24.8)	35 (23.3)	22 (28.2)	20 (25.3)
Mixed stress/urgency incontinence	9 (11.5)	8 (10.7)	10 (13.2)	10 (13.2)	25 (16.8)	11 (14.5)	21 (14.5)	19 (13.0)	18 (12.8)	18 (12.0)	13 (16.7)	10 (12.7)
Frequency/urgency without incontinence	55 (70.5)	40 (53.3)	48 (63.2)	49 (64.5)	86 (57.7)	46 (60.5)	84 (57.9)	94 (64.4)	88 (62.4)	97 (64.7)	43 (55.1)	49 (62.0)
Duration of OAB symptoms, mo (SD)	48.5 (38.6)	60.6 (68.6)	57.3 (66.9)	55.1 (60.4)	62.9 (79.5)	53.5 (57.3)	56.7 (68.6)	57.0 (67.3)	55.8 (85.4)	57.8 (82.2)	65.8 (102.3)	58.0 (80.4)
Previous OAB medication, no. (%)	40 (50.0)	42 (55.3)	38 (49.4)	29 (37.7)	70 (46.7)	29 (38.2)	73 (50.0)	65 (44.2)	64 (45.4)	71 (47.3)	42 (53.8)	40 (50.0)
Micturitions per 24 h, no. (SD)	10.4 (2.0)	11.3 (2.6)	10.8 (2.3)	11.1 (3.1)	11.4 (3.2)	11.3 (2.9)	11.2 (3.6)	11.0 (2.3)	10.9 (2.3)	11.3 (3.1)	11.1 (2.2)	11.2 (2.4)
Volume voided per micturition, ml (SD)	157.0 (52.8)	153.4 (56.4)	154.9 (50.0)	159.1 (52.0)	145.5 (59.9)	148.8 (53.1)	158.1 (61.6)	149.8 (50.2)	153.5 (54.2)	153.5 (52.0)	140.1 (51.2)	155.9 (62.2)
Urgency episodes per 24 h, no. (SD)	5.3 (3.1)	6.3 (3.3)	6.6 (4.0)	6.3 (3.9)	6.4 (4.2)	6.4 (4.6)	6.1 (3.7)	6.8 (3.4)	6.2 (3.9)	6.5 (4.2)	6.9 (4.3)	6.9 (4.3)
Mean level of urgency (SD)	2.4 (0.5)	2.5 (0.4)	2.6 (0.5)	2.5 (0.5)	2.5 (0.5)	2.5 (0.5)	2.5 (0.4)	2.6 (0.4)	2.5 (0.5)	2.5 (0.4)	2.6 (0.5)	2.5 (0.5)
Nocturia episodes, no. (SD)	2.2 (1.6)	2.2 (1.4)	2.3 (1.5)	2.5 (1.9)	2.2 (1.4)	2.5 (1.9)	2.6 (2.2)	2.1 (1.2)	2.3 (1.4)	2.3 (1.3)	2.7 (2.6)	2.4 (2.0)
FAS-I population, no.	17	13	18	15	35	15	35	33	32	24	24	20
Incontinence episodes per 24 h, no. (SD)	0.9 (0.8)	1.9 (1.6)	1.3 (1.0)	1.8 (1.2)	1.3 (1.2)	1.4 (1.3)	1.3 (1.1)	1.1 (0.8)	1.2 (1.1)	1.2 (1.2)	1.5 (1.2)	1.3 (0.9)

BMI = body mass index; FAS = full analysis set; MIRA = mirabegron; OAB = overactive bladder; PBO = placebo; SAF = safety analysis set; SD = standard deviation; SOLI = solifenacin. Demographic and baseline characteristics are reported for the safety analysis set. OAB characteristics are reported for the FAS and for the subset of FAS patients who reported one incontinence episode or more in the baseline diary.

^{*} Based on prescreening medical history.

Table 2 – Baseline mean volume voided per micturition and adjusted change in mean volume voided per micturition from baseline to end of treatment

Mirabegron, mg	Solifenacin, mg			
	0	2.5	5	10
0				
No.	80	77	150	76
Mean baseline (SE)	157.1 (6.0)	159.0 (6.0)	145.5 (4.9)	148.8 (6.1)
Adjusted mean change (SE) [95% CI]	14.0 (6.0) [2.4–25.6]	36.4 (6.0) [24.6–48.2]	36.0 (4.3) [27.5–44.4]	36.2 (6.1) [24.3–48.1]
Adjusted difference compared with solifenacin 5 mg, mean (SE) [95% CI] [‡]	–	–	–	0.3 (7.4) [–14.3 to 14.9]
<i>p</i> value [†]	–	–	–	0.97
Adjusted difference compared with placebo, mean (SE) [95% CI] [‡]	–	22.4 (8.4) [6.0–39.0]	22.0 (7.3) [8.0–36.3]	22.2 (8.5) [6.0–39.0]
<i>p</i> value [†]	–	0.008 [*]	0.003 [*]	0.009 [*]
25				
No.	76	146	141	78
Mean baseline (SE)	153.4 (6.5)	158.1 (5.1)	153.5 (4.6)	140.1 (6.0)
Adjusted mean change (SE) [95% CI]	25.0 (6.1) [13.1–37.0]	39.4 (4.4) [31.0–48.0]	54.0 (4.5) [45.0–62.3]	58.0 (6.0) [46.0–69.4]
Adjusted difference compared with solifenacin 5 mg, mean (SE) [95% CI] [‡]	–	3.4 (6.2) [–9.0 to 16.0]	18.0 (6.2) [5.4–30.0]	22.0 (7.4) [7.2–36.1]
<i>p</i> value [†]	–	0.58	0.005 [*]	0.003 [*]
Adjusted difference compared with placebo, mean (SE) [95% CI] [‡]	11.0 (8.5) [–6.0 to 28.0]	25.4 (7.4) [11.0–40.0]	40.0 (7.4) [25.1–54.1]	44.0 (8.4) [27.1–60.1]
<i>p</i> value [†]	0.20	<0.001 [*]	<0.001 [*]	<0.001 [*]
50				
No.	77	147	150	80
Mean baseline (SE)	154.9 (5.7)	149.7 (4.1)	153.5 (4.2)	156.0 (7.0)
Adjusted mean change (SE) [95% CI]	35.0 (6.0) [23.0–46.3]	42.0 (4.4) [33.3–50.4]	54.2 (4.3) [46.0–63.0]	62.3 (6.0) [51.0–74.0]
Adjusted difference compared with solifenacin 5 mg, mean (SE) [95% CI] [‡]	–	6.0 (6.1) [–6.1 to 18.0]	18.2 (6.1) [6.2–30.2]	26.3 (7.3) [12.0–41.0]
<i>p</i> value [†]	–	0.33	0.003 [*]	<0.001 [*]
Adjusted difference compared with placebo, mean (SE) [95% CI] [‡]	21.0 (8.4) [4.0–37.1]	28.0 (7.3) [14.0–42.3]	40.2 (7.3) [26.0–55.0]	48.3 (8.4) [32.0–65.0]
<i>p</i> value [†]	0.015 [*]	<0.001 [*]	<0.001 [*]	<0.001 [*]

CI = confidence interval; SE = standard error.

^{*} Statistically significantly superior compared with solifenacin 5 mg or placebo.[†] *p* values were from pairwise comparison of the combination treatment groups versus solifenacin 5 mg or placebo within the analysis of covariance model.[‡] Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin 5 mg or placebo from the adjusted mean of the combination treatment group.

confusional state (mirabegron 10 mg) and acute urinary retention (solifenacin 2.5 mg plus mirabegron 25 mg combination); there were no deaths reported during the double-blind treatment period.

The maximum mean change in pulse rate from baseline to EOT occurred in the solifenacin 5 mg plus mirabegron 25 mg combination group (+1.5 bpm, [95% CI, 0.3–2.8]). The changes in pulse rate were independent of the solifenacin dose. The differences in the mean change from baseline to EOT in pulse rate for the combination treatments compared with mirabegron 50 mg, from –0.5 bpm (95% CI, –2.9 to 1.9) to +0.5 bpm (95% CI, –1.6 to 2.6), did not indicate any additive effects on pulse rate with combination therapy compared with monotherapy (Table 4).

Changes from baseline to EOT in systolic BP and diastolic BP were similar across all treatment groups. Only one patient (in the 10 mg plus 25 mg group), based on patient-recorded diary, met the criteria for a clinically significant increase in SBP, DBP, or pulse rate. There was no increase from baseline to EOT in systolic BP with solifenacin monotherapy or any combination. The maximum mean increase from baseline to EOT in systolic BP (+0.7 mm Hg

[95% CI, –1.5 to 2.8]) and diastolic BP (+0.3 mm Hg [95% CI, –1.2 to 1.8]) was reported with mirabegron 50 mg monotherapy (Table 4).

No dose-related differences between combination and monotherapy groups were observed in mean change from baseline to EOT in ECG parameters, with small increases in the QT interval corrected with Fridericia's correction (QTcF interval) in solifenacin monotherapy and combination groups (Table 3). There was no important change in PVR volume across treatment groups; the largest mean change from baseline to EOT in PVR volume (13.9 ml) was observed in the solifenacin 10 mg plus mirabegron 50 mg combination group (Table 4).

4. Discussion

The rationale for this phase 2 study, the first to combine an AM agent and a β 3-adrenoceptor agonist in OAB patients, was to explore whether solifenacin and mirabegron combination therapy enhances efficacy compared with solifenacin monotherapy, as well as to explore the safety and tolerability of this combination.

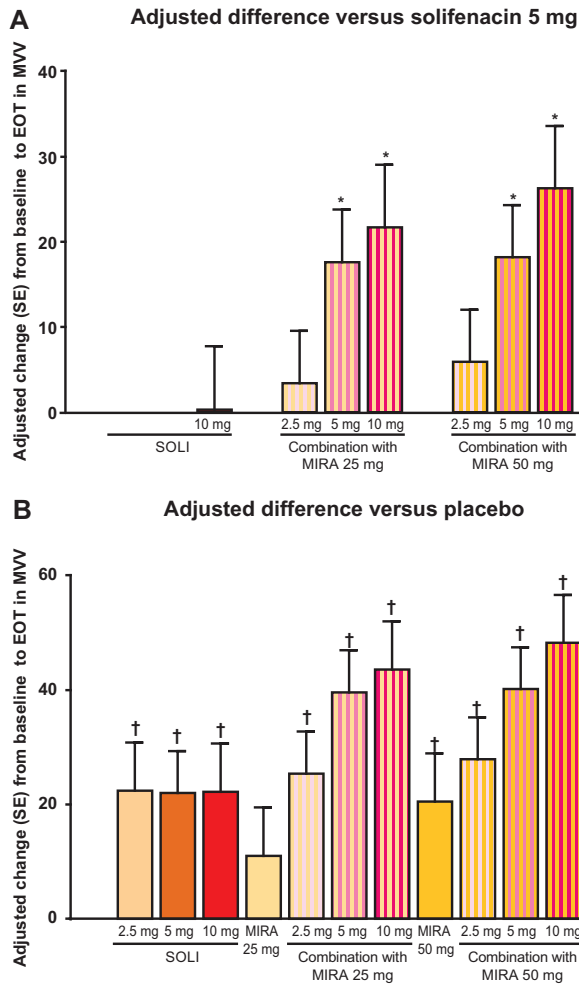


Fig. 3 – Change from baseline to end of treatment in mean volume voided per micturition (in millilitres) compared with (A) solifenacin 5 mg and (B) placebo.
 EOT = end of treatment; MIRA = mirabegron; MVV = mean volume voided per micturition; SOLI = solifenacin.
 * = $p < 0.05$ compared with solifenacin 5 mg.
 † = $p < 0.05$ compared with placebo.

This study employed a factorial design, allowing for the simultaneous comparison of a wide range of monotherapy and combination doses selected according to their clinical relevance [9]. The primary efficacy variable, MVV, is the most sensitive diary parameter and is strongly correlated with OAB symptoms (urgency, frequency, and incontinence) [10]. Because of its subjective nature and related concerns of regulators, urgency, the key OAB symptom, is usually assessed as a secondary end point in OAB trials; MVV was selected as the primary efficacy variable for this phase 2 study because of its being an objective measurement, with low intersubject and intrasubject measurement variability.

Combination therapy demonstrated significant improvements compared with solifenacin 5 mg monotherapy in MVV, with a clear dose–response relationship with increasing doses of solifenacin and mirabegron and a greater improvement in MVV compared with mirabegron monotherapy. Treatment effects with solifenacin and mirabegron monotherapies on MVV were similar in magnitude to those

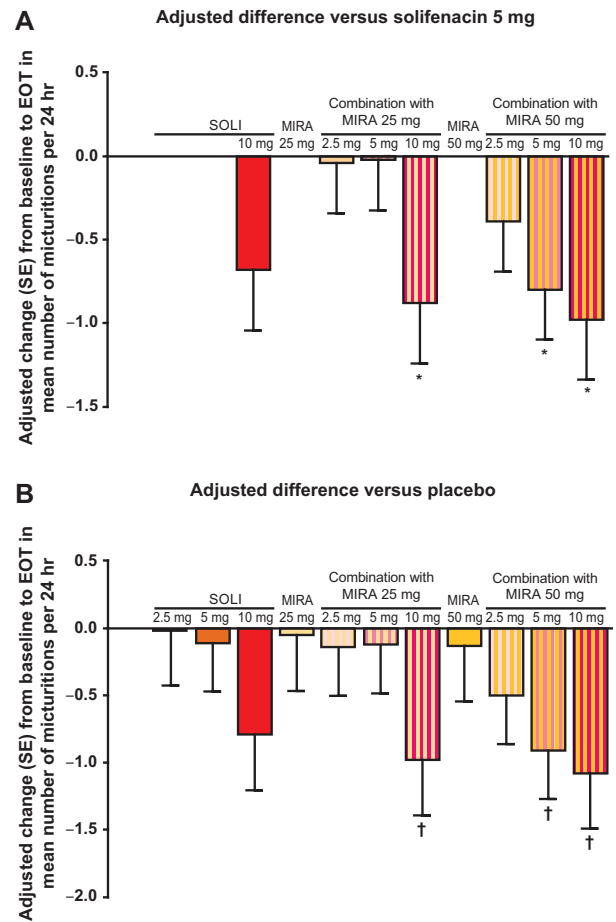


Fig. 4 – Change from baseline to end of treatment in mean number of micturitions per 24 h compared with (A) solifenacin 5 mg and (B) placebo.
 EOT = end of treatment; MIRA = mirabegron; SOLI = solifenacin.
 * = $p < 0.05$ compared with solifenacin 5 mg.
 † = $p < 0.05$ compared with placebo.

observed in previous OAB studies [2–4,11]. As previous studies have shown a relationship between increasing dose of solifenacin and MVV, it may be that the smaller and variable-sized patient groups in this phase 2 study have not allowed a similar relationship to show.

For all treatment combinations, a trend towards a decrease in mean number of micturitions per 24 h from baseline to EOT was observed with increasing solifenacin and mirabegron doses, while three combinations (solifenacin 5 mg plus mirabegron 50 mg, solifenacin 10 mg plus mirabegron 25 mg, and solifenacin 10 mg plus mirabegron 50 mg) demonstrated statistically significant improvements compared with both solifenacin 5 mg and placebo. This treatment effect was seen in the presence of a lower baseline severity in the placebo group, with the appreciable change from baseline to EOT in the placebo group (–2.43 micturitions per 24 h) being among the highest reported in OAB studies [12].

In all treatment groups, including placebo, a reduction in the number of incontinence episodes per 24 h at EOT was observed. Presumably because of the small proportion of incontinent patients (21.5%), low baseline levels of

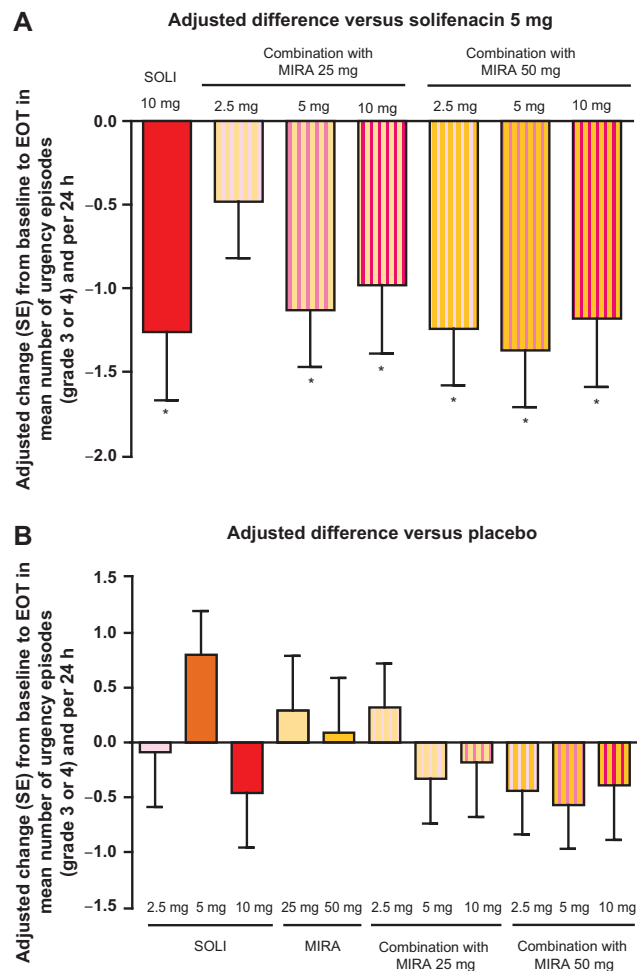


Fig. 5 – Change from baseline to end of treatment in mean number of urgency episodes (grade 3 or 4) per 24 h compared with (A) solifenacin 5 mg and (B) placebo.

EOT = end of treatment; MIRA = mirabegron; SOLI = solifenacin.

* = $p < 0.05$ compared with solifenacin 5 mg.

incontinence (mean: 1.35 episodes per 24 h), and substantial baseline variation (range: 0.9–1.9 episodes per 24 h), treatment differences were of a similar magnitude compared with solifenacin 5 mg (except solifenacin 5 mg plus mirabegron 25 mg) and placebo. The significant improvement in urgency episodes per 24 h in all but one of the combination therapy groups is broadly consistent with that observed for MVV and mean number of micturitions per 24 h and suggests a reduction of more than one urgency episode per 24 h, compared with solifenacin 5 mg monotherapy. Evaluation of urgency remains a problem in OAB trials: A number of factors contribute, including the undoubted difficulty patients have with the concept and its variability with different micturitions. Nevertheless, there are clear indications that reduction in both urgency and the severity of urgency occurs in OAB trials. The subjectivity required to evaluate urgency, random variability, and consequent underpowering may have contributed to the absence of a dose-response effect in this study.

These efficacy results suggest that combination therapy is more effective than solifenacin 5 mg and mirabegron

monotherapy with respect to the solifenacin 5 mg–adjusted and placebo-adjusted differences from baseline to EOT for MVV, micturition frequency, and urgency. The most effective combinations appear to be those combining 5 or 10 mg solifenacin with 25 or 50 mg mirabegron.

All active treatments were well tolerated and concordant with the known safety profile of mirabegron and solifenacin monotherapy. The two most commonly reported TEAEs were dry mouth and hypertension. Changes in BP were negligible in all treatment groups and decreased in most cases. The relatively high frequency of hypertension and tachycardia reported as AEs in all treatment groups (including placebo) may be because of the protocol-defined criteria for reporting these events during vital sign assessment.

The absence of important effects on PVR volume across treatment groups and the small increases in PVR volume with increasing dose suggest that the combined actions of a β_3 -adrenoceptor agonist and an AM are unlikely to increase the risk of urinary retention. There was only one serious adverse event (a case of acute urinary retention in the solifenacin 2.5 mg plus mirabegron 25 mg group) in which a relationship to combination treatment could not be excluded.

The frequency of AM-associated AEs (dry mouth, constipation, blurred vision, and dyspepsia) showed a dose-response relationship with solifenacin monotherapy but did not increase with combination therapy (except constipation); it was generally similar to the corresponding solifenacin monotherapy, indicating an absence of additive effects with combination therapy.

The lack of supra-additive effects on safety parameters demonstrates that the mild pharmacokinetic interaction between mirabegron (100 mg, an unapproved dose) and solifenacin (10 mg) that was recently described [13] does not appear to be clinically relevant. Based on the criteria for clinically significant effects on vital signs and the absence of urinary retention or effects on ECG and laboratory parameters, there were no clinically relevant safety concerns with combination or monotherapy. There was no dose-related difference in pulse rate or BP between combination and mirabegron or solifenacin monotherapy. The negligible effects observed on pulse rate, BP, and QTcF interval were consistent with previous data.

The lower incidence of AEs with combination therapy compared with solifenacin 10 mg, as well as the lack of clinically significant additive effects regarding hypertension and pulse rate, suggests a potential benefit with combination therapy in patients intolerant to AM dose escalation who require additional efficacy.

Study limitations include the relatively low proportion of incontinent individuals in the study population and, because of small sample sizes, a lack of power to detect a meaningful effect in secondary efficacy parameters. Such limitations may have contributed to the absence of dose-related improvements in the monotherapy and combination groups for some efficacy parameters.

The efficacy and safety results in this study compare favourably with previous OAB studies investigating combination or add-on therapy using an α_1 -adrenoceptor

Table 3 – Overview of treatment-emergent adverse events and the most common treatment-emergent adverse events[†]

	PBO (n = 81)	MIRA 25 mg (n = 77)	MIRA 50 mg (n = 78)	SOLI 2.5 mg (n = 79)	SOLI 5 mg (n = 156)	SOLI 10 mg (n = 78)	SOLI 2.5 mg + MIRA 25 mg (n = 149)	SOLI 2.5 mg + MIRA 50 mg (n = 149)	SOLI 5 mg + MIRA 25 mg (n = 144)	SOLI 5 mg + MIRA 50 mg (n = 153)	SOLI 10 mg + MIRA 25 mg (n = 81)	SOLI 10 mg + MIRA 50 mg (n = 81)
TEAEs, no. (%)	32 (39.5)	38 (49.4)	41 (52.6)	32 (40.5)	70 (44.9)	47 (60.3)	69 (46.3)	61 (40.9)	71 (49.3)	67 (43.8)	47 (58.0)	48 (59.3)
Drug-related [‡] TEAEs, no. (%)	14 (17.3)	20 (26.0)	15 (19.2)	12 (15.2)	49 (31.4)	28 (35.9)	46 (30.9)	37 (24.8)	44 (30.6)	32 (20.9)	29 (35.8)	36 (44.4)
Serious TEAEs, no. (%)	0	0	2 (2.6)	1 (1.3)	0	1 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	2 (1.3)	1 (1.2)	1 (1.2)
Serious drug-related TEAEs, no. (%)	0	0	0	0	0	1 (1.3)	1 (0.7)	0	0	0	0	0
TEAEs leading to discontinuation, [†] no. (%)	0	1 (1.3)	2 (2.6)	0	1 (0.6)	2 (2.6)	2 (1.3)	1 (0.7)	4 (2.8)	1 (0.7)	1 (1.2)	3 (3.7)
Common TEAEs, [§] no. (%)												
Dry mouth	3 (3.7)	2 (2.6)	4 (5.1)	6 (7.6)	18 (11.5)	23 (29.5)	19 (12.8)	13 (8.7)	21 (14.6)	20 (13.1)	16 (19.8)	14 (17.3)
Hypertension ^a	7 (8.6)	9 (11.7)	11 (14.1)	8 (10.1)	18 (11.5)	5 (6.4)	11 (7.4)	11 (7.4)	11 (7.6)	9 (5.9)	7 (8.6)	11 (13.6)
Nasopharyngitis	2 (2.5)	5 (6.5)	5 (6.4)	5 (6.3)	6 (3.8)	2 (2.6)	4 (2.7)	6 (4.0)	7 (4.9)	6 (3.9)	6 (7.4)	6 (7.4)
Constipation	0	0	3 (3.8)	1 (1.3)	3 (1.9)	4 (5.1)	7 (4.7)	6 (4.0)	4 (2.8)	2 (1.3)	6 (7.4)	8 (9.9)
Tachycardia ^b	1 (1.2)	3 (3.9)	2 (2.6)	2 (2.5)	6 (3.8)	2 (2.6)	3 (2.0)	7 (4.7)	5 (3.5)	3 (2.0)	4 (4.9)	3 (3.7)
Headache	2 (2.5)	3 (3.9)	1 (1.3)	2 (2.5)	4 (2.6)	2 (2.6)	4 (2.7)	3 (2.0)	3 (2.1)	2 (1.3)	3 (3.7)	2 (2.5)
Escherichia UTI	2 (2.5)	1 (1.3)	2 (2.6)	1 (1.3)	6 (3.8)	5 (6.4)	3 (2.0)	2 (1.3)	3 (2.1)	4 (2.6)	3 (3.7)	1 (1.2)
Influenza	1 (1.2)	1 (1.3)	2 (2.6)	2 (2.5)	3 (1.9)	0	1 (0.7)	3 (2.0)	2 (1.4)	3 (2.0)	0	3 (3.7)
Dyspepsia	0	1 (1.3)	0	1 (1.3)	4 (2.6)	3 (3.8)	2 (1.3)	3 (2.0)	1 (0.7)	1 (0.7)	3 (3.7)	1 (1.2)
UTI	3 (3.7)	1 (1.3)	2 (2.6)	1 (1.3)	4 (2.6)	5 (6.4)	1 (0.7)	2 (1.3)	2 (1.4)	3 (2.0)	0	3 (3.7)
Dizziness	0	1 (1.3)	0	1 (1.3)	1 (0.6)	3 (3.8)	5 (3.4)	3 (2.0)	1 (0.7)	0	0	0
ECG QT prolonged	1 (1.2)	0	0	0	0	2 (2.6)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.7)	0	4 (4.9)
Fatigue	1 (1.2)	1 (1.3)	0	0	6 (3.8)	0	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.3)	1 (1.2)	1 (1.2)
Blurred vision	0	0	1 (1.3)	0	0	1 (1.3)	1 (0.7)	0	2 (1.4)	2 (1.3)	2 (2.5)	1 (1.2)

ECG = electrocardiography; MIRA = mirabegron; PBO = placebo; SOLI = solifenacin; TEAE = treatment-emergent adverse event; UTI = urinary tract infection.

[†] ≥3% in any group.

[‡] Includes the antimuscarinic-associated TEAE blurred vision (based on the preferred terms *vision blurred* and *accommodation disorder*), which was reported in <3% of patients in any treatment group.

[§] Possible or probable, as assessed by the investigator, or records where relationship was missing.

[¶] Permanent discontinuation of study drug.

^a An adverse event of hypertension was to be recorded if one of the following criteria was met: (1) the average systolic blood pressure (SBP) was ≥140 mm Hg and/or the average diastolic blood pressure (DBP) was ≥90 mm Hg at two consecutive visits after visit three/baseline in patients who were normotensive (average SBP <140 mm Hg and average DBP <90 mm Hg at baseline); (2) average SBP increased ≥20 mm Hg and/or the average DBP increased ≥10 mm Hg at two consecutive visits as compared with visit three/baseline in patients with hypertension at baseline; (3) 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.

^b An adverse event of tachycardia was reported if the mean pulse rate, in the resting state, from patient-reported measurements at home, over the prior three diary days, was >100 bpm, either morning or evening (or both), or if the patient had a resting heart rate frequency >100 bpm at a site visit.

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Table 4 – Change from baseline to end of treatment in blood pressure and pulse rate, QT interval, and postvoid residual volume (safety analysis set)

	PBO (n = 81)	MIRA 25 mg (n = 77)	MIRA 50 mg (n = 78)	SOLI 2.5 mg (n = 79)	SOLI 5 mg (n = 156)	SOLI 10 mg (n = 78)	SOLI 2.5 mg + MIRA 25 mg (n = 149)	SOLI 2.5 mg + MIRA 50 mg (n = 149)	SOLI 5 mg + MIRA 25 mg (n = 144)	SOLI 5 mg + MIRA 50 mg (n = 153)	SOLI 10 mg + MIRA 25 mg (n = 81)	SOLI 10 mg + MIRA 50 mg (n = 81)
Pulse rate, bpm												
Mean baseline (SE)	73.2 (1.01)	71.6 (1.22)	72.1 (1.13)	72.5 (1.15)	73.0 (0.79)	72.8 (1.03)	72.9 (0.78)	72.4 (0.85)	72.5 (0.81)	71.5 (0.76)	73.2 (1.23)	72.0 (0.93)
Adjusted mean change from baseline (SE) [95% CI]	0.1 (0.85) [-1.6 to 1.8]	-0.2 (0.87) [-1.9 to 1.5]	1.0 (0.87) [-0.7 to 2.7]	0.1 (0.87) [-1.6 to 1.8]	0.1 (0.62) [-1.1 to 1.3]	0.1 (0.87) [-0.9 to 2.6]	0.7 (0.63) [-0.5 to 1.9]	1.1 (0.63) [-0.1 to 2.3]	1.5 (0.64) [0.3-2.8]	0.6 (0.62) [-0.7 to 1.8]	0.6 (0.85) [-1.1 to 2.2]	1.3 (0.85) [-0.3 to 3.0]
Difference vs SOLI 5 mg, mean (SE) [95% CI]	-	-	-	-	-	-	0.6 (0.88) [-1.1 to 2.3]	1.0 (0.88) [-0.8 to 2.7]	1.4 (0.89) [-0.3 to 3.2]	0.4 (0.88) [-1.3 to 2.2]	0.5 (1.05) [-1.6 to 2.5]	1.2 (1.05) [-0.9 to 3.3]
Difference vs MIRA 50 mg, mean (SE) [95% CI]	-	-	-	-	-	-	-0.3 (1.07) [-2.5 to 1.8]	0.0 (1.07) [-2.1 to 2.2]	0.5 (1.08) [-1.6 to 2.6]	-0.5 (1.07) [-2.6 to 1.6]	-0.5 (1.22) [-2.9 to 1.9]	0.3 (1.22) [-2.1 to 2.7]
Difference vs PBO, mean (SE) [95% CI]	-	-0.3 (1.22) [-2.7 to 2.1]	0.9 (1.22) [-1.5 to 3.3]	-0.0 (1.22) [-2.4 to 2.4]	0.0 (1.05) [-2.1 to 2.1]	0.8 (1.22) [-1.6 to 3.1]	0.6 (1.06) [-1.5 to 2.7]	1.0 (1.06) [-1.1 to 3.1]	1.4 (1.07) [-0.7 to 3.5]	0.5 (1.06) [-1.6 to 2.5]	0.5 (1.21) [-1.9 to 2.8]	1.2 (1.21) [-1.1 to 3.6]
Systolic BP, mm Hg												
Mean baseline (SE)	128.8 (1.52)	128.4 (1.97)	128.6 (1.54)	130.6 (1.60)	128.1 (1.12)	130.9 (1.54)	128.0 (1.31)	129.5 (1.25)	128.7 (1.22)	128.0 (1.15)	130.1 (1.67)	128.0 (1.78)
Adjusted mean change from baseline (SE) [95% CI]	-2.6 (1.09) [-4.8 to -0.5]	-0.2 (1.12) [-2.4 to 2.0]	0.7 (1.11) [-1.5 to 2.8]	-2.0 (1.11) [-4.2 to 0.2]	-1.7 (0.79) [-3.3 to -0.1]	-2.7 (1.12) [-4.9 to -0.5]	-1.3 (0.81) [-2.9 to 0.2]	-0.6 (0.81) [-2.2 to 1.0]	-0.7 (0.83) [-2.4 to 0.9]	-2.1 (0.80) [-3.7 to -0.6]	-2.6 (1.09) [-4.7 to -0.4]	-0.4 (1.09) [-2.6 to 1.7]
Difference vs SOLI 5 mg, mean (SE) [95% CI]	-	-	-	-	-	-	0.4 (1.13) [-1.9 to 2.6]	1.1 (1.13) [-1.1 to 3.4]	1.0 (1.14) [-1.3 to 3.2]	-0.4 (1.13) [-2.7 to 1.8]	-0.9 (1.35) [-3.5 to 1.8]	1.3 (1.35) [-1.4 to 3.9]
Difference vs MIRA 50 mg, mean (SE) [95% CI]	-	-	-	-	-	-	-2.0 (1.37) [-4.7 to 0.7]	-1.2 (1.37) [-3.9 to 1.5]	-1.4 (1.39) [-4.1 to 1.3]	-2.8 (1.37) [-5.5 to -0.1]	-3.2 (1.56) [-6.3 to -0.2]	-1.1 (1.56) [-4.1 to 2.0]
Difference vs PBO, mean (SE) [95% CI]	-	2.4 (1.57) [-0.7 to 5.5]	3.3 (1.56) [0.2 to 6.3]	0.6 (1.56) [-2.5 to 3.6]	0.9 (1.35) [-1.7 to 3.6]	-0.1 (1.57) [-3.2 to 2.9]	1.3 (1.36) [-1.4 to 3.9]	2.0 (1.36) [-0.6 to 4.7]	1.9 (1.37) [-0.8 to 4.6]	0.5 (1.35) [-2.2 to 3.1]	0.0 (1.55) [-3.0 to 3.1]	2.2 (1.55) [-0.8 to 5.2]
Diastolic BP, mm Hg												
Mean baseline (SE)	76.2 (0.86)	75.9 (0.96)	76.7 (0.88)	75.4 (0.97)	75.8 (0.65)	76.8 (0.76)	76.4 (0.77)	77.4 (0.75)	75.8 (0.68)	76.9 (0.68)	78.3 (0.94)	75.6 (1.05)
Adjusted mean change from baseline (SE) [95% CI]	-1.2 (0.74) [-2.7 to 0.2]	-0.3 (0.76) [-1.8 to 1.2]	0.3 (0.76) [-1.2 to 1.8]	-1.2 (0.76) [-2.6 to 0.3]	-0.6 (0.54) [-1.7 to 0.4]	0.0 (0.76) [-1.5 to 1.5]	-0.3 (0.55) [-1.4 to 0.7]	0.2 (0.55) [-0.9 to 1.3]	-0.0 (0.56) [-1.1 to 1.1]	-0.8 (0.55) [-1.9 to 0.2]	-1.0 (0.75) [-2.4 to 0.5]	-0.2 (0.74) [-1.6 to 1.3]
Difference vs SOLI 5 mg, mean (SE) [95% CI]	-	-	-	-	-	-	0.3 (0.77) [-1.2 to 1.8]	0.9 (0.77) [-0.7 to 2.4]	0.6 (0.78) [-0.9 to 2.1]	-0.2 (0.77) [-1.7 to 1.3]	-0.3 (0.92) [-2.1 to 1.5]	0.5 (0.92) [-1.3 to 2.3]
Difference vs MIRA 50 mg, mean (SE) [95% CI]	-	-	-	-	-	-	-0.7 (0.94) [-2.5 to 1.2]	-0.1 (0.94) [-1.9 to 1.7]	-0.3 (0.94) [-2.2 to 1.5]	-1.1 (0.93) [-3.0 to 0.7]	-1.3 (1.06) [-3.4 to 0.8]	-0.5 (1.06) [-2.6 to 1.6]
Difference vs PBO, mean (SE) [95% CI]	-	1.0 (1.07) [-1.1 to 3.1]	1.6 (1.06) [-0.5 to 3.6]	0.1 (1.06) [-2.0 to 2.2]	0.6 (0.92) [-1.2 to 2.4]	1.3 (1.07) [-0.8 to 3.4]	0.9 (0.92) [-0.9 to 2.7]	1.5 (0.92) [-0.4 to 3.3]	1.2 (0.93) [-0.6 to 3.1]	0.4 (0.92) [-1.4 to 2.2]	0.3 (1.05) [-1.8 to 2.4]	1.1 (1.05) [-1.0 to 3.1]
QTcF interval, ms												
Mean baseline (SD)	407.8 (15.9)	408.6 (17.0)	408.8 (16.1)	411.5 (15.6)	408.1 (18.1)	411.2 (18.5)	408.7 (15.2)	410.0 (15.7)	409.1 (16.7)	406.9 (18.4)	407.5 (16.3)	407.4 (19.1)
Mean change from baseline (SD)	2.7 (11.9)	1.8 (13.2)	1.2 (13.4)	2.0 (14.7)	3.4 (11.4)	4.9 (13.4)	3.3 (14.1)	2.2 (12.7)	2.3 (11.7)	3.0 (11.6)	5.3 (12.7)	3.5 (15.8)
PVR volume, ml												
Mean baseline (SD)	13.1 (19.6)	16.1 (22.0)	12.8 (20.0)	14.6 (22.2)	13.7 (23.2)	18.2 (27.9)	16.3 (24.0)	13.2 (24.4)	14.7 (23.5)	13.4 (21.5)	17.1 (29.3)	11.6 (15.1)
Mean change from baseline (SD)	-1.4 (21.3)	1.8 (23.5)	0.2 (21.7)	10.7 (49.5)	7.5 (34.8)	6.6 (31.0)	2.0 (28.9)	3.5 (25.2)	6.0 (32.4)	10.7 (32.8)	6.3 (31.8)	13.9 (32.9)

BP = blood pressure; CI = confidence interval; MIRA = mirabegron; PBO = placebo; PVR = postvoid residual; QTcF = QT interval corrected with Fridericia's correction; SD = standard deviation; SE = standard error; SOLI = solifenacin.

Vital signs (pulse rate and BP) assessed using standard office device. Clinically significant criteria for systolic BP were defined as ≥ 180 mm Hg and ≥ 20 mm Hg change from baseline. Clinically significant criteria for diastolic BP were defined as ≥ 105 mm Hg and ≥ 15 mm Hg change from baseline. Clinically significant criteria for pulse rate were defined as ≥ 120 bpm and ≥ 15 bpm change from baseline.

antagonist and AM agent [14–17] and with OAB studies using mirabegron or solifenacin monotherapy [2–4,7,11].

5. Conclusions

Combination therapy of solifenacin and mirabegron demonstrated significant improvements over monotherapy (solifenacin 5 mg) in MVV, micturition frequency, and urgency, without increasing bothersome adverse effects associated with AM therapy, compared with mirabegron or solifenacin monotherapy (with the possible exception of constipation).

The combination of mirabegron and an AM agent may provide an attractive therapeutic approach to maximise efficacy and minimise the side effect burden.

The results from this study have previously been presented in poster format at the following scientific congresses: American Urological Association 2012, International Continence Society 2013, and Société Internationale d'Urologie 2013. A full list of study investigators is provided in Supplemental Table 3.

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

Study concept and design: Abrams, Kelleher, Staskin, Rechberger, Kay, Martina, Ridder, Newgreen.

Acquisition of data: Abrams, Kelleher, Rechberger, van Maanen.

Analysis and interpretation of data: Abrams, Kelleher, Staskin, Rechberger, Kay, Martina, Ridder, Newgreen, van Maanen, Pairedy.

Drafting of the manuscript: Abrams, Kelleher, Staskin, Kay, Martina, Ridder, Newgreen, van Maanen, Pairedy.

Critical revision of the manuscript for important intellectual content: Abrams, Kelleher, Staskin, Rechberger, Kay, Martina, Ridder, Newgreen, van Maanen, Pairedy.

Statistical analysis: Kay, Martina.

Obtaining funding: Ridder.

Administrative, technical, or material support: Pairedy.

Supervision: van Maanen.

Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2014.02.012>.

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