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Platinum Priority – Voiding Dysfunction

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Long-term Safety and Efficacy of Mirabegron and Solifenacin in Combination Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II)

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Abstract

Background: The long-term potential of solifenacin and mirabegron combination treatment for patients with overactive bladder (OAB) has not been previously assessed.
Objectives: To evaluate the safety and efficacy of solifenacin succinate 5 mg plus mirabegron 50 mg tablets (combination treatment) versus solifenacin or mirabegron monotherapy in patients with OAB over 12 mo.
Design, setting, and participants: Randomised, double-blind, multicentre, phase 3 trial (SYNERGY II) of patients with "wet" OAB symptoms (urinary frequency and urgency with incontinence) for ≥3 mo. The study was conducted from March 2014 to September 2016; with 1829 patients randomised. The full analysis set was comprised of 1794 patients.
Outcome measurements and statistical analysis: The primary objective was safety, measured as treatment-emergent adverse events (TEAEs). Efficacy was measured as the change from baseline to the end of treatment in the mean number of incontinence episodes/24 h and micturitions/24 h.
Results and limitations: The median age was 60 yr (range 19–86 yr) and 1434 patients (80%) were female. Overall, 856 patients (47%) experienced ≥1 TEAE. TEAE frequency was slightly higher in the combination group (596 patients, 49%; mirabegron 126 patients, 41%; solifenacin 134 patients, 44%). Serious TEAEs were reported by 67 patients (3.7%); one was considered possibly treatment-related (mirabegron group, atrial fibrillation). Dry mouth was the most common TEAE (combination 74 patients, 6.1%; solifenacin 18 patients, 5.9%; mirabegron 12 patients, 3.9%). Combination therapy was statistically superior to mirabegron and solifenacin for the number of incontinence episodes (vs mirabegron: adjusted mean difference [AMD] −0.5, 95% confidence interval [CI] −0.7 to −0.2, $p < 0.001$; vs solifenacin: AMD −0.1, 95% CI −0.4 to 0.1, $p = 0.002$) and micturitions (vs mirabegron: AMD −0.5, 95% CI −0.8 to −0.2, $p < 0.001$; vs solifenacin: AMD −0.4, 95% CI −0.7 to −0.1, $p = 0.004$).
Conclusions: Mirabegron and solifenacin combination treatment for OAB symptoms was well tolerated over 12 mo and led to efficacy improvements over each monotherapy. This innovative combination is a treatment option that could become widely used in the clinic.
Patient summary: This study looked at the safety and efficacy of a combination of solifenacin succinate 5 mg plus mirabegron 50 mg tablets over 12 mo in patients with the overactive bladder (OAB) symptoms of increased urination frequency, heightened urgency to urinate, and unintentional passing of urine. We compared this treatment with solifenacin succinate 5 mg or mirabegron 50 mg alone, and found that the combination treatment was well tolerated by patients and led to greater improvements in symptoms. This novel combination could be an improved treatment option in the clinical setting for patients with OAB.
This study is registered at ClinicalTrials.gov as NCT02045862.

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1. Introduction

Individuals are diagnosed with overactive bladder (OAB) if they experience urinary urgency, usually with increased daytime frequency and nocturia, that is not caused by a proven infection or other obvious pathology [1]. Pharmacotherapy options principally include antimuscarinics, including solifenacin, and the β_3-adrenoreceptor agonist mirabegron.

Mirabegron and solifenacin have different mechanisms of action [2,3] and co-administration appears to have no noticeable effect on their pharmacokinetics [4]. Studies have demonstrated that combination treatment for 12 wk leads to improved efficacy without a substantial impact on the safety profile when compared with monotherapy [5–7].

In the 12-wk phase 3 SYNERGY study, clinically relevant improvements in incontinence episodes and micturitions were apparent with solifenacin 5 mg in combination with mirabegron 25 or 50 mg when compared with the individual monotherapies in the general OAB population with urinary incontinence [8]. The overall safety profile was acceptable, with a slightly higher frequency of treatment-emergent adverse events (TEAEs) for the combination groups versus the monotherapies.

To address our hypothesis that the positive results from SYNERGY would be maintained in the longer term, we evaluated the safety and efficacy of combination treatment with solifenacin 5 mg and mirabegron 50 mg in comparison with each monotherapy over 12 mo in patients with OAB (SYNERGY II).

2. Patients and methods

2.1. Study design

This was a multinational, randomised, double-blind, parallel-group, active-controlled, multicentre phase 3 study in men and women with symptoms of "wet" OAB (urinary frequency and urgency with incontinence) for ≥3 mo. The study was conducted from March 2014 to September 2016 at 251 sites in 32 countries. The majority of patients were recruited from the SYNERGY [8] or BESIDE [6] studies. Demographic data were collected at screening; the inclusion and exclusion criteria are presented in Supplementary Table 1.

SYNERGY II comprised a single-blind, 2-wk placebo run-in (to washout prior OAB treatment); a randomised, double-blind, active-controlled, 12-mo treatment period; and a 2-wk follow-up during which no OAB treatments were permitted (Fig. 1). Eligible patients were randomised 4:1:1 into the treatment period and received solifenacin succinate 5 mg plus mirabegron 50 mg (combination 5 + 50 mg), solifenacin succinate 5 mg, or mirabegron 50 mg. Patients took two tablets orally per day; placebo and the corresponding active tablets were indistinguishable in appearance and shape.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and International Council for Harmonisation guidelines. An independent ethics committee or institutional review board reviewed the ethical, scientific, and medical appropriateness of the study at each site. Signed informed consent forms were obtained before any study-related procedures were performed.

2.2. Safety assessments

Evaluation of safety was the primary study objective. The frequency of TEAEs was assessed throughout the study, including TEAEs of special interest. Site-based vital sign, laboratory, electrocardiogram, and postvoid residual (PVR) volume assessments were also conducted. Deaths and serious potential cardiovascular events were categorised as major adverse cardiovascular events (MACEs), non-MACEs, or non-cardiovascular events by an independent cardiovascular adjudication committee.

2.3. Efficacy assessments

Before each visit, patients completed a micturition eDiary using a validated electronic handheld device for 7 consecutive days (3 d for volume voided). The primary efficacy variables were change from baseline to the end of treatment (EOT) in mean number of incontinence episodes/24 h and micturitions/24 h.

Secondary efficacy variables were change from baseline to EOT in mean volume voided (MVV) per micturition, overactive bladder questionnaire (OAB-q) health-related quality of life (HRQoL) total and symptom bother score, and treatment satisfaction-visual analogue scale (TS-VAS) score. Changes over time were analysed for all of the primary and secondary variables at 1, 3, 6, 9, and 12 mo, with the exception of MVV per micturition, which was assessed at 3, 6, and 12 mo only.

Responder variables included the percentage of patients with zero incontinence episodes/24 h at EOT, micturition frequency normalisation at EOT (≥8 micturitions/24 h at baseline and <8 micturitions/24 h post-baseline), and ≥10-point improvement from baseline in OAB-q HRQoL total and symptom bother scores at EOT.

2.4. Statistical analyses

All statistical analyses were performed using SAS version 9.3 or higher (SAS, Cary, NC, USA). Using a randomisation ratio of 4:1:1 and assuming that 1200 and 300 patients were enrolled in the combination and monotherapy groups, respectively, and that 23–25% of the patients

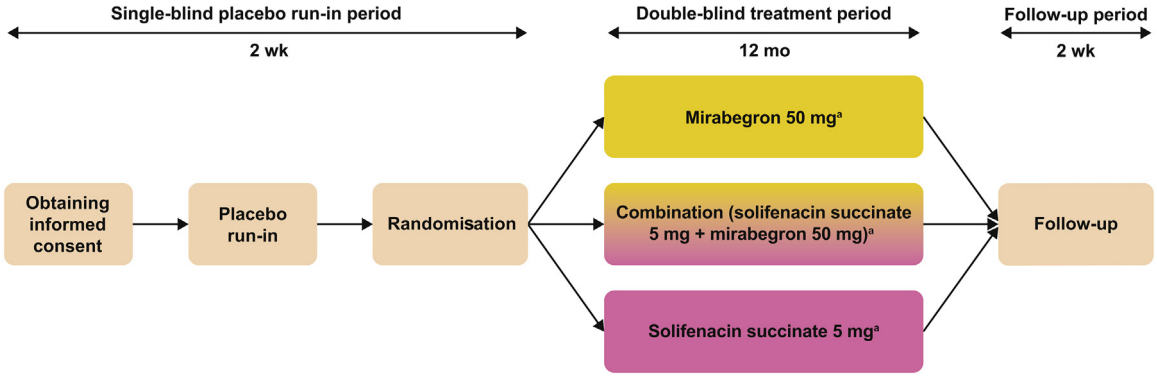

Fig. 1 – Study design. [a] Once daily.

would not complete the study, it was possible to ensure a probability of ≥90% for observing ≥1 case of a TEAE with a true frequency of ≥1/300 (combination) or ≥1/100 (monotherapy) patients. No formal statistical analyses were performed on the safety data. The study had power of 86% for demonstrating the superiority of the combination versus each monotherapy in terms of change from baseline to EOT in mean number of incontinence episodes/24 h at a two-sided significance level of 0.05 based on a Wilcoxon rank-sum test using ordered categories. The study also had power of 88% for detecting a reduction in the mean number of micturitions/24 h by 0.55 for the combination versus each monotherapy, assuming a common standard deviation (SD) of 2.7 and power of >99% for detecting an increase in MVV per micturition of 17.3 ml in the combination arm over the monotherapy arms, assuming a SD of 50 ml.

Randomisation was stratified by sex, age group (<65 vs ≥65 yr), and geographic region (North America, Latin America, Western Europe, Eastern Europe, Asia, or Southern Hemisphere). Further details on the randomisation process are included in the supplementary material.

The change from baseline to EOT in the mean number of incontinence episodes/24 h was analysed using a stratified rank analysis of covariance (ANCOVA) for each pairwise treatment group comparison. This rank ANCOVA was used for exploratory hypothesis testing and for calculating the p values. The least-squares mean estimates and two-sided 95% confidence intervals (CIs) for changes from baseline within each treatment group, as well as for differences between treatment groups, were derived from the corresponding ANCOVA model, with treatment group, sex, age group, previous study history, and geographic region as factors, and baseline value as a covariate. This ANCOVA model was also used to analyse the number of micturitions/24 h, the secondary efficacy variables, and the vital sign data. As efficacy was a secondary objective, no adjustment for multiplicity was applied. As fluid intake is a post-randomisation variable, data were not corrected for potential between-group differences.

A preplanned sensitivity analysis was performed by using a mixed-effects Poisson (negative binomial) regression model for the number of incontinence episodes at EOT, with treatment group, age group, sex, previous study history, and geographic region as factors and the number of incontinence episodes at baseline as a covariate.

3. Results

3.1. Study population

In total, 2070 patients entered the placebo run-in period, 1829 were randomised to double-blind treatment, and 1814 and 1794 were included in the safety and full analysis sets, respectively (Fig. 2). Of the patients in the full analysis set, 1622 (90%) were from the SYNERGY study, 136 (7.6%) were from BESIDE, and 36 (2.0%) were new patients. In these studies, a total of 392 patients were exposed to mirabegron, 313 to solifenacin, and 858 to combination treatment. In general, all treatment groups were similar with respect to patient demographics and baseline characteristics (Table 1).

3.2. Safety

Overall, 47% of patients (856/1814) experienced ≥1 TEAE (Table 2). The frequency of TEAEs was 49% in the combination group versus 44% and 41% in the solifenacin and mirabegron groups, respectively. Across all groups, the majority of the TEAEs were mild or moderate in severity (mild 24% of all patients, moderate 19%, severe 4.0%). There were no clinically relevant differences across groups in the frequency of TEAEs leading to permanent treatment discontinuation (difference vs combination −0.2% for mirabegron and 0.4% for solifenacin).

In total, 3.7% of patients (67/1814) reported 90 serious TEAEs (combination 4.2% of patients, each monotherapy 2.6%). Of the 12 serious cardiovascular or cerebrovascular TEAEs, 10 events were reported by eight patients (0.7%) in the combination group (one patient with two episodes of amaurosis fugax and one episode of carotid artery stenosis; two patients with events of atrial fibrillation; and one patient each with right coronary artery blockage, myocardial ischaemia, thrombosis, subdural haematoma, and cardiac arrest) and one event was reported by one patient (0.3%) each in the mirabegron (atrial fibrillation) and solifenacin (worsening hypertension) groups. In all patients, these events were confounded by a medical history of cardiovascular disease. Of the serious TEAEs reported, only one event was considered possibly treatment-related by the investigator (atrial fibrillation in the mirabegron group). Two patients died from TEAEs, one from sepsis under immunosuppression and one from a cardiac arrest (supplementary material). Neither event was considered related to study treatment by the investigator.

In terms of specific TEAEs, dry mouth was observed more frequently in the combination and solifenacin groups than in the mirabegron group. Constipation was reported more frequently following combination therapy in comparison with both monotherapies. Tachyarrhythmias were reported at a similar frequency in the combination (3.0%) and mirabegron (2.6%) groups and at a slightly higher frequency than in the solifenacin (1.0%) group. Most tachyarrhythmia events started after 3 mo of treatment without a clear temporal pattern across treatment groups. A slightly higher frequency of urinary tract infection events was reported for the combination group (8.4%) compared with the mirabegron (6.2%) and solifenacin (5.9%) groups.

No clinically relevant differences in vital signs were observed between treatment groups (mean difference [standard error] vs combination: systolic blood pressure, mirabegron −0.7 [0.7] mm Hg, solifenacin −1.1 [0.7] mm Hg; diastolic blood pressure, mirabegron −0.0 [0.5] mm Hg; solifenacin −0.1 [0.5] mm Hg; pulse rate, mirabegron −0.2 [0.5] bpm, solifenacin 0.7 [0.5] bpm; Supplementary Table 2). Increases in pulse rate of approximately 1 bpm were observed for the mirabegron and combination groups; minimal changes (0.3 bpm) were reported for the solifenacin group. Changes from baseline in systolic blood pressure were lower for the combination group compared with both monotherapy groups. No clinically relevant changes in diastolic blood pressure were observed for any treatment group.

No safety concerns were observed in laboratory parameters, including liver function tests. The incidence of QT interval prolongation TEAEs was low (mirabegron 1.0%, combination 0.2%, solifenacin 0%). The mean change from baseline in QT interval corrected for heart rate using Fridericia's formula did not show any additive or synergistic

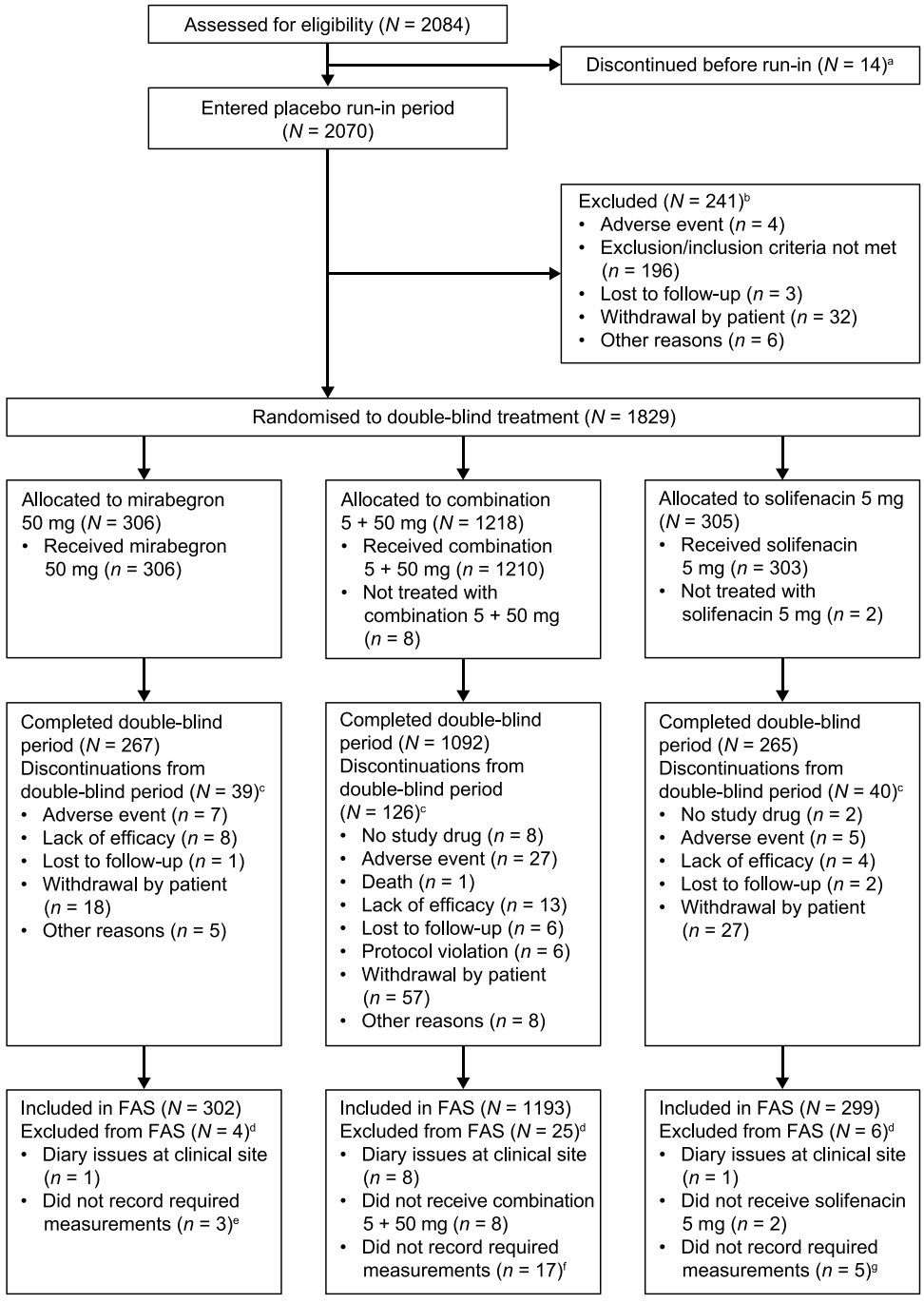

Fig. 2 – Patient disposition. FAS = full analysis set. [a] Includes patients who were dispensed a run-in study drug but did not take any. One patient should have been a screen failure but was allocated a run-in kit by mistake and was subsequently withdrawn. [b] Only the primary reason for run-in failure was collected. [c] Only the primary reason for discontinuation is included. [d] All reasons for exclusion from the FAS are shown. A patient may have more than one reason for exclusion from the FAS. [e] Did not record ≥1 micturition post-baseline (*n* = 3). [f] Did not record ≥1 micturition in the baseline eDiary (*n* = 9), ≥1 incontinence episode in the baseline eDiary (*n* = 10), or ≥1 micturition post-baseline (*n* = 15). [g] Did not record ≥1 micturition in the baseline eDiary (*n* = 2), ≥1 incontinence episode in the baseline eDiary (*n* = 2), or ≥1 micturition post-baseline (*n* = 5).

effects for the combination group beyond those of the monotherapies. The frequency of urinary retention–related TEAEs was slightly higher in the combination group (0.7%) compared with both monotherapy groups (0.3%). Concurrently, PVR volume was slightly higher in the combination group compared with both monotherapy groups at most visits.

3.3. *Efficacy*

The primary efficacy analysis showed that combination therapy was statistically superior to both monotherapies in terms of change from baseline to EOT in the mean number of incontinence episodes/24 h (adjusted mean difference [AMD]: mirabegron, −0.5, 95% CI −0.7 to −0.2, $p < 0.001$;

Table 1 – Patient demographics and baseline characteristics [a]

Parameter	Mirabegron (*n* = 302)	Combination (*n* = 1193)	Solifenacin (*n* = 299)
Sex, *n* (%)			
Male	63 (21)	239 (20)	58 (19)
Female	239 (79)	954 (80)	241 (81)
Age in yr, median (range)	61 (19–83)	60 (20–86)	60 (19–86)
<65 yr, *n* (%)	200 (66)	784 (66)	196 (66)
≥65 yr, *n* (%)	102 (34)	409 (34)	103 (34)
Race, *n* (%)			
White	262 (87)	1042 (87)	259 (87)
Black or African American	5 (1.7)	27 (2.3)	4 (1.3)
Asian	31 (10)	118 (9.9)	33 (11)
Other	4 (1.3)	6 (0.5)	3 (1.0)
Body mass index in kg/m^2, mean (SD)	29 (5.7)	29 (5.9)	28 (5.3)
Geographic region, *n* (%)			
North America	62 (21)	250 (21)	60 (20)
Latin America	1 (0.3)	4 (0.3)	3 (1.0)
Western Europe	37 (12)	147 (12)	38 (13)
Eastern Europe	167 (55)	657 (55)	164 (55)
Asia	22 (7.3)	91 (7.6)	23 (7.7)
Southern Hemisphere	13 (4.3)	44 (3.7)	11 (3.7)
Type of OAB at screening, *n* (%)			
Urgency urinary incontinence only	209 (69)	849 (71)	225 (75)
Mixed incontinence	93 (31)	344 (29)	74 (25)
Duration of "wet" OAB symptoms in mo, mean (SD)	72 (75)	73 (84)	77 (96)
Received previous OAB medications, *n* (%) [b]	159 (53)	655 (55)	165 (55)
Received previous treatment with solifenacin, *n* (%) [b,c]	84 (53)	377 (58)	72 (44)
Received previous treatment with mirabegron, *n* (%) [b,c]	15 (9.4)	71 (11)	10 (6.1)
7-d micturition eDiary baseline characteristics			
Incontinence episodes/24 h, mean (SD)	3.2 (3.6)	3.0 (3.2)	3.1 (3.6)
Micturitions/24 h, mean (SD)	10.5 (2.4)	10.6 (2.7)	10.8 (2.8)
MVV per micturition in ml, mean (SD)	161 (60)	159 (58)	161 (58)
Urgency urinary incontinence episodes/24 h, mean (SD)	2.9 (3.3)	2.7 (2.8)	2.9 (3.5)

MVV = mean volume voided; OAB = overactive bladder; SD = standard deviation.
[a] Data are shown for the full analysis set (randomised patients who took ≥1 dose of study drug and recorded ≥1 micturition and ≥1 incontinence episode in the baseline eDiary and ≥1 micturition post-baseline).
[b] Previous OAB medication was defined as medication that was received prior to starting, or after the end, of the SYNERGY [8] or BESIDE [6] studies.
[c] Percentages shown use the number of patients who had received previous OAB medications as the denominator.

solifenacin, −0.1, 95% CI −0.4 to 0.1, $p = 0.002$; 95% CIs based on ANCOVA, *p* values based on stratified rank ANCOVA) and the mean number of micturitions/24 h (AMD: mirabegron, −0.5, 95% CI −0.8 to −0.2, $p < 0.001$; solifenacin, −0.4, 95% CI −0.7 to −0.1, $p = 0.004$; 95% CIs and *p* values based on ANCOVA; Table 3). At baseline, the majority of urinary incontinence episodes were urgency urinary incontinence (Table 1).

The Poisson regression analysis of the number of incontinence episodes at EOT (reported in the 7-d eDiary) is presented in Supplementary Table 3. The rate ratios indicated that the reduction in the number of incontinence episodes was 33% and 23% greater in the combination group compared with the mirabegron group ($p < 0.001$) and the solifenacin group ($p = 0.029$), respectively.

For all the secondary variables (change from baseline to EOT in MVV per micturition, OAB-q HRQoL total and symptom bother scores, and TS-VAS score), statistically superior results were consistently achieved with combination therapy in comparison with the monotherapies (Table 4).

Time course analysis showed that statistically superior results were typically achieved with combination therapy compared with both monotherapies for all primary (Supplementary Fig. 1) and secondary (Supplementary Fig. 2) variables from 1 mo onwards (3 mo for MVV per micturition). The only exceptions were the OAB-q HRQoL total score results at 1, 6, and 9 mo, and the OAB-q symptom bother score results at 1 mo (all versus solifenacin).

For the majority of responder variables, statistically superior results were achieved following combination therapy compared with both monotherapies (Supplementary Table 4). The only exception was for zero incontinence episodes/24 h at EOT versus solifenacin.

4. Discussion

This large study of 1829 patients with OAB demonstrated the safety and efficacy of mirabegron and solifenacin combination therapy over a period of 12 mo. This information is key for OAB, as patients require long-term treatment to achieve adequate symptom control [9].

Consistent with the profile for each monotherapy, the combination regimen appeared to be well tolerated with no unanticipated safety findings. The slightly higher frequency of TEAEs in the combination group compared with the monotherapy groups agrees with the findings from the previous 12-wk SYNERGY study [8].

Table 2 – Overview of treatment-emergent adverse events (TEAEs) [a]

TEAE	Patients, *n* (%)		
	Mirabegron (*n* = 305)	Combination (*n* = 1206)	Solifenacin (*n* = 303)
TEAE	126 (41)	596 (49)	134 (44)
Drug-related TEAE	35 (11)	200 (17)	42 (14)
Serious TEAE	8 (2.6)	51 (4.2)	8 (2.6)
Drug-related serious TEAE	1 (0.3)	0	0
TEAE leading to permanent discontinuation of study drug	7 (2.3)	25 (2.1)	5 (1.7)
Drug-related TEAE leading to permanent discontinuation of study drug	4 (1.3)	17 (1.4)	4 (1.3)
Deaths	1 (0.3)	1 (0.1)	0
TEAEs by preferred term (≥1.0% for any group)			
Dry mouth	12 (3.9)	74 (6.1)	18 (5.9)
Nasopharyngitis	16 (5.2)	43 (3.6)	15 (5.0)
Urinary tract infection	11 (3.6)	41 (3.4)	12 (4.0)
Constipation	3 (1.0)	40 (3.3)	7 (2.3)
Headache	5 (1.6)	35 (2.9)	5 (1.7)
Escherichia urinary tract infection	6 (2.0)	35 (2.9)	3 (1.0)
Influenza	8 (2.6)	26 (2.2)	9 (3.0)
Bronchitis	12 (3.9)	24 (2.0)	5 (1.7)
Hypertension	4 (1.3)	23 (1.9)	4 (1.3)
Tachycardia	5 (1.6)	23 (1.9)	1 (0.3)
Urinary tract infection, bacterial	1 (0.3)	26 (2.2)	1 (0.3)
Upper respiratory tract infection	5 (1.6)	11 (0.9)	8 (2.6)
Back pain	6 (2.0)	14 (1.2)	0
Cystitis	2 (0.7)	12 (1.0)	5 (1.7)
Arthralgia	2 (0.7)	14 (1.2)	2 (0.7)
Cough	5 (1.6)	9 (0.7)	4 (1.3)
Dizziness	4 (1.3)	13 (1.1)	0
Pain in extremity	3 (1.0)	9 (0.7)	5 (1.7)
Osteoarthritis	1 (0.3)	13 (1.1)	2 (0.7)
Pharyngitis	1 (0.3)	10 (0.8)	5 (1.7)
Diarrhoea	3 (1.0)	8 (0.7)	4 (1.3)
Sinusitis	4 (1.3)	4 (0.3)	0
TEAEs of special interest			
Hypertension [b]	4 (1.3)	23 (1.9)	4 (1.3)
Increased blood pressure [c]	6 (2.0)	30 (2.5)	7 (2.3)
QT interval prolongation [c]	3 (1.0)	3 (0.2)	0
Tachyarrhythmias (increased heart rate, tachycardia, atrial fibrillation and palpitations) [c]	8 (2.6)	36 (3.0)	3 (1.0)
Urinary tract infection [d]	19 (6.2)	101 (8.4)	18 (5.9)
Urinary retention [d]	1 (0.3)	9 (0.7)	1 (0.3)
Hypersensitivity reactions [c]	3 (1.0)	16 (1.3)	0
Glaucoma [c]	0	3 (0.2)	0
Somnolence [d]	14 (4.6)	63 (5.2)	8 (2.6)

[a] TEAEs were coded using Medical Dictionary for Regulatory Activities v.16.0 and were summarised by system organ class and preferred term. Data are shown for the safety analysis set (randomised patients who took ≥1 dose of study drug). Evaluating the safety of the combination regimen and both monotherapies was the primary objective of this study.
[b] Based on the preferred term.
[c] Based on a standard Medical Dictionary for Regulatory Activities query.
[d] Based on a sponsor-defined list of preferred terms.

Although the frequency of serious TEAEs was low, the slightly higher incidence observed for the combination group compared with the monotherapy groups may be explained by the unequal 4:1:1 randomisation. This ensured that the safety of combination treatment was adequately studied, but increased the probability of observing rare background events. For example, osteoarthritis, cholecystectomy, cholelithiasis, and clavicle fracture were each only reported by two combination-group patients (not considered to be treatment-related). No clustering around specific serious events was noted.

Owing to the presence of β_3-adrenoreceptors in cardiovascular tissues [10], there is a concern that mirabegron may have an effect on the cardiovascular system [11]. Although the frequency of serious cerebrovascular and cardiovascular events was marginally higher with combination treatment, it was not possible to draw any conclusions because of the low number of patients affected, the substantial confounders present, and the potential bias of the unequal randomisation. Our findings are consistent with a subanalysis from the SYNERGY study that reported generally comparable cardiovascular safety following combination and monotherapy treatment [12].

Despite the longer treatment period, similar incidence rates for the anticholinergic-associated events of dry mouth (6.1%) and constipation (3.3%) were observed following combination treatment in this study and previous 12–16-wk trials involving similar regimens (dry mouth 0–13%, constipation 1.3–5.4%) [5,6,8,13]. This finding might be explained by a number of possibilities: longer-term

Table 3 – Change from baseline to EOT in mean number of incontinence episodes/24 h and mean number of micturitions/24 h [a]

	Mirabegron (n = 301)	Combination (n = 1184)	Solifenacin (n = 297)
Incontinence episodes/24 h			
Baseline, mean (SE)	3.2 (0.2)	3.0 (0.1)	3.1 (0.2)
EOT, mean (SE)	1.5 (0.2)	1.0 (0.1)	1.2 (0.1)
Adjusted change from baseline to EOT, mean (SE)	−1.6 (0.1)	−2.0 (0.1)	−1.9 (0.1)
Difference combination vs monotherapy, mean (SE)	−0.5 (0.1)	NA	−0.1 (0.1)
95% CI	−0.7 to −0.2		−0.4 to 0.1
p value	<0.001		0.002
Micturitions/24 h			
Baseline, mean (SE)	10.5 (0.1)	10.5 (0.1)	10.7 (0.2)
EOT, mean (SE)	8.4 (0.2)	8.0 (0.1)	8.5 (0.2)
Adjusted change from baseline to EOT, mean (SE)	−2.1 (0.1)	−2.6 (0.1)	−2.2 (0.1)
Difference combination vs monotherapy, mean (SE)	−0.5 (0.2)	NA	−0.4 (0.2)
95% CI	−0.8 to −0.2		−0.7 to −0.1
p value	<0.001		0.004

CI = confidence interval; EOT = end of treatment; NA = not applicable; SE = standard error.

[a] Data are shown for the full analysis set (randomised patients who took ≥1 dose of study drug and recorded ≥1 micturition and ≥1 incontinence episode in the baseline eDiary and ≥1 micturition post-baseline). Evaluating the efficacy of the combination regimen and both monotherapies was the secondary objective of this study. A last observation carried forward approach was applied for the analysis at EOT for patients who withdrew before 12 mo and did not have efficacy or safety measurements available for that visit. Adjusted change from baseline values as well as the 95% CIs were generated from an analysis of covariance (ANCOVA) model with treatment group, sex, age group (<65 vs ≥65 yr), previous study history, and geographic region as factors and the baseline value as a covariate. The two-sided p values were generated from pairwise comparisons between the combination therapy group and the corresponding monotherapy group from a stratified rank ANCOVA model for incontinence episodes or an ANCOVA model for micturition frequency.

Table 4 – Change from baseline to EOT in MVV per micturition, OAB-q HRQoL total score, OAB-q symptom bother score, and TS-VAS score [a]

	Mirabegron	Combination	Solifenacin
MVV per micturition in ml, *n*	289	1162	293
Baseline, mean (SE)	160 (3.5)	159 (1.7)	161 (3.4)
EOT, mean (SE)	182 (4.3)	197 (2.3)	186 (3.9)
Adjusted change from baseline to EOT, mean (SE)	21.8 (3.1)	37.7 (1.6)	24.9 (3.1)
Difference combination vs monotherapy, mean (SE)	15.8 (3.5)	NA	12.8 (3.5)
95% CI	9.0 to 22.7		6.0 to 19.6
p value	<0.001		<0.001
OAB-q HRQoL total score, *n*	290	1163	294
Baseline, mean (SE)	60.1 (1.3)	59.3 (0.7)	58.7 (1.3)
EOT, mean (SE)	76.1 (1.3)	80.6 (0.6)	77.5 (1.2)
Adjusted changed from baseline to EOT, mean (SE)	16.6 (1.0)	21.3 (0.5)	18.5 (1.0)
Difference combination vs monotherapy, mean (SE)	4.8 (1.1)	NA	2.9 (1.1)
95% CI	2.6 to 7.0		0.7 to 5.0
p value	<0.001		0.010
OAB-q symptom bother score, *n*	290	1163	294
Baseline, mean (SE)	54.2 (1.1)	55.7 (0.6)	55.2 (1.2)
EOT, mean (SE)	33.0 (1.4)	26.0 (0.6)	30.3 (1.3)
Adjusted change from baseline to EOT, mean (SE)	−22.0 (1.1)	−29.5 (0.6)	−24.9 (1.1)
Difference combination vs monotherapy, mean (SE)	−7.6 (1.3)	NA	−4.6 (1.3)
95% CIs	−10.1 to −5.1		−7.1 to −2.1
p value	<0.001		<0.001
TS-VAS score, *n*	289	1163	294
Baseline, mean (SE)	5.8 (0.2)	5.4 (0.1)	5.4 (0.2)
EOT, mean (SE)	7.8 (0.1)	8.2 (0.1)	7.6 (0.2)
Adjusted change from baseline to EOT, mean (SE)	2.2 (0.1)	2.7 (0.1)	2.2 (0.1)
Difference combination vs monotherapy, mean (SE)	0.6 (0.1)	NA	0.6 (0.1)
95% CI	0.3 to 0.8		0.3 to 0.9
p value	<0.001		<0.001

CI = confidence interval; EOT = end of treatment; HRQoL = health-related quality of life; MVV = mean volume voided; NA = not applicable; OAB-q = overactive bladder questionnaire; SE = standard error; TS-VAS = treatment satisfaction-visual analogue scale.

[a] Data are shown for the full analysis set (randomised patients who took ≥1 dose of study drug and recorded ≥1 micturition and ≥1 incontinence episode in the baseline eDiary and ≥1 micturition post-baseline). Evaluating the efficacy of the combination regimen and both monotherapies was the secondary objective of this study. A last observation carried forward approach was applied for the analysis at EOT for patients who withdrew before 12 mo and did not have efficacy or safety measurements available for that visit. Adjusted change from baseline values as well as the 95% CIs were generated from an analysis of covariance (ANCOVA) model with treatment group, sex, age group (<65 vs ≥65 yr), previous study history, and geographic region as factors and the baseline value as a covariate. The two-sided p values were generated from pairwise comparisons between the combination therapy group and the corresponding monotherapy group from the ANCOVA model.

treatment might not increase the risk of such events; most patients were enrolled from previous studies and might have developed a tolerance to treatment; and potential selection bias, as patients intolerant of such effects might be unlikely to enrol in a further study.

Slightly higher increases in pulse rate were observed in the combination and mirabegron groups compared with the solifenacin group (1.0, 1.2, and 0.3 bpm, respectively). This finding was expected given the known effect of mirabegron on heart rate [14–16].

Statistical improvements in all efficacy variables were observed with the combination regimen compared with the monotherapies. A maximal effect was generally reached by 1 mo, the first time point analysed, and was maintained throughout the study.

In support of our study, the SYNERGY study demonstrated that statistical improvements in micturitions could be achieved with combination therapy compared with the monotherapies [8]. However, the improvements observed in incontinence episodes were not statistically different between combination therapy and mirabegron in SYNERGY. In agreement with results from the BESIDE study [7], the improvements seen in the primary and secondary variables following combination therapy in this study were statistically different and considered to be clinically relevant versus both monotherapies in three of four responder analyses and versus mirabegron for incontinence responders. In particular, this 12-mo study showed that OAB-q HRQoL total score and OAB-q symptom bother score were statistically improved with combination therapy in comparison with each monotherapy at EOT.

For patients who withdrew before 12 mo without efficacy or safety measurements available for that visit, we applied a last observation carried forward approach for the EOT analysis. With low and similar discontinuation rates between treatment groups, this analysis was not expected to impact the results. A repeated-measures model used in a sensitivity analysis revealed similar 12-mo results to the EOT estimates obtained using the ANCOVA model.

Limitations of our trial include the fact that most of the patients enrolled had completed the SYNERGY [8] or BESIDE [6] studies, potentially skewing the population towards those who had experienced a favourable response and/or positive safety outcome following combination treatment or monotherapy. However, following the washout period between studies, patients had to be symptomatic and require treatment. Hence, the randomisation and double-blinding protected against bias from participation in the previous trials by excluding those whose condition improved spontaneously and removing any carryover effects. No multiplicity adjustment was applied in this study, increasing the risk of false positive findings by chance due to multiple testing. Therefore, *p* values in this study have to be considered as descriptive. Furthermore, the *p* values for the analysis of change from baseline in incontinence were calculated using a stratified rank ANCOVA because of deviations of the data from a normal distribution; CIs were approximated using an ANCOVA model. These different techniques have led to some inconsistencies between *p* values and 95% CIs for the number of incontinence episodes/24 h. A Poisson regression of the numbers of incontinence episodes was performed as a secondary analysis and demonstrated statistically greater reductions in incontinence episodes with combination therapy over both monotherapies.

5. Conclusions

This study clearly demonstrated the safety and efficacy of mirabegron and solifenacin combination therapy over 12 mo in patients with “wet” OAB, supporting the findings from previous shorter studies [5,6,8,13]. These favourable long-term data showcase the potential of this novel combination treatment option for patients with OAB in the clinical setting [17].

Author contributions: Christian Gratzke and Rob van Maanen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: van Maanen, Ridder, Paireddy, Chapple, Abrams, Herschorn, Robinson, Yoon, Al-Shukri, Rechberger, Mueller, Gratzke.
Analysis and interpretation of data: van Maanen, Ridder, Stoelzel, Paireddy, Gratzke, Abrams, Herschorn, Robinson, Mueller.
Drafting of the manuscript: van Maanen, Ridder, Stoelzel, Paireddy, Chapple, Abrams, Herschorn, Robinson, Yoon, Al-Shukri, Rechberger, Mueller, Gratzke.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.05.005.

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