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Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study)

Sender Herschorn*, Christopher R. Chapple†, Paul Abrams‡, Salvador Arlandis§, David Mitcheson¶, Kyu-Sung Lee**, Arwin Ridder††, Matthias Stoelzel††, Asha Paireddy††, Rob van Maanen†† and Dudley Robinson‡‡

*Department of Surgery/Urology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, †Department of Urology, Royal Hallamshire Hospital, Sheffield, UK, ‡Bristol Urological Institute, Southmead Hospital, Bristol, UK, §Hospital Universitario La Fé, Valencia, Spain, ¶St. Elizabeth's Medical Center, Brighton, MA, USA, **Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ††Astellas Pharma Global Development, Leiden, The Netherlands, and ‡‡Kings College Hospital, London, UK

Objective

To evaluate the potential of solifenacin 5 mg combined with mirabegron 25 or 50 mg to deliver superior efficacy compared with monotherapy, with acceptable tolerability, in the general overactive bladder (OAB) population with urinary incontinence (UI).

Patients and Methods

After a 4-week placebo run-in, patients aged ≥18 years with wet OAB (urgency, urinary frequency and UI) for ≥3 months who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 UI episodes over the 7-day micturition diary, were eligible for randomisation to double-blind treatment [2:2:1:1:1:1 ratio, solifenacin 5 mg + mirabegron 25 mg (combined S5 + M25 group); solifenacin 5 mg + mirabegron 50 mg (combined S5 + M50 group); solifenacin 5 mg; mirabegron 25 mg; mirabegron 50 mg; or placebo for 12 weeks], and 2-weeks' single-blind, placebo run-out. Co-primary efficacy variables were change from baseline to end of treatment (EoT) in the mean number of UI episodes/24 h and micturitions/24 h, assessed using a 7-day electronic micturition diary. Secondary efficacy variables included change from baseline to EoT in the mean volume voided/micturition, change from baseline at weeks 4, 8, 12 and EoT in mean number of UI episodes/24 h, micturitions/24 h, urgency episodes/24 h, urgency UI (UUI) episodes/24 h and nocturia episodes/24 h; the percentage of patients (responders) achieving zero UI episodes/24 h at EoT in the last 7 days prior to each visit, micturition frequency normalisation (<8 episodes/24 h) at weeks 4, 8, 12 and EoT; and the number of UUI episodes and nocturia episodes in the 7-day diary. Safety assessments included incidence and frequency of treatment-emergent adverse events (TEAEs), post-void residual (PVR) urine volume, and changes from baseline in laboratory parameters.

Results

Whilst the combined S5 + M50 group was superior to solifenacin 5 mg for UI, with a mean (standard error) adjusted difference of −0.20 (0.12) UI episodes/24 h (95% confidence interval −0.44, 0.04, $P = 0.033$), there was no statistical superiority vs mirabegron 50 mg [−0.23 (0.12) UI episodes/24 h; $P = 0.052$]. In secondary analyses, all active treatment groups had greater improvements in UI episodes/24 h vs placebo, with effect sizes for the combined therapy groups (combined S5 + M25 group: −0.70 episodes/24 h; combined S5 + M50 group: −0.65 episodes/24 h) that were substantially higher than those obtained with monotherapy (range −0.37 episodes/24 h for mirabegron 25 mg to −0.45 episodes/24 h for solifenacin 5 mg). For micturitions/24 h, adjusted change from baseline to EoT was greater in the combined therapy groups vs monotherapies (combined S5 + M50 group, nominal P values 0.006 and <0.001 vs solifenacin 5 mg and mirabegron 50 mg, respectively; combined S5 + M25 group, nominal P values 0.040 and 0.001 vs solifenacin 5 mg and mirabegron 25 mg, respectively). All active treatment groups had greater improvements in the mean numbers of micturitions/24 h vs placebo, with effect sizes for the combined therapy groups (combined S5 + M25 group: −0.85 micturitions/24 h; combined S5 + M50 group: −0.95 micturitions/24 h) higher than with mirabegron monotherapy (25 mg: −0.36; 50 mg: −0.39 micturitions/24 h) and solifenacin 5 mg (−0.56 micturitions/24 h). The combined S5 + M50 group was statistically significantly superior to both monotherapies at

EoT for UUI episodes, urgency episodes and nocturia, with effect sizes that appeared to be additive. The combined S5 + M25 group was statistically significantly superior to mirabegron 25 mg for the same variables, except for nocturia. In responder analyses at the EoT, odds ratios in favour of both combined therapies vs monotherapies were shown for the proportion of patients with zero UI episodes and those achieving micturition frequency normalisation. There was a slightly increased frequency of TEAEs in the combined therapy groups vs monotherapies and placebo. Most of the TEAEs were mild or moderate in severity. Events indicative of urinary retention were reported slightly more frequently in the combined therapy groups vs monotherapy and placebo. PVR volume was slightly increased in the combined therapy groups vs solifenacin 5 mg, mirabegron monotherapy, and placebo groups. There were slightly higher frequencies of dry mouth, constipation, and dyspepsia in the combined therapy groups vs monotherapies. There were no concerns regarding electrocardiograms and laboratory data.

Conclusion

In the largest OAB study to date, combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg provided consistent improvements in efficacy compared with the respective monotherapies across most of the outcome parameters, with effect sizes generally consistent with an additive effect. Although the combined S5 + M50 group did not achieve a statistically significant effect vs mirabegron 50 mg in the primary analysis of one of the co-primary endpoints (change from baseline in mean number of UI episodes/24 h), it approached statistical significance ($P = 0.052$), and the nominal P values for the other co-primary endpoint (micturitions/24 h) were <0.05. Most effects of combined therapy vs monotherapy were observable by week 4. The clinical relevance of the improvements seen with combined therapy for several objective OAB outcome measures was also supported by the improvements of combined therapy vs monotherapy in the responder analyses.

Introduction

Overactive bladder (OAB) syndrome is characterised by urinary urgency, with or without urgency urinary incontinence (UUI), usually accompanied by increased daytime frequency and nocturia, in the absence of UTI or other obvious pathology [1]. UUI is present in about one-third of cases [2], but is not a prerequisite. However, of all the OAB symptoms, it has the greatest impact on health-related quality of life (HRQoL) [3,4], and is associated with significantly lower productivity and higher healthcare resource utilisation [5].

Oral pharmacotherapy for OAB comprises antimuscarinics and mirabegron, a β_3-adrenoceptor agonist. Antimuscarinics and β_3-adrenoceptor agonists modulate bladder function through different molecular pathways; nevertheless, efficacy is similar for both drug classes [6]. In clinical practice, antimuscarinics are often initially prescribed; however, increasing the dose may exacerbate antimuscarinic adverse events (AEs) such as dry mouth and constipation, which may result in treatment discontinuation [7–10]. Analyses of medical claims databases indicate that treatment persistence is better with mirabegron vs antimuscarinics [11–13].

A phase II European dose-finding study (SYMPHONY; NCT01340027) investigating six dose combinations of mirabegron with solifenacin compared with monotherapy with mirabegron, solifenacin, or placebo, reported that combined therapy had greater efficacy than solifenacin 5 mg alone on the change from baseline to end of treatment (EoT) in the mean volume voided (MVV)/micturition, frequency of micturitions/24 h, and urgency episodes. All combinations were well tolerated compared with the monotherapies or placebo [14]. Solifenacin 5 mg combined with mirabegron 25 mg or 50 mg appeared optimal in terms of the benefit/risk profile in that study [15]. In addition, in a trial of patients remaining incontinent after initial treatment with solifenacin for 4 weeks (BESIDE; NCT01908829), solifenacin + mirabegron combined therapy further improved OAB symptoms and was well tolerated compared with solifenacin monotherapy [16]. The present study (SYNERGY) evaluated the potential of solifenacin 5 mg (the recommended daily starting dose and the most widely used dose in clinical practice) combined with mirabegron 25 or 50 mg, to deliver superior efficacy to the individual monotherapies with acceptable tolerability, in the general OAB population with UI.

Patients and methods

Study design

This was a multinational, multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled Phase III study (NCT01972841), performed in accordance with the International Conference on Harmonization, Good Clinical Practice and the Declaration of Helsinki. Independent Review Board/Independent Ethics Committee-approved written

informed consent was obtained from each patient before the study. Patients enrolled at sites in the USA also signed a Health Insurance Portability and Accountability Act (HIPAA) authorisation form.

The study duration was 18 weeks, comprising a single-blind, 4-week placebo run-in, a 12-week double-blind treatment period, and a 2-week, single-blind, placebo run-out period (supplementary data online entitled Fig. S1). Patients aged ≥18 years who had had symptoms of wet OAB (urgency, urinary frequency and UI) for ≥3 months were eligible for screening. In patients with mixed stress UI/UUI, UUI had to be the predominant factor as evidenced by diary data and determined by the investigator. Those who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h (grade 3 or 4 on the Patient Perception of Intensity of Urgency Scale [PPIUS]/24 h [17]), and ≥3 UI episodes over the 7-day micturition diary were eligible for randomisation to double-blind treatment in a 2:2:1:1:1:1 ratio to daily:

- Solifenacin 5 mg + mirabegron 25 mg (combined S5 + M25)
- Solifenacin 5 mg + mirabegron 50 mg (combined S5 + M50)
- Placebo
- Mirabegron 25 mg
- Mirabegron 50 mg
- Solifenacin 5 mg

Exclusion criteria are shown in supplementary data online entitled Table S1.

Efficacy assessments

Co-primary efficacy variables were change from baseline to EoT in the mean number of UI episodes/24 h and micturitions/24 h, assessed using a 7-day electronic micturition diary. Key secondary efficacy variables were change from baseline to EoT in the MVV/micturition and in patient-reported outcomes (PROs). PROs, which will be the subject of a separate manuscript, included change from baseline to EoT in Overactive Bladder Questionnaire Symptom Bother score, HRQoL total score, Patient Perception of Bladder Condition (PPBC), Treatment Satisfaction-Visual Analogue Scale (TS-VAS) and responder analyses.

Other secondary efficacy variables derived from the 7-day micturition diary included: change from baseline at weeks 4, 8, 12 and EoT in: the mean number of UI episodes/24 h, micturitions/24 h, urgency episodes 24 h, UUI episodes/24 h and nocturia episodes/24 h; the percentage of patients (responders) achieving zero UI episodes/24 h at EoT in the last 7 days prior to each visit, micturition frequency normalisation (<8 episodes/24 h) at weeks 4, 8, 12 and EoT; and the number of UUI episodes and nocturia episodes in the 7-day diary.

Safety assessments

Safety assessments at each study visit and during the 2-week placebo run-out period included: frequency of treatment-emergent AEs (TEAEs), post-void residual (PVR) urine volume (assessed by ultrasonography), changes from baseline in laboratory parameters and AEs known to be associated with antimuscarinics (e.g. dry mouth, blurred vision, constipation, and dyspepsia). Cardiovascular AEs and change from baseline in vital signs, including vital signs in a subset of patients participating in an ambulatory blood pressure monitoring study will be presented in a manuscript focusing on cardiovascular results. Cardiovascular and neoplasm events were adjudicated by independent adjudication committees. AEs were coded using MedDRA version 16.0 and summarised by System Organ Class and Preferred Term. TEAEs for urinary retention were also summarised by lower level term and treatment group. TEAEs reported by the investigator as increased PVR or urinary retention were coded to 'PVR increased' or 'urinary retention', respectively. An AE of acute urinary retention was coded to the lower level term of 'acute urinary retention' under the Preferred Term of 'urinary retention'.

Statistical analysis

The planned sample size was based on the change from baseline in mean micturitions/24 h at EoT. Using a 2:1 randomisation ratio between the combined therapy, monotherapy, and placebo treatment arms, 762 patients in each combined therapy arm and 381 patients in each of the monotherapy and placebo arms provided 90% power to detect a clinically relevant reduction of 0.55 in mean number of micturitions/24 h over each monotherapy component at a two-sided significance level of 0.05. A standard deviation (SD) of 2.7 was assumed, based on a previous study with solifenacin, mirabegron and solifenacin + mirabegron combinations [14]. As the combined therapy groups were compared vs both monotherapies, the combined power for both tests was at least 81% (assuming independence and a similar effect size of the combined therapy groups over each monotherapy).

Change from baseline to EoT in the mean number of UI episodes/24 h was analysed using a separate stratified rank analysis of covariance (ANCOVA) model for each pairwise treatment group difference of interest (e.g. combined treatment vs each monotherapy). The stratified rank ANCOVA methodology was used to calculate *P* values for differences between treatment groups. Point estimates and 95% CIs for differences between treatment groups were estimated in an ANCOVA model with treatment group, sex, age group, previous OAB treatment and geographic region as fixed factors and baseline value as a covariate. Due to the different methodology used to calculate non-parametric

P values and parametric 95% CIs for differences between treatment groups, there is a chance that a 95% CI includes zero even though the *P* value is <0.05 or vice versa.

Change from baseline to EoT in the mean number of micturitions/24 h and key secondary endpoints were analysed using an ANCOVA model with treatment group, sex, age group, previous OAB treatment and geographic region as fixed factors and baseline value as a covariate.

As there were co-primary and multiple key secondary endpoints and because two combined therapy groups were compared vs their monotherapy components, the type 1 error was controlled at the one-sided 0.025 level by a sequential Bonferroni-based testing procedure following the graphical approach proposed by Bretz et al. [18] (supplementary data online entitled Fig. S2). To reduce complexity, the MVV was the only key secondary variable included in the testing procedure. The first statistical comparison was between the combined S5 + M50 group and the monotherapies for change from baseline to EoT in UI episodes/24 h (more detailed information on the statistical analysis is provided online and entitled Table S2).

Results

Patient demographics and baseline characteristics

The study was conducted at 435 sites in 42 countries. In general, all treatment arms were similar for demographics and baseline characteristics (Table 1). Most patients were female (77%); most patients were White (80%). There were no major differences across treatment groups in baseline values for the mean number of UI episodes/24 h (range 3.2 for the combined S5 + M50 group to 3.6 for the solifenacin 5 mg group) or the mean number of micturitions/24 h (range 10.7 for the combined therapy groups to 11.2 for the mirabegron 50 mg group). The MVV ranged from 152 to 159 mL. The duration of OAB symptoms was similar across treatment groups (overall mean duration 67 months). Most patients (65%) had UUI only; all other patients had mixed stress UI/UUI with urgency as the predominant factor. Overall, 46% of patients had received previous OAB medications; 23% of patients had previously received solifenacin and 4% of patients had previously received mirabegron. Pre-specified subgroup analyses showed that patients who were previously treated with OAB medication had more UUI only (71%) and less mixed stress UI/UUI with urgency as the predominant factor (29%) than treatment-naïve patients (61% and 39%, respectively). β-blockers were used by 13% of patients prior to the run-in period and by 13% of patients during the double-blind period.

In all, 6991 patients were screened, 6275 patients received placebo run-in medication, 3527 patients were randomised, and 3494 (99%) received double-blind treatment. Of these, 3398 (96%) patients were included in the safety population (SAF) and 3308 (94%) in the full analysis set (FAS). Patients (n = 96) from one site were excluded from the SAF and FAS due to protocol non-compliance. The primary reasons for discontinuation were AEs or withdrawal by the patient (Fig. 1).

Efficacy

Whilst the combined S5 + M50 group was superior to solifenacin 5 mg for UI, with a mean (SE) adjusted difference of −0.20 (0.12) UI episodes/24 h (95% CI −0.44, 0.04, P = 0.033), statistical superiority vs mirabegron 50 mg was not demonstrated [mean (SE) adjusted difference of −0.23 (0.12) UI episodes/24 h (95% CI −0.47, 0.01, P = 0.052)] (Fig. 2A). Therefore, the primary objective for the combined S5 + M50 therapy was not met. Because the null hypothesis for this test was not rejected, the subsequent hypotheses for mean number of micturitions/24 h and the MVV/micturition could not be tested. Also, no hypothesis testing could be performed for the combined S5 + M25 group.

Nonetheless, UI episodes/24 h at EoT decreased vs baseline for all treatment arms. The mean adjusted change from baseline to EoT was greater in the combined therapy groups vs monotherapies and placebo (Fig. 2A). In secondary analyses, all active treatment groups had greater improvements in UI episodes/24 h vs placebo (nominal *P* values all <0.05), with effect sizes for the combined therapy groups (combined S5 + M25 group: −0.70 episodes/24 h; combined S5 + M50 group: −0.65 episodes/24 h) that were substantially higher than those obtained with monotherapy (range −0.37 episodes/24 h for mirabegron 25 mg to −0.45 episodes/24 h for solifenacin 5 mg).

The EoT values for micturitions/24 h decreased vs baseline for all treatment arms. Adjusted change from baseline to EoT was greater in the combined therapy groups vs monotherapies (combined S5 + M50 group, nominal *P* values 0.006 and <0.001 vs solifenacin 5 mg and mirabegron 50 mg, respectively; combined S5 + M25 group, nominal *P* values 0.040 and 0.001 vs solifenacin 5 mg and mirabegron 25 mg, respectively) and placebo (nominal *P* values <0.05; Fig. 2B). All active treatment groups had greater improvements in the mean number of micturitions/24 h vs placebo (nominal *P* values < 0.05). The effect size was similar across mirabegron monotherapy groups (25 mg: −0.36; 50 mg: −0.39 micturitions/24 h) and slightly higher for solifenacin 5 mg (−0.56 micturitions/24 h). The effect size in the combined therapy groups (combined S5 + M25 group: −0.85; combined S5 + M50 group: −0.95 micturitions/24 h) suggests a fully additive effect of the monotherapies.

Table 1 Patient demographic and other baseline characteristics (Safety Analysis Set).

	Treatment group						Total (*n* = 3398)
	Placebo (*n* = 429)	M 25 mg (*n* = 423)	M 50 mg (*n* = 422)	S 5 mg (*n* = 423)	S5 + M25 (*n* = 853)	S5 + M50 (*n* = 848)	
Sex, *n* (%)							
Male	102 (23.8)	96 (22.7)	99 (23.5)	92 (21.7)	197 (23.1)	197 (23.2)	783 (23.0)
Female	327 (76.2)	327 (77.3)	323 (76.5)	331 (78.3)	656 (76.9)	651 (76.8)	2615 (77.0)
Age, years							
Mean, SD	57.9 (13.0)	56.9 (13.6)	56.7 (13.3)	58.2 (12.8)	57.1 (13.9)	57.6 (13.4)	57.4 (13.4)
Age group, years, *n* (%)							
≥65	146 (34.0)	139 (32.9)	131 (31.0)	138 (32.6)	283 (33.2)	285 (33.6)	1122 (33.0)
≥75	38 (8.9)	32 (7.6)	32 (7.6)	35 (8.3)	70 (8.2)	70 (8.3)	277 (8.2)
Race, *n* (%)							
White	346 (80.7)	331 (78.3)	336 (79.6)	335 (79.2)	678 (79.5)	680 (80.2)	2706 (79.6)
Black/African American	14 (3.3)	17 (4.0)	8 (1.9)	13 (3.1)	34 (4.0)	28 (3.3)	114 (3.4)
Asian	60 (14.0)	69 (16.3)	68 (16.1)	66 (15.6)	123 (14.4)	123 (14.5)	509 (15.0)
Other	5 (1.2)	4 (0.9)	6 (1.4)	6 (1.4)	15 (1.8)	12 (1.4)	48 (1.4)
Unknown	4 (0.9)	2 (0.5)	4 (0.9)	3 (0.7)	3 (0.4)	5 (0.6)	21 (0.6)
BMI, kg/m^2, mean (SD)	28.72 (6.07)	28.19 (6.76)	28.33 (6.03)	28.46 (5.90)*	28.59 (5.86)	28.60 (5.88)	28.51 (6.03)†
Type of OAB at screening, *n* (%)							
UUI only	285 (66.4)	267 (63.1)	268 (63.5)	275 (65.0)	561 (65.8)	567 (66.9)	2223 (65.4)
Mixed stress UI/UUI with urgency predominant	144 (33.6)	156 (36.9)	154 (36.5)	148 (35.0)	292 (34.2)	281 (33.1)	1175 (34.6)
Duration of wet OAB symptoms, months							
Mean (SD)	67.52 (76.02)	69.27 (88.94)	66.78 (80.67)	66.75 (88.76)	68.16 (87.48)	64.34 (81.17)	66.92 (84.03)
Previous OAB medication, *n* (%)							
Yes	205 (47.8)	196 (46.3)	195 (46.2)	204 (48.2)	389 (45.6)	388 (45.8)	1577 (46.4)
Previous treatment with solifenacin, *n* (%)							
Yes	83 (19.3)	92 (21.7)	96 (22.7)	97 (22.9)	198 (23.2)	201 (23.7)	767 (22.6)
Previous treatment with mirabegron, *n* (%)							
Yes	19 (4.4)	18 (4.3)	19 (4.5)	18 (4.3)	27 (3.2)	34 (4.0)	135 (4.0)
7-day micturition diary baseline characteristics (FAS)	**(*n* = 418)**	**(*n* = 410)**	**(*n* = 411)**	**(*n* = 415)**	**(*n* = 827)**	**(*n* = 827)**	**(*n* = 3308)**
Number of UI episodes/24 h, mean (SD)	3.41 (3.37)	3.42 (3.40)	3.18 (3.47)	3.58 (3.51)	3.22 (3.17)	3.16 (3.08)	3.29 (3.29)
Number of micturitions/24 h, mean (SD)	10.97 (2.86)	10.81 (2.63)	11.19 (3.27)	10.76 (2.47)	10.73 (2.88)	10.74 (2.36)	10.84 (2.73)
MVV, mL, mean (SD)	**(*n* = 414)** 157.94 (58.78)	**(*n* = 407)** 152.46 (60.96)	**(*n* = 409)** 155.31 (60.78)	**(*n* = 413)** 151.94 (59.29)	**(*n* = 823)** 159.32 (58.29)	**(*n* = 824)** 153.57 (59.67)	**(*n* = 3290)** 155.43 (59.49)
Number of UUI episodes/24 h, mean (SD)	**(*n* = 415)** 3.14 (3.23)	**(*n* = 407)** 3.00 (3.09)	**(*n* = 405)** 2.89 (3.31)	**(*n* = 414)** 3.23 (3.34)	**(n = 823)** 2.85 (2.81)	**(*n* = 822)** 2.80 (2.64)	**(*n* = 3286)** 2.94 (3.00)
Number of urgency (Grade 3 or 4) episodes/24 h, mean (SD)	**(*n* = 417)** 6.52 (4.05)	**(*n* = 409)** 6.22 (3.89)	**(*n* = 411)** 6.46 (4.88)	**(*n* = 415)** 6.48 (3.88)	**(*n* = 827)** 6.22 (3.70)	**(*n* = 826)** 6.22 (3.56)	**(*n* = 3305)** 6.32 (3.92)
Number of nocturia episodes/24 h, mean (SD)	**(*n* = 368)** 1.57 (1.06)	**(*n* = 344)** 1.53 (1.02)	**(*n* = 356)** 1.59 (1.09)	**(*n* = 352)** 1.59 (0.96)	**(*n* = 710)** 1.56 (1.07)	**(*n* = 704)** 1.52 (0.97)	**(*n* = 2834)** 1.56 (1.03)

*BMI, body mass index; M, mirabegron; S, solifenacin; *n = 422; †n = 3397.*

Sensitivity analyses of co-primary efficacy variables

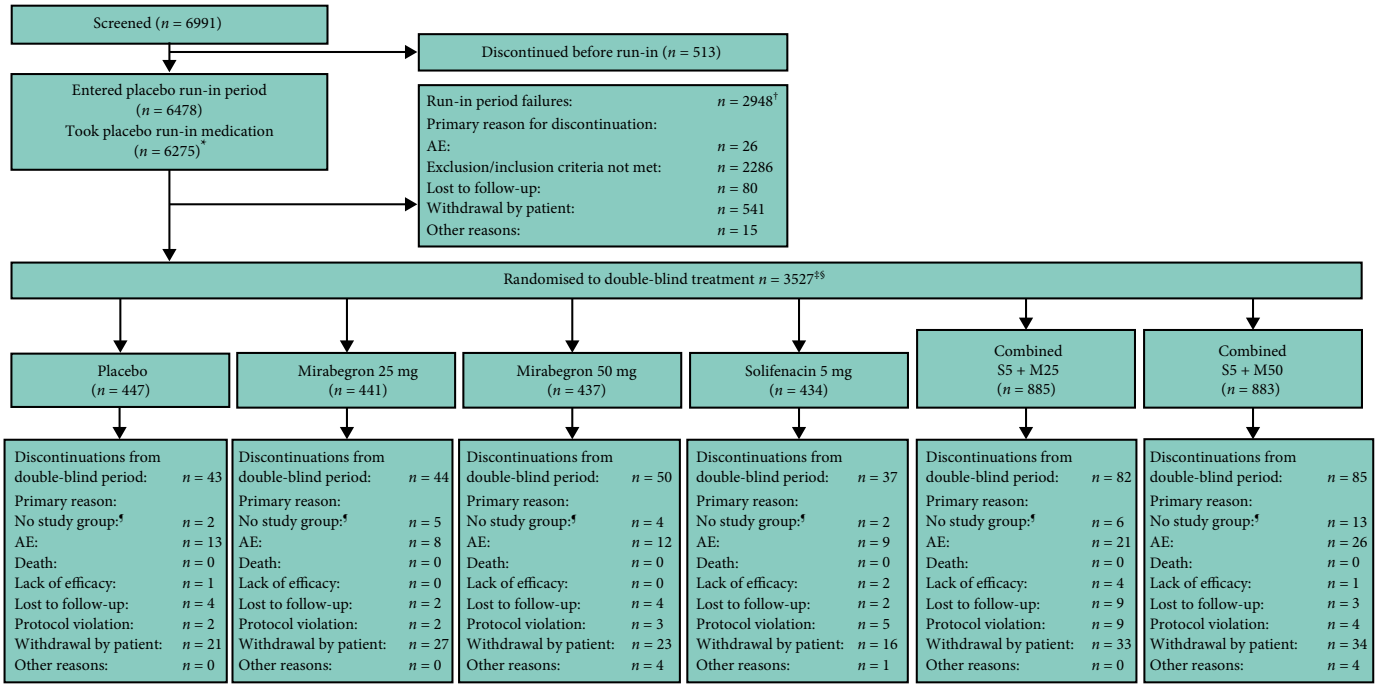
In sensitivity analyses, change from baseline in the mean number of micturitions/24 h and UI episodes/24 h generally showed consistent results for the effect size; some exceptions can be found (supplementary data online entitled Fig. S3).

Key secondary efficacy variables

The MVV/micturition at baseline was similar across treatment groups. The EoT values increased with respect to baseline for all treatment arms. The mean adjusted change from baseline to EoT was greater in the combined S5 + M25 group and combined S5 + M50 group (34.84 mL and 39.73 mL, respectively) vs solifenacin 5 mg (30.99 mL), mirabegron 25 mg (13.32 mL), mirabegron 50 mg (21.99 mL), and placebo (8.44 mL) (Fig. 2C).

Improvements in mean adjusted difference in the MVV/micturition for the combined S5 + M50 group vs solifenacin 5 mg and mirabegron 50 mg were 8.75 mL (nominal $P = 0.005$) and 17.74 mL (nominal $P < 0.001$), respectively. The combined S5 + M25 group showed an improvement of 21.52 mL (nominal $P < 0.001$) vs mirabegron 25 mg and 3.85 mL vs solifenacin 5 mg (nominal $P > 0.05$). All active treatment groups except mirabegron 25 mg had

Fig. 1 Patient disposition. *Excludes one patient who entered the placebo run-in period but did not take placebo run-in medication, and did not have end of run-in page provided but was randomised. †Excludes four patients who did not have end of run-in page provided. ‡Includes one patient who entered the placebo run-in period but did not take placebo run-in medication, and did not have end of run-in page provided but was randomised. §Patients from one site were excluded from the SAF and FAS due to protocol non-compliance. ¶Randomised/registered but never received/dispensed study drug.



improvements in the MVV/micturition vs placebo with nominal P values of <0.05. The effect size was largest in the combined S5 + M50 group (31.29 mL, nominal $P < 0.001$) and smallest in the mirabegron 25 mg group (4.88 mL, nominal $P = 0.178$). The effect size in the combined therapy groups was close to additive.

Other secondary efficacy variables

The combined S5 + M50 group was superior to both monotherapy groups at EoT for UUI episodes, urgency episodes and nocturia; effect sizes appeared to be additive. The combined S5 + M25 group was superior to mirabegron 25 mg for the same variables, except nocturia. In responder analyses at EoT, odds ratios in favour of both combined therapies vs the monotherapy components were shown for the proportion of patients with zero UI episodes (Table 2) and those achieving micturition frequency normalisation (Table 3).

For almost all parameters, differences were significant for combined therapy at week 4, and thereafter remained fairly constant vs monotherapy and placebo. All active treatment groups had nominal P values of < 0.05 compared with placebo at all time-points (more detailed data provided online as Table S3/Fig. S4).

A substantially greater effect of both combinations was observed in the pre-specified analysis of patients who received previous OAB treatment compared with treatment-naïve patients (Fig. 3 and supplementary data online entitled Table S4).

Pre-defined subgroup analysis of the mean number of UI episodes/24 h showed that patients who received previous OAB treatment had a considerably larger effect size on combined therapy vs monotherapy than treatment-naïve patients, except for the comparison of the combined S5 + M25 group vs mirabegron. In the subgroup of previously treated patients, the 95% CIs for the differences of combined therapy vs both monotherapy components excluded zero, except for the comparison of the combined S5 + M25 group vs mirabegron. Analysis of the mean number of micturitions/24 h showed that patients who received previous OAB treatment had a more than twice as high effect size of combined therapy vs monotherapy than treatment-naïve patients. In previously treated patients the 95% CIs for the differences of combined therapy vs both monotherapy components excluded zero, except for the comparison of the combined S5 + M25 group vs solifenacin (−0.81, 0.00).

An analysis of the MVV/micturition showed that patients who received previous OAB treatment had a much larger

Fig. 2 Adjusted change from baseline to EoT in (**A**) mean number of UI episodes/24 h, (**B**) mean number of micturitions/24 h, and (**C**) MVV/micturition. M, mirabegron; S, solifenacin.

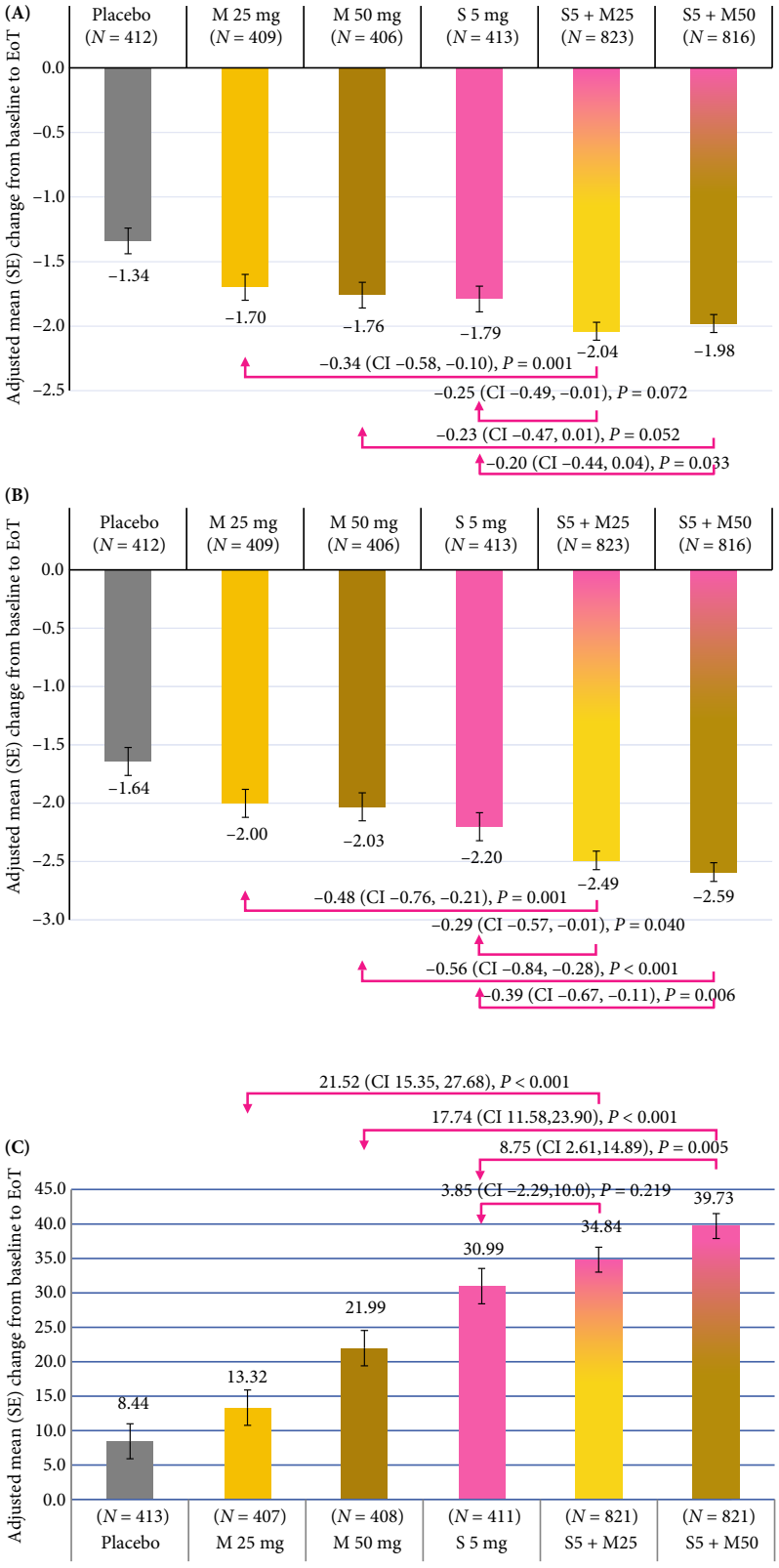


Table 2 Responders for zero UI episodes/24 h at EoT using the last 3 diary days.

	Treatment group					
	Placebo (*n* = 412)	**M 25 mg (*n* = 409)**	**M 50 mg (*n* = 406)**	**S 5 mg (*n* = 413)**	**S5 + M25 (*n* = 823)**	**S5 + M50 (*n* = 816)**
Responders, *n* (%)	155 (37.6)	166 (40.6)	188 (46.3)	177 (42.9)	417 (50.7)	426 (52.2)
Difference vs S, %	NA				7.8	9.3
95% CI					(1.9, 13.7)	(3.5, 15.2)
Odds ratio vs S	NA				1.31	1.40
95% CI					(1.02, 1.69)	(1.09, 1.81)
P					0.035*	0.009*
Difference vs M, %	NA				10.1	5.9
95% CI					(4.2, 15.9)	(0.0, 11.8)
Odds ratio vs M	NA				1.50	1.34
95% CI					(1.16, 1.93)	(1.04, 1.73)
P					0.002*	0.023*
Difference vs placebo, %	NA	3.0	8.7	5.2	13.0	14.6
95% CI		(−3.7, 9.6)	(1.9, 15.4)	(−1.4, 11.9)	(7.3, 18.8)	(8.8, 20.4)
Odds ratio vs placebo	NA	1.17	1.40	1.34	1.75	1.87
95% CI		(0.87, 1.57)	(1.04, 1.87)	(0.99, 1.79)	(1.36, 2.26)	(1.45, 2.42)
P		0.300	0.027*	0.055	<0.001*	<0.001*

*M, mirabegron; S, solifenacin; *P < 0.05. Odds ratio and P values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 years), previous OAB medication (yes, no) and geographic region as factors and baseline mean number of UI episodes/24 h during the last 3 days as a covariate. The two-sided P value is for pairwise comparisons between the combined therapy/active group and the corresponding monotherapy/placebo group from the same logistic regression model.*

Table 3 Responders for micturition frequency normalisation at EoT.

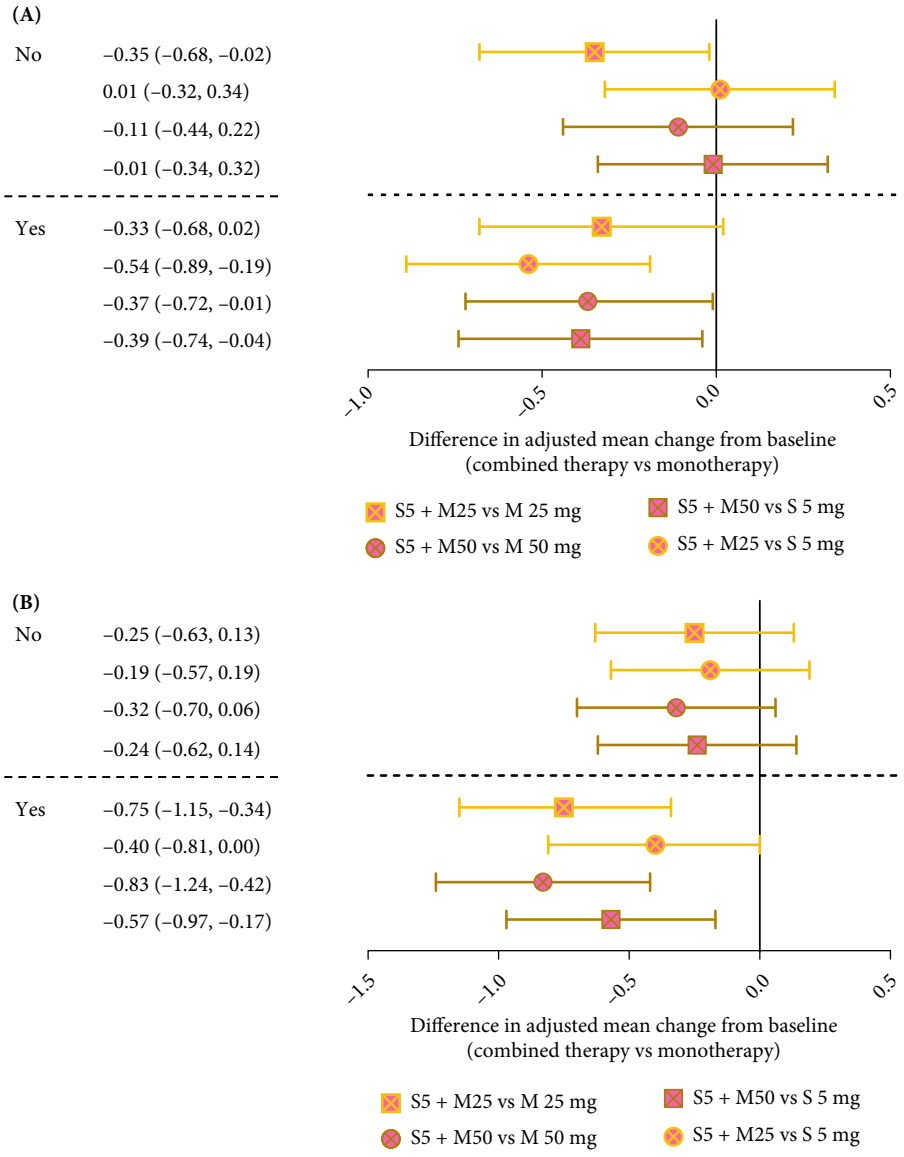
	Treatment group					
	Placebo (*n* = 412)	**M 25 mg (*n* = 409)**	**M 50 mg (*n* = 406)**	**S 5 mg (*n* = 413)**	**S5 + M25 (*n* = 823)**	**S5 + M50 mg (*n* = 816)**
Responders, *n* (%)	128 (31.1)	172 (42.1)	163 (40.1)	186 (45.0)	422 (51.3)	429 (52.6)
Difference vs S, %	NA				6.2	7.5
95% CI					(0.4, 12.1)	(1.6, 13.4)
Odds ratio vs S	NA				1.30	1.43
95% CI					(1.01, 1.67)	(1.11, 1.84)
P					0.044*	0.006*
Difference vs M, %	NA				9.2	12.4
95% CI					(3.3, 15.1)	(6.6, 18.3)
Odds ratio vs M	NA				1.47	1.60
95% CI					(1.13, 1.90)	(1.23, 2.08)
P					0.004*	<0.001*
Difference vs placebo, %	NA	11.0	9.1	14.0	20.2	21.5
95% CI		(4.4, 17.5)	(2.5, 15.6)	(7.4, 20.5)	(14.6, 25.8)	(15.9, 27.1)
Odds ratio vs placebo	NA	1.66	1.67	1.87	2.43	2.67
95% CI		(1.22, 2.25)	(1.23, 2.27)	(1.38, 2.54)	(1.86, 3.18)	(2.04, 3.49)
P		0.001*	0.001*	<0.001*	<0.001*	<0.001*

*M, mirabegron; S, solifenacin; *P < 0.05. Odds ratio and P values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 years), previous OAB medication (yes, no) and geographic region as factors and baseline mean number of micturitions/24 h during the last 3 days as a covariate. The two-sided P value is for pairwise comparisons between the combined therapy/active group and the corresponding monotherapy/placebo group from the same logistic regression model.*

effect size of combined therapy vs monotherapy than treatment-naïve patients, especially for the comparison with solifenacin (17.13 and 7.46 mL for the combined S5 + M50 group and combined S5 + M25 group, respectively, for previously treated patients; 1.48 and 0.59 mL for the combined S5 + M50 group and combined S5 + M25 group, respectively, for treatment-naïve patients). In previously treated patients, the 95% CIs for the differences of combined therapy vs both monotherapy components excluded zero, except for the comparison of the combined S5 + M25 group vs solifenacin (−1.50, 16.42 mL).

Analysis of the mean number of UUI episodes/24 h showed that patients who received previous OAB treatment had a much larger effect size of combined therapy compared to monotherapy than treatment-naïve patients, especially for the comparison with solifenacin (−0.43 and −0.53 episodes for the combined S5 + M50 group and combined S5 + M25 group, respectively, for previously treated patients; −0.06 and

Fig. 3 Forest plot for treatment difference and 95% CI of adjusted change from baseline in (**A**) mean number of UI episodes/24 h at EoT by previous medication for OAB (yes, no) and (**B**) micturitions/24 h. M, mirabegron; S, solifenacin.



0.02 episodes for the combined S5 + M50 group and combined S5 + M25 group, respectively, for treatment-naïve patients). Analysis of the mean number of urgency episodes (grade 3 or 4)/24 h showed that patients who received previous OAB treatment prior to entering the study had a considerably larger effect size of combined therapy vs monotherapy than treatment-naïve patients. In previously treated patients, the 95% CIs for the differences of combined therapy vs both monotherapy components excluded zero for both UUI episodes and urgency episodes.

Although differences were small, there seemed to be a trend towards slightly higher effect sizes for endpoints related to UI and urgency (the mean number of UI episodes, mean number of UUI episodes and mean number of urgency episodes) for patients with UUI at screening compared to patients with mixed stress UI/UUI with urgency as the predominant factor.

PRO data will be presented elsewhere.

Safety

Overall, 36% (1235/3398) of patients had more than one TEAE. There was a slightly increased frequency of TEAEs in the combined therapy groups vs monotherapies and placebo (Table 4). The incidence of TEAEs was lowest in the mirabegron 25 mg group (32%) and highest in the combined

Table 4 Overview of TEAEs (Safety Analysis Set).

N (%)	Treatment group					
	Placebo (*n* = 429)	M 25 mg (*n* = 423)	M 50 mg (*n* = 422)	S 5 mg (*n* = 423)	S5 + M25 (*n* = 853)	S5 + M50 (*n* = 848)
TEAEs	145 (33.8)	135 (31.9)	147 (34.8)	149 (35.2)	345 (40.4)	314 (37.0)
Drug-related TEAEs	45 (10.5)	37 (8.7)	52 (12.3)	63 (14.9)	157 (18.4)	150 (17.7)
Serious TEAEs	8 (1.9)	6 (1.4)	5 (1.2)	3 (0.7)	12 (1.4)	19 (2.2)
Drug-related serious TEAEs	0	1 (0.2)	1 (0.2)	0	2 (0.2)	3 (0.4)
TEAEs leading to permanent discontinuation of study drug	9 (2.1)	7 (1.7)	10 (2.4)	7 (1.7)	20 (2.3)	22 (2.6)
Drug-related TEAEs leading to permanent discontinuation of study drug	7 (1.6)	4 (0.9)	6 (1.4)	5 (1.2)	17 (2.0)	19 (2.2)
UTI*	21 (4.9)	18 (4.3)	16 (3.8)	21 (5.0)	60 (7.0)	44 (5.2)
95% CI	(2.9, 6.9)	(2.3, 6.2)	(2.0, 5.6)	(2.9, 7.0)	(5.3, 8.8)	(3.7, 6.7)
Urinary retention*	0	0	0	3 (0.7)	8 (0.9)	10 (1.2)
95% CI				(0.0, 1.5)	(0.3, 1.6)	(0.5, 1.9)
Urinary retention†	0	0	0	1 (0.2)	4 (0.5)	5 (0.6)
95% CI				(0.0, 0.7)	(0.0. 0.9)	(0.1, 1.1)
Acute urinary retention†	0	0	0	0	0	1 (0.1)
95% CI						(0.0, 0.3)
Increased residual urine volume†	0	0	0	0	3 (0.4)	3 (0.4)
95% CI					(0.0, 0.7)	(0.0, 0.8)
Residual urine†	0	0	0	0	1 (0.1)	0
95% CI					(0.0, 0.3)	
Incomplete bladder emptying†	0	0	0	1 (0.2)	1 (0.1)	0
95% CI				(0.0, 0.7)	(0.0, 0.3)	0
Hypersensitivity reactions‡	4 (0.9)	4 (0.9)	4 (0.9)	3 (0.7)	9 (1.1)	4 (0.5)
95% CI	(0.0, 1.8)	(0.0, 1.9)	(0.0, 1.9)	(0.0, 1.5)	(0.4, 1.7)	(0.0, 0.9)
Glaucoma‡	0	1 (0.2)	0	0	1 (0.1)	1 (0.1)
95% CI		(0.0, 0.7)			(0.0, 0.3)	(0.0, 0.3)
Somnolence*	11 (2.6)	11 (2.6)	15 (3.6)	12 (2.8)	29 (3.4)	13 (1.5)
95% CI	(1.1, 4.1)	(1.1, 4.1)	(1.8, 5.3)	(1.3, 4.4)	(2.2, 4.6)	(0.7, 2.4)
Common antimuscarinic TEAEs*						
Dry mouth*	8 (1.9)	17 (4.0)	14 (3.3)	25 (5.9)	74 (8.7)	61 (7.2)
Blurred vision*	3 (0.7)	1 (0.2)	0	2 (0.5)	5 (0.6)	6 (0.7)
Constipation*	6 (1.4)	6 (1.4)	11 (2.6)	6 (1.4)	38 (4.5)	31 (3.7)
Dyspepsia*	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)	10 (1.2)	16 (1.9)

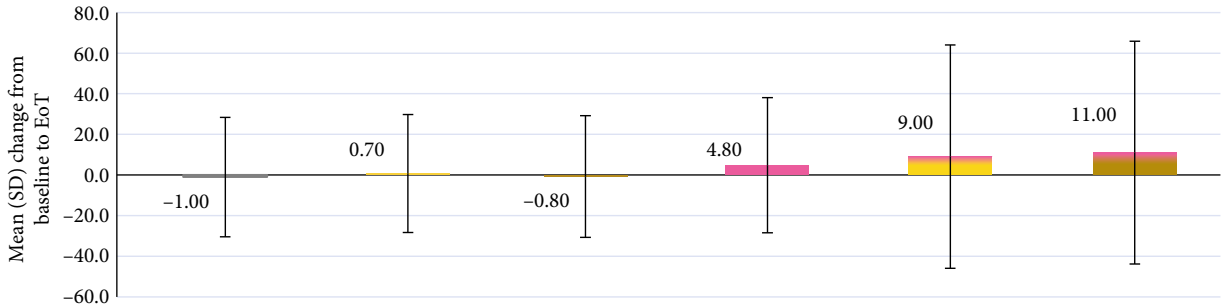
*M, mirabegron; S, solifenacin. *Based on a sponsor-defined list of Preferred Terms or Lower Level Terms (urinary retention only). †Based on Lower Level Terms. ‡Based on a standardised MedDRA query.*

S5 + M25 group (40%). The frequency of treatment-related TEAEs (as assessed by the investigator) was lowest in the mirabegron 25 mg group and highest in the combined S5 + M25 group. Most TEAEs in all treatment groups were mild or moderate in severity. There were no meaningful differences between treatment groups in the incidence of TEAEs that led to discontinuation.

The frequency of UTIs was slightly higher in the combined S5 + M25 group compared with other treatment groups, in which the frequency was similar to placebo (Table 4). Events indicative of urinary retention were reported slightly more frequently in the combined therapy groups compared with monotherapy and placebo. Four of these required catheterisation, two in the combined S5 + M25 group and two in the combined S5 + M50 group. Consistent with these findings, the PVR volume was slightly increased in the combined therapy groups compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups (Fig. 4). More patients in the combined therapy groups had a shift towards higher PVR categories. There were no notable differences between sexes. The frequency of hypersensitivity reactions was similar between groups, and only in the combined S5 + M25 group was it slightly higher than placebo and monotherapies. No increased risk of somnolence was identified with combined therapy or monotherapy compared with placebo. There were slightly higher frequencies for dry mouth, constipation, and dyspepsia in the combined therapy groups compared with each monotherapy group (Table 4).

Detailed data on vital signs and cardiovascular AEs results will be presented elsewhere. However, in brief, there were no relevant differences between active treatment groups and placebo or between combined therapy and monotherapy in site-based systolic blood pressure, diastolic blood pressure, and pulse rate. No relevant differences appeared to be present between patients using β-blockers vs patients not on β-blockers (data not shown). There were no concerns for electrocardiograms and laboratory data, including QTcF interval (QT corrected interval using Fridericia formula) and liver function tests.

Fig. 4 Change in PVR from baseline to EoT.



		Placebo (N = 429)	M 25 mg (N = 423)	M 50 mg (N = 422)	S 5 mg (N = 423)	S5 + M25 (N = 853)	S5 + M50 (N = 848)
BL	*n*	423	418	417	422	848	840
	Mean	21.3	20.0	22.5	21.1	21.3	21.4
	(SD)	30.6	27.4	32.1	29.0	29.3	29.5
EOT	*n*	415	404	406	415	822	818
	Mean	20.6	21.3	22.1	25.5	30.5	32.6
	(SD)	29.7	29.3	33.5	33.9	57.7	57.0
	95% CI	(17.8, 23.5)	(18.5, 24.2)	(18.8, 25.3)	(22.2, 28.8)	(26.6, 34.5)	(28.7, 36.5)
	Change from BL						
	n	410	401	404	414	821	815
	Mean	−1.0	0.7	−0.8	4.8	9.0	11.0
	(SD)	29.4	29.1	30.0	33.3	55.0	54.9

Discussion

In the largest OAB study to date, combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg provided improvements in efficacy compared with the respective monotherapies, with effect sizes generally consistent with an additive effect. Most effects of combined therapy vs monotherapy were observable by week 4 and had an additive effect for many parameters. The clinical relevance of the improvements seen with combined therapy for several objective OAB outcome measures was also supported by the improvements of combined therapy vs monotherapy in the responder analyses. The odds of achieving zero UI was 31–50% higher in the combined therapy groups than in the respective monotherapy groups, and the *P* values for these odds ratios were statistically significant.

Although the combined S5 + M50 group did not achieve a statistically significant effect vs mirabegron 50 mg in the primary analysis of one of the co-primary endpoints (change from baseline in the mean number of UI episodes/24 h), differences between the combined S5 + M50 group and both solifenacin 5 mg and mirabegron 50 mg groups showed nominal P values < 0.05 when expressed as change from baseline in the number of UI episodes reported in the 7-day diary. Also, improvements in efficacy of combined therapy were seen vs monotherapy for most of the other variables including the co-primary endpoint of the mean number of micturitions and the key secondary variable of MVV (except for the combined S5 + M25 group vs solifenacin 5 mg). The effect sizes of combined therapy vs placebo in general were similar to the sum of the effect sizes observed in the monotherapy groups vs placebo, indicating the additive effect of combined therapy on many parameters.

The combined S5 + M50 group appeared superior to both monotherapies at the EoT and most other time-points for UUI episodes and urgency episodes. The combined S5 + M25 group appeared superior to mirabegron 25 mg for the same variables. The improvement in the combined S5 + M50 group over monotherapy for nocturia is notable, as improvements for nocturia are uncommon. However, the effect size of −0.17 vs monotherapy is small and may not be clinically relevant.

Consistent with previous clinical studies, the proportion of women in SYNERGY was higher than men (ratio 3:1). Randomised patients in SYNERGY had an average of just over three UI episodes/24 h, comparable with just under three UI episodes/24 h for the patients with UI in the mirabegron monotherapy studies [19]. In all, 46% of patients had previously received OAB medication, compared with prior Phase III studies with mirabegron monotherapy, in which 50–60% of patients had previously received OAB medication [19]. As previously noted, there was a larger effect size in patients who had received prior OAB treatment vs

treatment-naïve patients, with nominal 95% CIs excluding zero for combined therapies vs monotherapies for the primary and key secondary endpoints. All patients in the BESIDE study had received previous anticholinergic treatment for OAB as part of the 4-week solifenacin run-in period [16].

Solifenacin at a dose of 10 mg was not included in SYNERGY. The Phase II dose-finding study (SYMPHONY) observed that the efficacy of the 10 + 25 mg and 10 + 50 mg combinations was only marginally increased above the efficacy of 5 + 50 mg combination; however, this was at the expense of an important increase in antimuscarinic side-effects in the 10 mg solifenacin combined therapy groups [14]. Therefore, it was judged that the benefit/risk of 10 mg combinations was unfavourable and these combinations were not taken to the Phase III studies, of which SYNERGY is the second.

Only patients with OAB with UI (wet OAB) were enrolled in SYNERGY, as it is expected that combined therapy in clinical practice will be used mostly in highly symptomatic patients. Nevertheless, many patients do not experience UI. Indeed, prior Phase III studies with mirabegron monotherapy included the general OAB population, of which about two-thirds of patients are not incontinent [2]. In BESIDE, patients were those remaining incontinent after 4 weeks' treatment with solifenacin 5 mg and who then received additional mirabegron. In support of the efficacy of combined therapy demonstrated in SYNERGY, results from BESIDE demonstrated, with similar effect sizes, that combined therapy with solifenacin and mirabegron for 12 weeks statistically significantly reduced both mean daily UUI episodes and micturition frequency in patients who remained incontinent after treatment with solifenacin 5 mg [16].

Differences between patient recruitment and study design in SYNERGY and BESIDE may partially explain the differences in the primary outcomes between the two studies, and may be clinically relevant in considering how to select patients for combined therapy. It is possible that incomplete responders may require more treatment than treatment-naïve patients and that combined therapy may therefore be more effective than monotherapy in this patient subset. Indeed, at baseline, patients who were previously treated with OAB medication had more UUI only and less mixed stress UI/UUI with urgency as the predominant factor than treatment-naïve patients.

It should be noted that for all OAB compounds the USA Food and Drug Administration (FDA) historically required all UI episodes as the primary outcome. The number of UUI episodes in SYNERGY was very similar to the total number of UI episodes, signalling that the vast majority of episodes were urgency; therefore this element does not materially affect the interpretation of the study. For unknown reasons, the effect only for UI does not seem to be fully additive. A possible mechanism could be that in most, if not all patients with UI, some degree of decreased urinary sphincter function must be present. This factor is not amenable to drug effects, which could perhaps explain the presence of a ceiling effect on UI.

In SYNERGY, the combined therapy had a similar safety profile to that expected for the monotherapy components [19,20], with no new safety findings. A similar proportion of patients discontinued from all groups and the incidence of TEAEs in the combined therapy groups (37–40%) was similar to that in the BESIDE study (36%) [16]. TEAEs of special interest (hypersensitivity, glaucoma, somnolence, and blurred vision) were reported at a similar frequency in the combined therapy groups in SYNERGY vs monotherapy groups or placebo, while there was a slightly higher frequency of UTI in the combined S5 + M25 group vs other groups. All events that could signify a potential risk of urinary retention were captured in the present study. Events indicative of urinary retention were reported slightly more frequently in the combined therapy groups vs monotherapy and placebo; however, most did not require catheterisation. Consistent with these findings, PVR was slightly increased in the combined therapy groups vs solifenacin 5 mg and mirabegron monotherapy groups. Dry mouth, constipation, and dyspepsia were also reported at a slightly higher frequency in the combined therapy groups vs monotherapy groups and placebo. However, compared with previous solifenacin 5 mg monotherapy studies, where frequencies of dry mouth, constipation and dyspepsia were around 10%, 5%, and 1% [20], the frequencies of common antimuscarinic side-effects were lower in SYNERGY. As exposures in the combined therapy groups were very similar to the monotherapies (data not shown), this increase may not be the result of a drug interaction between mirabegron and solifenacin. Of note, a previous study did appear to suggest the possibility of a drug–drug interaction between mirabegron and solifenacin at high doses [21].

In conclusion, in the present study of patients with wet OAB, who had previously been exposed to anticholinergic therapy and those who were treatment naïve, combined therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg provided improvements in efficacy compared with the respective monotherapies, with effect sizes generally consistent with an additive effect. Although the primary objective was not met, by a small margin, it approached statistical significance for one of the co-primary endpoints (UI episodes/24 h, $P = 0.052$) and the nominal P values for the other co-primary endpoint (micturitions/24 h) were < 0.05. In general, the effect size in the combined S5 + M50 group was larger and more pronounced than in the combined S5 + M25 group, with no obvious differences in safety profile. The improvements seen with combined therapy compared with monotherapy translated into significant improvements in responder rates, supporting the clinical

relevance of the effect. Solifenacin + mirabegron combined therapy once daily for 12 weeks had an acceptable safety profile without new safety concerns compared with its monotherapy components and was well tolerated, similar to the monotherapies. It should be noted that the population for the SYNERGY study was large and adequately powered, and was also clinically relevant (comprising only wet patients; a more severe group), but was otherwise very comparable with populations of previous mirabegron monotherapy studies. In addition, the monotherapies performed as expected, and the results of multiple outcome parameters (both subjective and objective) all indicated improvements with combined therapy compared with monotherapy. The most relevant OAB symptoms, urgency and UI episodes, were improved in the combined therapy vs monotherapy groups.

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Conflict of Interest

Sender Herschorn receives grants and personal fees from Astellas and Allergan; and personal fees from Pfizer and Merus. Christopher R. Chapple is a Consultant, Researcher and Speaker for Astellas, Allergan, Medtronic and Recordati; a Consultant and Speaker for Lilly; a Researcher and Speaker for Ono and Pfizer; and a Speaker for Ranbaxy. Paul Abrams is a Consultant for Astellas, Ipsen and Ferring, and a Speaker for Astellas and Pfizer. Salvador Arlandis is a Consultant for Astellas, Allergan, Medtronic, Gebro and AMS, a speaker for Astellas, Pfizer, Allergan, Medtronic, Gebro and AMS, a Researcher for Astellas, and has received a research grant from Pfizer. David Mitcheson is a Consultant, Researcher and Speaker for Astellas. Kyu-Sung Lee is a researcher for Astellas. Dudley Robinson is a consultant for Astellas, Pfizer, Allergan and Ferring and a speaker for Astellas, Pfizer, Allergan. Arwin Ridder, Matthias Stoelzel, Asha Paireddy and Rob van Maanen, are full-time employees of Astellas Pharma Europe BV.

References

1 **Drake MJ**. Do we need a new definition of the overactive bladder syndrome. ICI-RS 2013. *Neurourol Urodyn* 2014; 33: 622–4

2 **Tubaro A**. Defining overactive bladder: epidemiology and burden of disease. *Urology* 2004; 64(Suppl. 1): 2–6

3 **Bartoli S**, **Aguzzi G**, **Tarricone R**. Impact on quality of life of urinary incontinence and overactive bladder: a systematic literature review. *Urology* 2010; 75: 491–500

4 **Chiaffarino F**, **Parazzini F**, **Lavezzari M**, **Giambanco V**. Impact of urinary incontinence and overactive bladder on quality of life. *Eur Urol* 2003; 43: 535–8

5 **Coyne KS**, **Wein A**, **Nicholson S**, **Kvasz M**, **Chen CI**, **Milsom I**. Comorbidities and personal burden of urgency urinary incontinence: a systematic review. *Int J Clin Pract* 2013; 67: 1015–33

6 **Maman K**, **Aballea S**, **Nazir J et al.** Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol* 2014; 65: 755–65

7 **Sexton CC**, **Notte SM**, **Maroulis C et al.** Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract* 2011; 65: 567–85

8 **Benner JS**, **Nichol MB**, **Rovner ES et al.** Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010; 105: 1276–82

9 **Wagg A**, **Compion G**, **Fahey A**, **Siddiqui E**. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012; 110: 1767–74

10 **Wagg A**, **Diles D**, **Berner T**. Treatment patterns for patients on overactive bladder therapy: a retrospective statistical analysis using Canadian claims data. *JHEOR* 2015; 3: 43–55

11 **Chapple CR**, **Cardozo L**, **Nitti VW**, **Siddiqui E**, **Michel MC**. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 2014; 33: 17–30

12 **Wagg A**, **Franks B**, **Ramos B**, **Berner T**. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: Early experience in Canada. *Can Urol Assoc J* 2015; 9: 343–50

13 **Nitti V**, **Rovner ES**, **Franks B et al.** Persistence with mirabegron versus tolterodine in patients with overactive bladder. *Am J Pharm Benefits* 2016; 8: e25–33

14 **Abrams P**, **Kelleher C**, **Staskin D et al.** 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). *Eur Urol* 2015; 67: 577–88

15 **de Greef-van der Sandt I**, **Newgreen D**, **Schaddelee M et al.** A quantitative benefit-risk assessment approach to improve decision making in drug development: Application of a multicriteria decision analysis model in the development of combination therapy for overactive bladder. *Clin Pharmacol Ther* 2016; 99: 442–51

16 **Drake MJ**, **Chapple C**, **Esen AA et al.** Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: A randomised double-blind multicentre phase 3B study (BESIDE). *Eur Urol* 2016; 70: 136–45

17 **Notte SM**, **Marshall TS**, **Lee M et al.** Content validity and test-retest reliability of Patient Perception of Intensity of Urgency Scale (PPIUS) for overactive bladder. *BMC Urol* 2012; 12: 26

18 **Bretz F**, **Maurer W**, **Brannath W**, **Posch M**. A graphical approach to sequentially rejective multiple test procedures. *Stat Med* 2009; 28: 586–604

19 **Astellas Pharma US Inc.** MYRBETRIQ™ (mirabegron) Prescribing Information, 2012. Available at: https://www.us.astellas.com/docs/myrbetriq-full-pi.pdf. Accessed May 2017.

20 **Astellas Pharma US Inc.** VESIcare® Prescribing Information, 2016. Available at: https://www.astellas.us/docs/vesicare.pdf. Accessed May 2017.

21 **Krauwinkel WJ**, **Kerbusch VM**, **Meijer J**, **Tretter R**, **Strabach G**, **Van Gelderen EM**. Evaluation of the pharmacokinetic interaction between the β3-adrenoceptor agonist mirabegron and the muscarinic receptor antagonist solifenacin in healthy subjects. *Clin Pharmacol Drug Dev* 2013; 2: 255–63

Correspondence: Sender Herschorn, Department of Surgery/Urology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

e-mail: Sender.Herschorn@sunnybrook.ca

Abbreviations: (TE)AE, (treatment-emergent) adverse event; ANCOVA, analysis of covariance; combined S5 + M25, solifenacin 5 mg + mirabegron 25 mg; combined S5 + M50, solifenacin 5 mg + mirabegron 50 mg; EoT, end of treatment; FAS, full analysis set; HRQoL, health-related quality of life MVV, mean volume voided; OAB, overactive bladder; PRO, patient-reported outcome; PVR, post-void residual; SAF, safety population; (U)UI, (urgency) urinary incontinence.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design.
Figure S2. Testing procedure for the co-primary and key secondary variables based on the micturition diary.
Figure S3. Forest plots for treatment difference and 95% CIs of adjusted change from baseline to EoT in (A) mean number of UI episodes/24 h and (B) micturitions/24 h. ANCOVA, analysis of covariance; FAS, full analysis set; LOCF, last observation carried forward; M, mirabegron; PPS, per protocol set; S, solifenacin.
Figure S4. Adjusted change from baseline in (A) mean number of UI episodes/24 h and (B) micturitions/24 h. M, mirabegron; S, solifenacin.
Table S1. Exclusion criteria.
Table S2. Statistical analysis.
Table S3. Other secondary efficacy variables.
Table S4. Subgroup analyses by use of previous OAB medication.

