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Mirabegron as Add-on Treatment to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Solifenacin Monotherapy: Responder Analyses and Patient-Reported Outcomes from the BESIDE study

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ABSTRACT (250 words; words used = 249)

Purpose: To investigate improvements in overactive bladder (OAB) and patient-reported outcomes in refractory incontinent OAB patients treated with mirabegron 50 mg plus solifenacin 5 mg vs solifenacin 5 or 10 mg.

Materials and Methods: Incontinent OAB patients, despite 4-weeks single-blind daily solifenacin 5 mg, were randomized 1:1:1 to double-blind, daily combination (mirabegron 50 mg/solifenacin 5 mg), solifenacin 5 or 10 mg for 12 weeks. Mirabegron dose was increased from 25 mg to 50 mg after week 4. Symptom Bother, health-related quality of life (HRQoL), and patient perception of bladder condition (PPBC) were assessed using respective OAB-q and PPBC questionnaires; responder rates were based on 50% reduction in daily incontinence, zero incontinence episodes and <8 micturitions/24 hours, and minimal important differences in OAB-q and PPBC.

Results: Overall 2,174 patients, median age 59 years, were randomized to combination (n=727), solifenacin 5 mg (n=728) or 10 mg (n=719). Symptom Bother, total HRQoL and its subscales (Coping, Concern, and Social) and PPBC were significantly improved with combination vs solifenacin monotherapy (P<0.05). The odds of achieving clinically meaningful improvements in incontinence and micturition frequency, Symptom Bother, HRQoL and PPBC, was significantly higher with combination vs solifenacin monotherapy. The odds (95% CI) of becoming continent was 47% (OR 1.47; 1.17, 1.84; p=0.001) and 28% (OR 1.28; 1.02, 1.61; p=0.033) higher with combination vs solifenacin 5 and 10 mg, respectively.

Conclusion: Significantly more patients on combination achieved clinically meaningful improvements in incontinence and micturition frequency, which were accompanied by similar improvements in PPBC, Symptom Bother and HRQoL.

Overactive bladder (OAB) is defined by symptoms of urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology.[1,2] Urgency urinary incontinence affects approximately one third of all OAB cases.[3] Compared with continent ("dry") OAB patients, incontinent ("wet") OAB patients experience greatly diminished quality of life (QoL), reporting higher rates of depression, psychological and emotional distress, and social isolation.[4,5] The severity of urgency urinary incontinence is strongly correlated with reductions in QoL,[6] suggesting that incontinent OAB patients who are refractory to treatment are likely to be extremely dissatisfied with their QoL. Daily activities are often severely disrupted, and incontinent patients are more likely to require assistance with daily activities, placing an additional financial burden on society.[7] OAB patients are more likely to seek treatment once symptoms affect health-related quality of life (HRQoL),[8] and to persist with treatment if HRQoL improves.[9]

Objective efficacy assessments are essential in OAB trials. However, the greatest treatment benefit experienced by patients is likely to be related to improvements in QoL. It is, therefore, equally important to assess subjective, patient-reported outcomes (PROs) including HRQoL and perception of symptoms, and how these correlate with clinically meaningful improvements in OAB symptoms. Bladder health questionnaires such as the overactive bladder questionnaire (OAB-q) assess overall HRQoL, symptom bother and domains related to daily activities, social functioning and sleep. Understanding the impact of OAB symptoms and their treatment from the perspective of the patient, in addition to

clinically relevant improvements in symptoms based on the micturition diary, will improve treatment satisfaction and the effective management of OAB symptoms.

Antimuscarinics (eg solifenacin) and the β3-adrenoceptor agonist, mirabegron, are the oral pharmacotherapies for treating OAB. Both classes of drugs exhibit similar efficacy, but unlike antimuscarinics, mirabegron is not associated with anticholinergic side effects.[10–12] Patients are usually initiated on an antimuscarinic, with dose escalation if symptom improvement is inadequate. This may increase the anticholinergic burden, the risk of bothersome side effects and treatment discontinuation.[13] Other patients may be switched to an alternative antimuscarinic or mirabegron. Those who do not meet their treatment goal with medical therapy are potential candidates for intravesical onabotulinumtoxinA, an invasive treatment that may require intermittent self-catheterization and is often characterized by a fluctuating response over time, and urinary tract infection.[14] Other alternatives include percutaneous tibial nerve stimulation and sacral nerve stimulation.[15, 16]

The BESIDE study (NCT01908829) demonstrated a significant benefit with 12 weeks' solifenacin 5 mg plus add-on mirabegron in incontinent OAB patients vs solifenacin 5 and 10 mg monotherapy in terms of improving daily incontinence, micturition frequency and urgency. Furthermore, the safety profile of the combination was similar to that of mirabegron or solifenacin monotherapy.[17]

This analysis assessed whether improvements in objective endpoints translated into improvements in subjective HRQoL endpoints. PROs were investigated using bladder health questionnaires to evaluate HRQoL, treatment satisfaction and each patient's perception of their bladder condition. In addition, responder analyses assessed the proportion of patients who achieved clinically meaningful improvements in incontinence (asymptomatic ["dry"] or

≥50% reduction in incontinence episodes) and micturition frequency (<8 micturitions/24 hours) at the end of treatment (EoT). The objectives were to compare combination (solifenacin 5 mg/mirabegron 50 mg) with solifenacin 5 and 10 mg in terms of PROs related to HRQoL, and to explore the relationship between clinically relevant improvements in PROs and in micturition frequency and incontinence.

METHODS

Study Design and Patient Demographics

In this randomized, double-blind, parallel-group, multicenter phase IIIb study, patients ≥18 years of age, with OAB for ≥3 months, including an average of ≥2 incontinence episodes/24 hours entered a 2-week screening/wash-out period to remove the effects of previous OAB medication and familiarize with the patient-recorded electronic micturition diary. After 4 weeks of single-blind daily solifenacin 5 mg, patients remaining incontinent (≥1 episode during the 3-day diary) at baseline, were eligible for double-blind treatment (Fig. 1).

Patients who satisfied inclusion and did not meet exclusion criteria (Appendix A1) were randomized 1:1:1 to 12 weeks of double-blind daily treatment with combination (solifenacin 5 mg plus mirabegron 25 mg for first 4 weeks, increasing to mirabegron 50 mg for the remaining 8 weeks), solifenacin 5 or 10 mg (Appendix A2).

Patient-reported Outcomes

QoL was assessed using the OAB-q (Symptom Bother score, total HRQoL and subscales of Coping [toilet mapping], Concern, Sleep and Social Interaction), the patient perception of bladder condition (PPBC) questionnaire, and the treatment satisfaction-visual analog scale (TS-VAS) (Table 1); the OAB-q and PPBC have been validated in OAB trials.[18-20] Questionnaire scores were recorded by the patient using an electronic handheld device at baseline, weeks 4, 8 and 12/EoT. The primary analysis was change from baseline to EoT in scores for Symptom Bother, HRQoL and subscales, TS-VAS and PPBC.

Responder Analyses

Seven responder analyses, 3 based on objective efficacy outcomes for incontinence and micturition frequency, and 4 based on PROs related to HRQoL and PPBC, were selected for inclusion. Based on the 3-day micturition diary prior to each study visit, efficacy responders were defined as patients with ≥50% decrease from baseline in mean number of incontinence episodes/24 hours at EoT, zero incontinence episodes at EoT ("dry" OAB patients), and ≥8 micturitions/24 hours at baseline and <8 micturitions/24 hours at EoT.

PRO responders were defined as a patient who achieved a change from baseline to EoT that exceeded the minimal important difference (MID) in the OAB-q or PPBC. The MID is defined as "the smallest difference in score in the domain of interest that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in patient management",[21] and equates to 10 points for the total OAB-q and its subscales (HRQoL and Symptom Bother)[22-24] and a 1-point improvement in PPBC.[20] Based on the change from baseline to EoT, PRO responders were those patients with: ≥10-point improvement in OAB-q Symptom Bother; ≥10-point improvement in OAB-q

total HRQoL score; ≥1-point improvement in PPBC; and a major (≥2-point) improvement in PPBC.

Exploratory Variables: Double and Triple Responder Analyses

Double and triple responder analyses based on a composite of efficacy (≥50% reduction in incontinence episodes/24 hours at EoT) and PROs (MIDs achieved in OAB-q [Symptom Bother and total HRQoL] and/or PPBC) were investigated as exploratory variables.

Statistical Analysis

Sample size was based on previous studies with mirabegron and mirabegron/solifenacin combination, and mirabegron 50 mg vs placebo results.[25-28] A total of 614 patients in each treatment group provided 90% power to detect a reduction of 0.50 in the mean number of daily micturitions for combination vs solifenacin 5 mg; 610 patients provided 80% power for the analysis of mean number of daily incontinence episodes and 90% power to detect a reduction of 20% in the number of incontinence episodes during the 3-day diary. Assuming 15% dropout during the double-bind period, 724 patients were to be randomized to each group.

PROs and responder analyses were assessed in the full analysis set (FAS; randomized patients who received ≥1 dose of double-blind medication, with ≥ 1 micturition and incontinence episode reported at baseline and ≥1 post baseline micturition). Changes from baseline in PPBC, Symptom Bother, HRQoL and subscales and TS-VAS scores were analyzed using an analysis of covariance model with treatment and randomization stratification

factors and baseline value as covariate. Missing EoT data were imputed using the last observation carried forward method.

For dichotomous variables (eg ≥50% decrease in incontinence episodes), the difference in the proportion of responders between combination vs solifenacin 5 or 10 mg, odds ratios, 95% confidence intervals (CIs), and p values were calculated from a logistic regression model including treatment group, randomization stratification factors (sex, age group, geographic region and 4-week incontinence episode reduction group) and baseline measurement.

A similar logistic regression model was used to analyze the proportion of double/triple responders, however, the baseline measurement was log-transformed to improve model fit. Changes and responders from baseline were only calculated if data from baseline and post baseline visits were available (Appendix A3).

RESULTS

Patient Demographics

Overall 2,174 patients were randomized to combination (n=727), solifenacin 5 mg (n=728) or solifenacin 10 mg (n=719) (Fig. 2). Patient demographics and baseline characteristics were similar across groups and included a median age 59.0 years, mean number of incontinence episodes/24 hours >3, mean number of micturitions/24 hours >8, and OAB-q scores indicative of significantly impaired QoL (Symptom Bother score >50 [scores range from 0 to 100; higher scores indicate greater symptom bother] and total HRQoL score ~60 [scores range from 0 to 100; higher scores indicate better QoL]) (Table 2).

Patient-reported Outcomes

Combination demonstrated superiority over solifenacin 5 and 10 mg for change from baseline to EoT in the Symptom Bother score, total HRQoL and subscales (with the exception of Sleep vs solifenacin 5 mg) and the PPBC (Fig. 3). The mean adjusted (95% CI) difference in the Symptom Bother score was −4.96 (−6.88, −3.04; p<0.001) and −3.30 (−5.23, −1.37; p=0.001) for the combination vs solifenacin 5 and 10 mg, respectively. The mean (95% CI) adjusted difference in the total HRQoL was 3.15 (1.35, 4.95; p=0.001) and 3.38 (1.58, 5.19; p <0.001) for the combination vs solifenacin 5 and 10 mg, respectively. The change from baseline to EoT in the TS-VAS was statistically significantly higher for combination compared with solifenacin 5 mg (Fig. 3D).

Efficacy and PRO Responder Analyses

At EoT, there were statistically significant differences in favor of combination vs both solifenacin 5 and 10 mg for the proportion of responders who became continent, and vs solifenacin 5 mg for those with a ≥50% decrease in incontinence episodes/24 hours and normalization of micturition frequency (<8 micturitions/24 hours) (Fig. 4A–C). Odds ratios for combination treatment vs solifenacin 5 and 10 mg, respectively, indicated that patients receiving combination were 47% (OR 1.47; 95% CI 1.17, 1.84; p=0.001) and 28% (OR 1.28; 95% CI 1.02, 1.61; p=0.033) more likely to achieve zero incontinence, 51% and 25% more likely to achieve a ≥50% reduction in incontinence episodes/24 hours and 29% and 12% more likely to achieve normalization of micturition frequency. There were statistically

significant odds ratios in favor of combination vs solifenacin 5 and 10 mg in the proportion of responders with ≥10-point improvement in Symptom Bother score, the total HRQoL and a major (≥2 point) improvement in PPBC (Fig. 4D–G). The odds of achieving MIDs in Symptom Bother, total HRQoL and a major improvement in PPBC, respectively, was 75%, 50% and 55% higher with combination vs solifenacin 5 mg, and 54%, 47% and 29% higher vs solifenacin 10 mg.

Exploratory Variables: Double and Triple Responder Analyses

At EoT, statistically significant improvements were demonstrated for all 5 exploratory variables in favor of the combination group vs solifenacin 5 mg, and for 3 of the 5 variables vs solifenacin 10 mg (Table 3). Compared with solifenacin 5 and 10 mg, respectively, patients on combination were 73% and 26% more likely to simultaneously achieve a ≥50% reduction in incontinence episodes/24 hours, ≥10-point improvement in Symptom Bother score, and ≥1-point improvement in PPBC, and 55% and 39% more likely to achieve this triple responder status but with a ≥10-point improvement in total HRQoL rather than Symptom Bother.

DISCUSSION

QoL encompasses socio-demographic, clinical, psychological and social factors highlighting the importance of assessing the patients' perceptions of treatment on their OAB symptoms. OAB patients with refractory incontinence are more likely to have a poor QoL and negative experience of their treatment than "dry" OAB patients.[4,5] Alternative options in patients

who do not respond to, or cannot tolerate, antimuscarinic dose escalation may involve invasive, intravesical onabotulinumtoxinA or neuromodulation therapies.

The validity of the bladder health questionnaires, OAB-q and PPBC, and the clinical utility of the respective MIDs have been confirmed in previous studies and demonstrate a strong correlation with symptom improvement based on bladder diary assessment.[18–20] Responder analyses in this study identified the proportion of patients achieving clinically meaningful improvements in subjective measures of HRQoL and treatment perception, and objective efficacy outcomes, individually or combined (double/triple responders).

In refractory incontinent OAB patients, combination significantly improved Symptom Bother, total HRQoL and its subscales vs solifenacin monotherapy, with the exception of the HRQoL subscale of "Sleep" vs solifenacin 5 mg. This may be related to the reduced treatment effect with combination and solifenacin monotherapy on nocturia, as previously reported.[17] Similar benefits were observed with combination vs solifenacin 5 mg for treatment satisfaction and patients' perception of major improvements in their condition.

A higher proportion of patients on combination compared with solifenacin 5 and 10 mg achieved clinically meaningful improvements in efficacy and PRO responder analyses, which was significant in most cases. Compared with solifenacin 5 mg, patients receiving combination were approximately 50% more likely to achieve full continence or a ≥50% reduction in incontinence. This benefit was less pronounced for micturition normalization, which may have been due to low baseline micturition frequency (~9 episodes/24 hours) resulting from the initial 4-week solifenacin 5 mg run-in period. The odds of achieving MIDs in the OAB-q (Symptom bother and total HRQoL) and a major improvement in PPBC was ≥ 50% higher with combination vs solifenacin 5 mg. The responder analyses confirm that OAB

patients who achieve significant reductions in symptoms experience significant benefits in HRQoL.

Double and triple responder analyses identified the proportion of patients who simultaneously achieved clinically meaningful improvements in incontinence, HRQoL and perception of bladder symptoms. The odds of achieving > 50% reduction in incontinence, MIDs in the OAB-q (Symptom bother and total HRQoL), and ≥ 1 point improvement in PPBC were > 50% higher with combination vs solifenacin 5 mg. The magnitude of improvements in QoL and the proportion of responders compares favorably with a *post hoc* analysis of pooled PRO data in phase III studies investigating mirabegron monotherapy and with corresponding groups in a dose-ranging phase II study of solifenacin 2.5/5/10 mg plus mirabegron 25/50 mg.[29, 30] In the primary analysis of the BESIDE study, the adverse event profile for the combination was consistent with the known profiles for mirabegron and solifenacin with no signal for new adverse events, nor was there any additive/synergistic effect on vital signs with combination.[17] The significant benefit in symptom resolution and positive patient experience in this study suggests that refractory incontinent OAB patients may be more likely to benefit with a combination of mirabegron and solifenacin rather than persisting with solifenacin 5 mg or dose escalating to solifenacin 10 mg.

Study limitations included lack of multiplicity adjustment across the PROs and responder analyses, increasing the risk of chance findings. Furthermore, like most OAB trials, the male population was underrepresented. Despite these limitations, BESIDE clearly demonstrated improved outcomes, and is the first study to explore PROs with combination therapy in a large population of refractory incontinent OAB patients. Further studies are

recommended with a larger male demographic, other antimuscarinics as active comparator, and patients with refractory urgency and/or frequency.

CONCLUSIONS

Compared with solifenacin monotherapy, combination therapy (solifenacin 5 mg and mirabegron 50 mg) was associated with clinically significant improvements in incontinence and micturition frequency, which were accompanied by clinically meaningful improvements in Symptom Bother, HRQoL and PPBC.

Words = 2502

Conflicts of Interest

Scott MacDiarmid has received consultancy and speaker fees from Astellas, Medtronic, Cogentix, and Allergan

Salman Al-Shukri, Aino Fianu-Jonasson and Philippe Grise have no financial disclosures to declare

Jack Barkin has received consultancy and speaker fees from Astellas and Pfizer

Sender Herschorn has received grants and personal fees from Astellas, Pfizer and Allergan

Tahir Saleem is a former Astellas employee

Moses Huang, Emad Siddiqui, Matthias Stölzel, Claire Hemsted, Jameel Nazir, and Zalmai Hakimi are employees of Astellas

Marcus J. Drake has received consultancy and speaker fees from Allergan, Astellas, and Ferring, and received research fees from Allergan, Astellas, Ferring, and Vysera.

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TABLES

Table 1. Summary of characteristics of bladder health questionnaires

Assessment Tool	Items	Scoring System	Clinical Relevance
OAB-q	Self-reported questionnaire comprising 33-items each rated on a 6-point Likert scale Consists of an 8-item Symptom Bother scale and 25 HRQoL items comprising 4 HRQoL subscales (Coping, Concern, Sleep and Social Interaction)	Scores are transformed onto a 0 to 100 scale Higher scores in HRQoL indicate better QoL (positive change indicates improvement) Lower scores on the Symptom Bother scale indicate a better QoL (negative change indicates improvement)	HRQoL scores are directly related to patient wellbeing; a 10-point improvement is recognized as a minimally important difference Symptom Bother scale is directly related to the degree of patient discomfort (bother) with the symptoms of OAB; a 10-point improvement is recognized as a minimally important difference[24] Validated in clinical and community settings and has demonstrated reliable internal consistency, test-retest

			reliability, construct validity and responsiveness among patients with a range of OAB symptoms[18,19, 23]
PPBC	One item questionnaire using a 6-point Likert scale, ranging from 1 “My bladder does not cause me any problems at all” to 6 “My bladder condition causes me many severe problems”	Lower scores and negative change indicates improvement in bladder condition	Indicates subjective impression of patient’s current bladder condition A 1-point and 2-point (major) improvement in PPBC are minimal important differences Offers a broad assessment of patient response that incorporates multiple elements of the disease in a simple question and has also demonstrated test-retest reliability, construct validity and responsiveness to change[20]
TS-VAS	Treatment Satisfaction Visual Analog Scale	Scale from 0 (No, not at all) to 10 (Yes, completely)	TS-VAS rates patient satisfaction with treatment

HRQoL, health-related quality of life, OAB-q, overactive bladder questionnaire, *PPBC*, patient perception of bladder condition, *TS-VAS*, treatment satisfaction-visual analog scale.

Table 2. Summary of demographics, baseline characteristics and OAB-related baseline characteristics (FAS)

	Combination N=707	Solifenacin 5 mg N=705	Solifenacin 10 mg N=698
Sex, n (%)			
Female	588 (83.2)	584 (82.8)	585 (83.8)
Male	119 (16.8)	121 (17.2)	113 (16.2)
Race, n (%)			
White	671 (94.9)	656 (93.0)	661 (94.7)
Black/African American	19 (2.7)	24 (3.4)	26 (3.7)
Asian	13 (1.8)	21 (3.0)	9 (1.3)
Other	4 (0.6)	4 (0.6)	2 (0.3)
Mean age (SD)	58.0 (13.2)	56.9 (13.4)	57.3 (13.2)
≥65 years, n (%)	223 (31.5)	214 (30.4)	214 (30.7)
≥75 years, n (%)	71 (10.0)	64 (9.1)	53 (7.6)
BMI (kg/m^2)			

Mean (SD)	29.0 (5.9)	29.1 (6.3)	29.0 (6.0)
Mean duration of OAB, months, (SD)	75.8 (86.2)	67.8 (71.6)	70.1 (77.1)
Previous OAB medication (prior to screening), n (%)	474 (67.0)	487 (69.1)	479 (68.6)
Number of previous OAB medications, n (%)			
0	233 (33.0%)	218 (30.9%)	219 (31.4%)
1	266 (37.6%)	268 (38.0%)	259 (37.1%)
2	114 (16.1%)	129 (18.3%)	116 (16.6%)
>2	94 (13.3%)	90 (12.8%)	104 (14.9%)
Previous OAB medication discontinued for [1] [2], n (%):			
Insufficient effect	423 (89.2%)	428 (87.9%)	417 (87.1%)
Poor tolerability	89 (18.8%)	96 (19.7%)	106 (22.1%)

Previous solifenacin treatment (prior to screening), n (%)	269 (38.0%)	297 (42.1%)	281 (40.3%)
Previous mirabegron treatment (prior to screening), n (%)	43 (6.1%)	39 (5.5%)	41 (5.9%)
Number of incontinence episodes during 3-day diary, mean (SD)	9.6 (8.9)	9.4 (8.1)	9.9 (9.1)
Incontinence episodes/24 hours, mean (SD)	3.23 (3.00)	3.16 (2.73)	3.31 (3.05)
Micturitions/24 hours, mean (SD)	9.12 (2.79)	8.90 (2.72)	8.96 (2.75)
TS-VAS, mean (SE) [n]	6.0 (0.1) [693]	6.0 (0.1) [683]	6.1 (0.1) [675]
PPBC, mean (SE) [n]	4.3 (0.0) [697]	4.2 (0.0) [688]	4.2 (0.0) [683]
OAB-q Symptom Bother score, mean (SE) [n]	53.51 (0.76) [694]	51.85 (0.78) [683]	52.63 (0.78) [676]
OAB-q total HRQoL, mean (SE) [n]	58.83 (0.85) [694]	59.32 (0.89) [683]	60.14 (0.87) [676]
HRQoL subscale Coping, mean (SE) [n]	52.26 (0.98) [694]	53.44 (1.01) [683]	54.09 (1.00) [676]
HRQoL subscale Concern, mean (SE) [n]	58.47 (0.95) [694]	58.73 (0.99) [683]	59.75 (0.97) [676]

HRQoL subscale Sleep, mean (SE) [n]	55.29 (0.93) [694]	56.00 (0.94) [683]	55.85 (0.94) [676]
HRQoL subscale Social, mean (SE) [n]	73.39 (0.92) [694]	72.90 (0.95) [683]	74.67 (0.91) [676]

BMI, body mass index, HRQoL, health-related quality of life, OAB, overactive bladder, *OAB-q*, overactive bladder questionnaire, *PPBC*, patient perception of bladder condition, *SD*, standard deviation. *TS-VAS*, treatment satisfaction-visual analog scale

The full analysis set (FAS) included all randomized patients who took at least 1 dose of double-blind study drug after randomization, reported at least 1 micturition and at least 1 incontinence episode in the baseline diary and at least 1 micturition post baseline.

[1] Only patients who used previous OAB medications

[2] Patients could have discontinued previous OAB medications for several reasons

Table 3. Double responder analyses at EoT: 50% reduction in mean number of incontinence episodes/24 hours and improvement ≥10 points on the Symptom Bother Scale (OAB-q); 50% reduction in mean number of incontinence episodes/24 hours and ≥ 10-point improvement on HRQoL Total score (OAB-q); 50% reduction in mean number of incontinence episodes/24 hours and ≥ 1-point improvement in PPBC; and triple responder analyses at EoT: 50% reduction in mean number of incontinence episodes/24 hours, improvement by ≥10 points on the Symptom Bother Scale (OAB-q) and ≥1-point improvement in PPBC; 50% reduction in mean number of incontinence episodes/24 hours, improvement by ≥10 points on the HRQoL Total Score (OAB-q) and ≥1-point improvement in PPBC.

	Combination (n=707)	Solifenacin 5 mg (n=705)	Solifenacin 10 mg (n=698)
Double responders at EoT			
50% reduction in incontinence and MID (≥10-point improvement) achieved on Symptom Bother score (OAB-q)			
Responders, n (%)	432 (62.2) [n=694]	342 (50.1) [n=683]	382 (56.5) [n=676]

Difference vs solifenacin 5 mg	12.17 (6.97 to 17.38)		
(95% CI)			
Odds ratio vs solifenacin 5 mg	1.66 (1.33 to 2.07)		
(95% CI)	p <0.001		
Difference vs solifenacin 10 mg	5.74 (0.55 to 10.93)		
(95% CI)			
Odds ratio vs solifenacin 10 mg	1.25 (1.00 to 1.56)		
(95% CI)	p = 0.050		
50% reduction in incontinence and MID (≥10-point improvement) achieved on total HRQoL score (OAB-q)			
Responders, n (%)	371 (53.5) [n=694]	294 (43.0) [n=683]	301 (44.5) [n=676]
Difference vs solifenacin 5 mg	10.41 (5.16 to 15.66)		
(95% CI)			
Odds ratio vs solifenacin 5 mg	1.59 (1.27 to 2.00)		
(95% CI)	p <0.001		

Difference vs solifenacin 10 mg	8.93 (3.66 to 14.20)		
(95% CI)			
Odds ratio vs solifenacin 10 mg	1.41 (1.13 to 1.77)		
(95% CI)	p = 0.003		
50% reduction in incontinence and ≥1-point improvement in PPBC			
Responders, n (%)	407 (58.4) [n=697]	337 (49.0) [n=688]	363 (53.1) [n=683]
Difference vs solifenacin 5 mg	9.41 (4.18 to 14.64)		
(95% CI)			
Odds ratio vs solifenacin 5 mg	1.49 (1.20 to 1.86)		
(95% CI)	p <0.001		
Difference vs solifenacin 10 mg	5.25 (0.01 to 10.48)		
(95% CI)			
Odds ratio vs solifenacin 10 mg	1.22 (0.97 to 1.52)		
(95% CI)	p = 0.083		
Triple responders: change from baseline to EoT			

50% reduction in incontinence, MID (≥10-point improvement) achieved on Symptom Bother score (OAB-q), ≥1-point improvement in PPBC			
Responders, n (%)	385 (55.5) [n=694]	288 (42.2) [n=683]	332 (49.1) [n=676]
Difference vs solifenacin 5 mg	13.31 (8.08 to 18.54)		
(95% CI)			
Odds ratio vs solifenacin 5 mg	1.73 (1.39 to 2.16)		
(95% CI)	p <0.001		
Difference vs solifenacin 10 mg	6.36 (1.08 to 11.64)		
(95% CI)			
Odds ratio vs solifenacin 10 mg	1.26 (1.01 to 1.58)		
(95% CI)	p = 0.037		
50% reduction in incontinence, MID (≥10-point improvement) achieved on total HRQoL score (OAB-q), ≥1-point improvement in PPBC			
Responders, n (%)	333 (48.0) [n=694]	260 (38.1) [n=683]	267 (39.5) [n=676]
Difference vs solifenacin 5 mg	9.92 (4.71 to 15.12)		
(95% CI)			

Odds ratio vs solifenacin 5 mg	1.55 (1.23 to 1.94)
(95% CI)	p <0.001
Difference vs solifenacin 10 mg	8.49 (3.25 to 13.72)
(95% CI)	
Odds ratio vs solifenacin 10 mg	1.39 (1.10 to 1.74)
(95% CI)	p = 0.005

CI, confidence interval, *EoT*, end of treatment, *HRQoL*, health-related quality of life, *MID*, minimal important difference, *OAB-q*, overactive bladder questionnaire, *PPBC*, patient perception of bladder condition.

Figure Legends

Figure 1. Study design.[17]

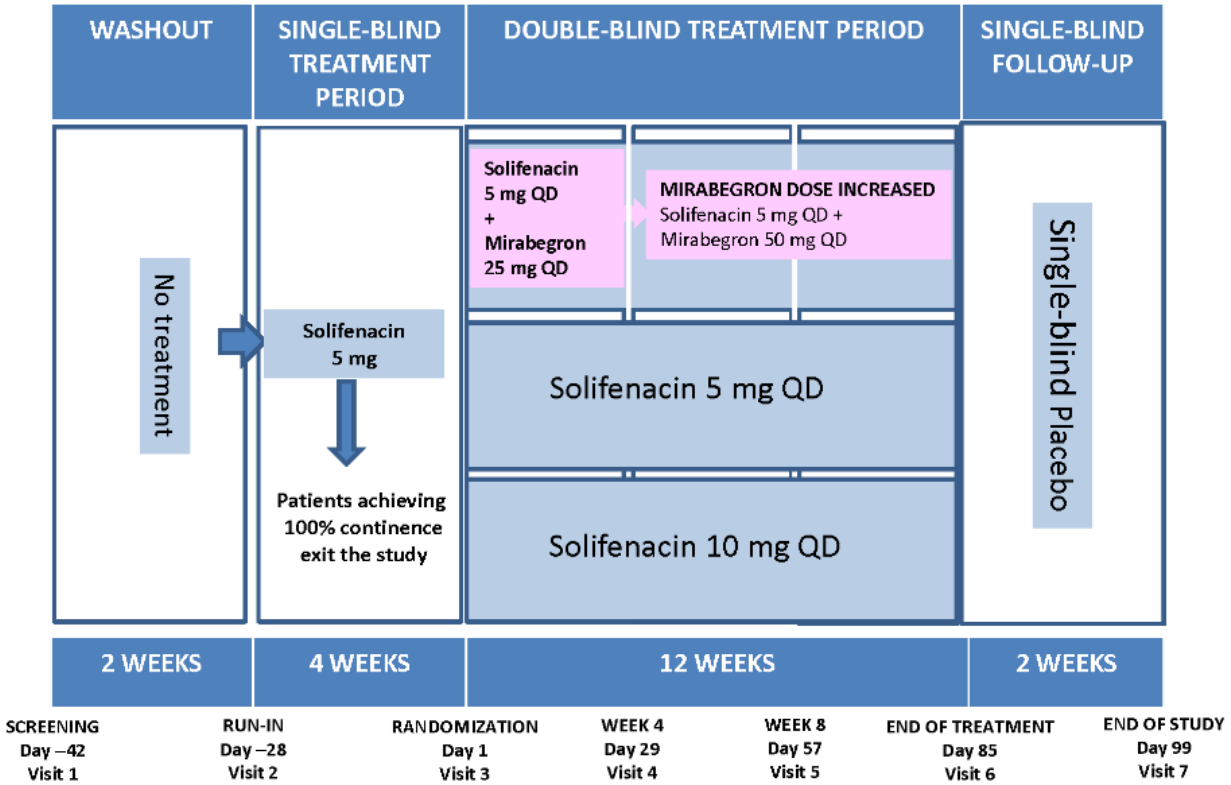


Figure 2. Patient disposition.[17]

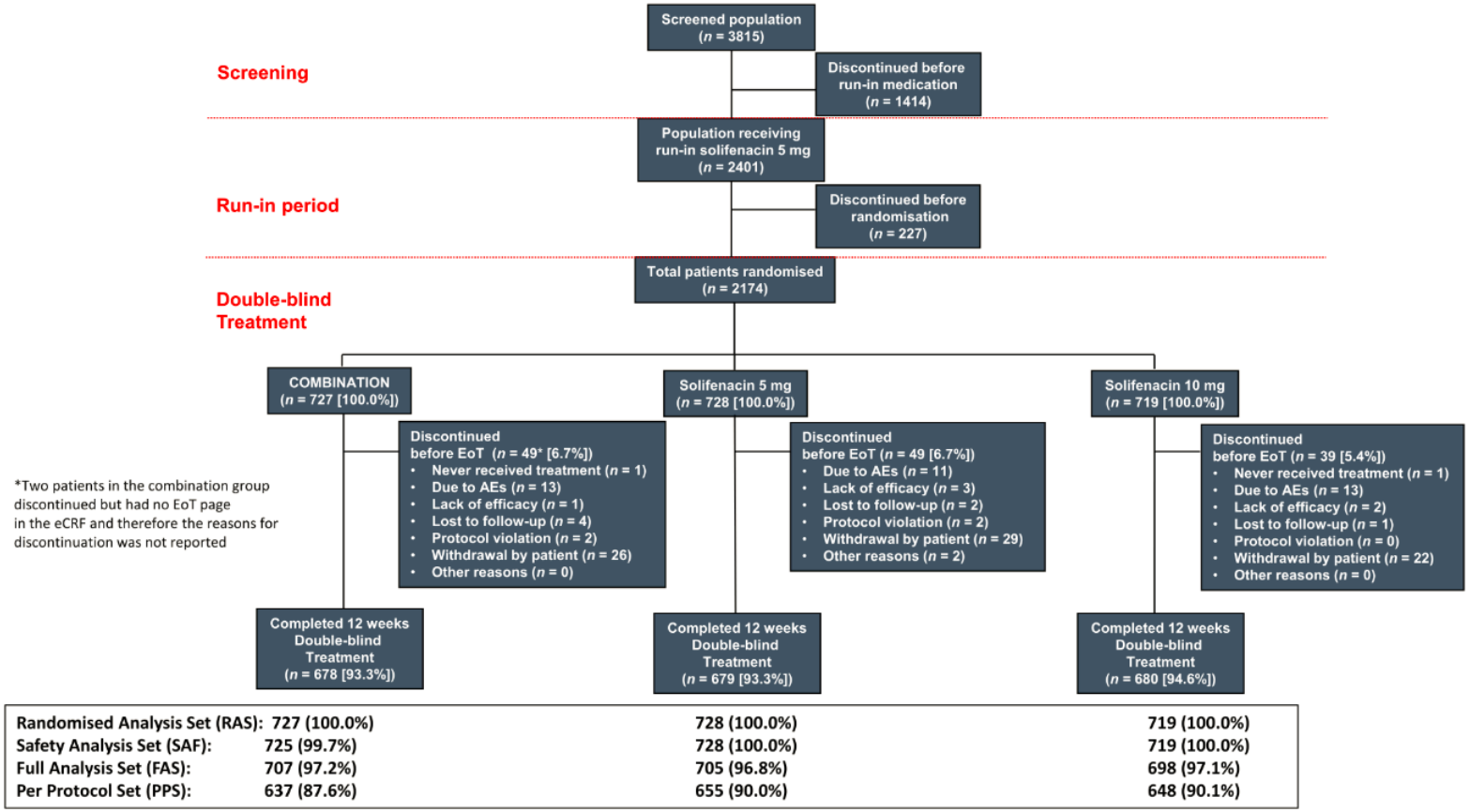
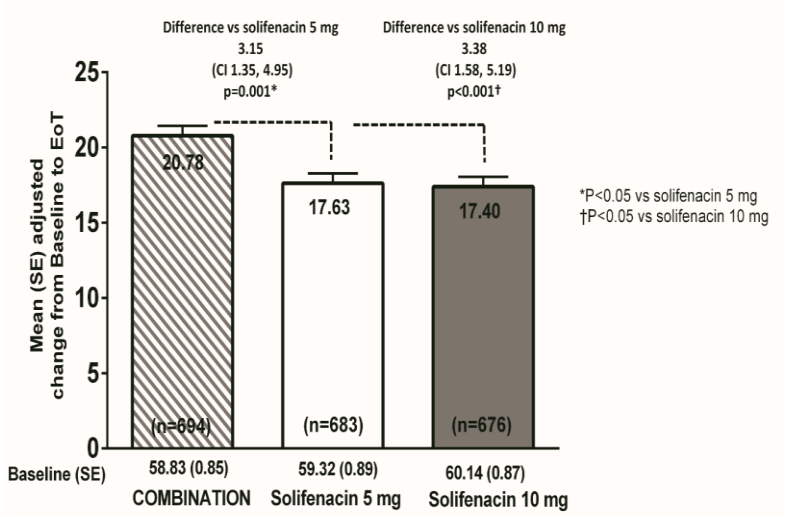
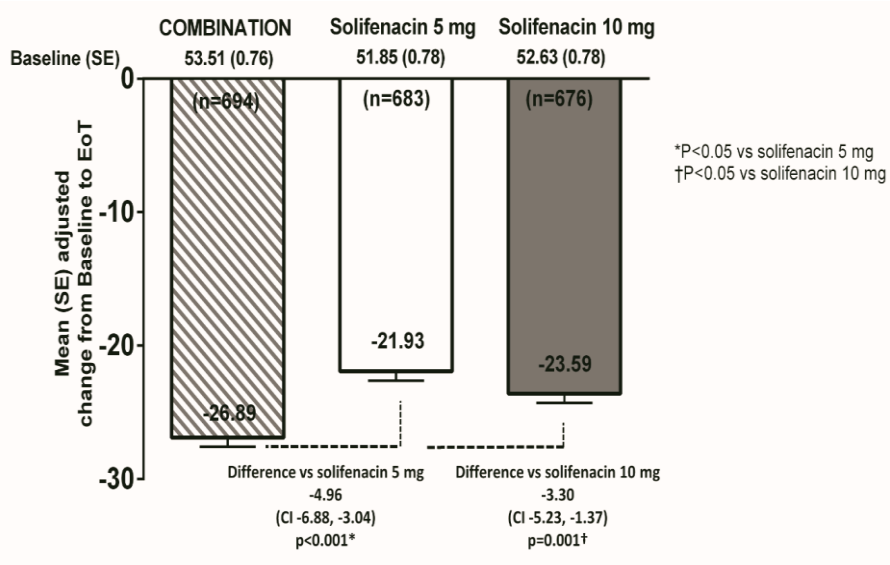


Figure 3. The adjusted mean change from baseline to EoT in patient-reported outcomes and treatment differences (95% CI and p value) vs solifenacin 5 mg and 10 mg. *A*, Total HRQoL, *B*, Symptom Bother score, *C*, HRQoL subscales (Concern, Coping, Sleep, Social), *D*, TS-VAS, *E*, PPBC.

A.

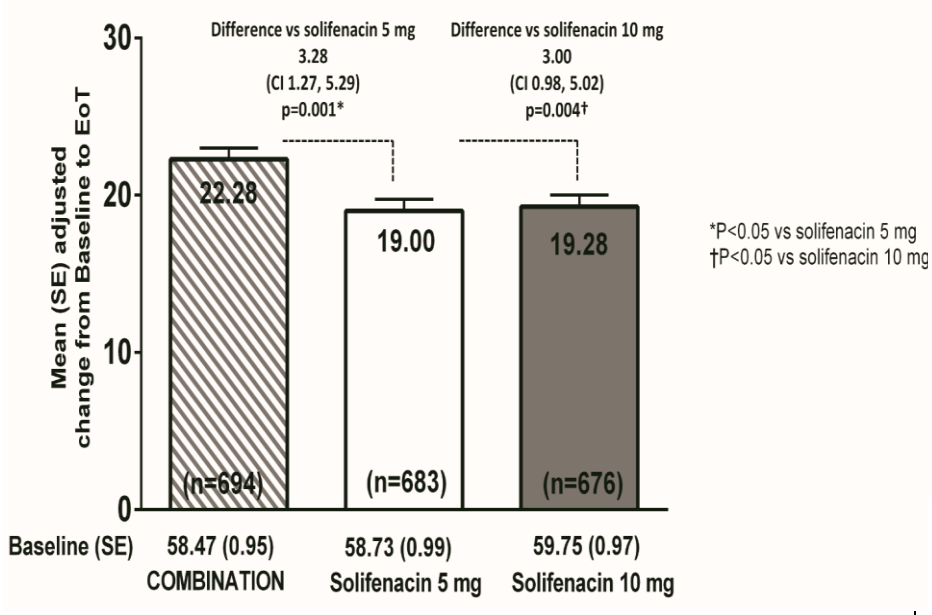


B.

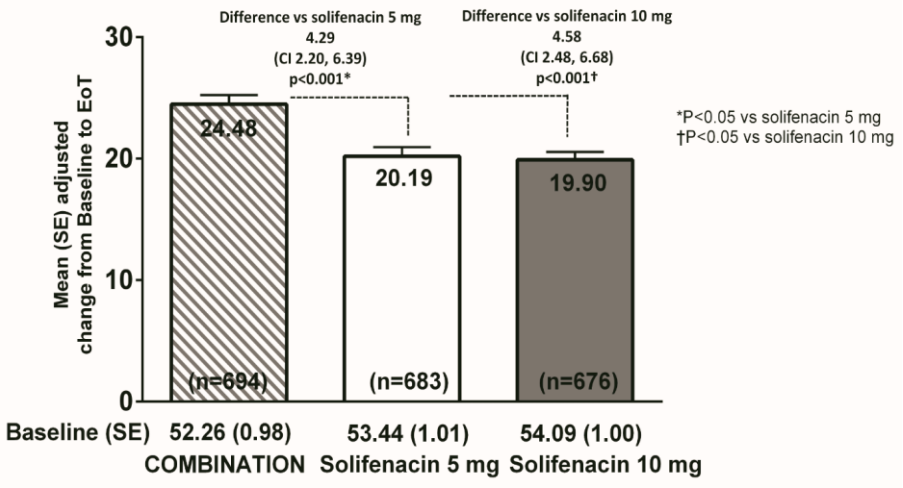


C. CONCERN

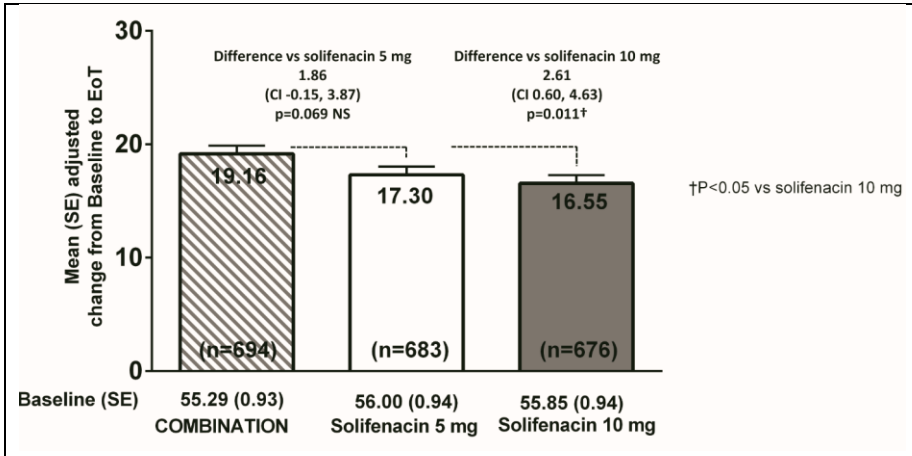
C. COPING

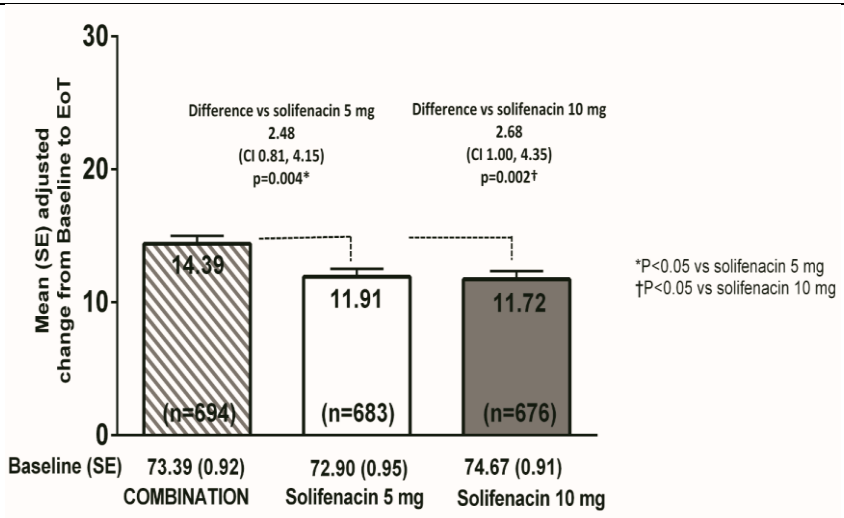


C. SLEEP

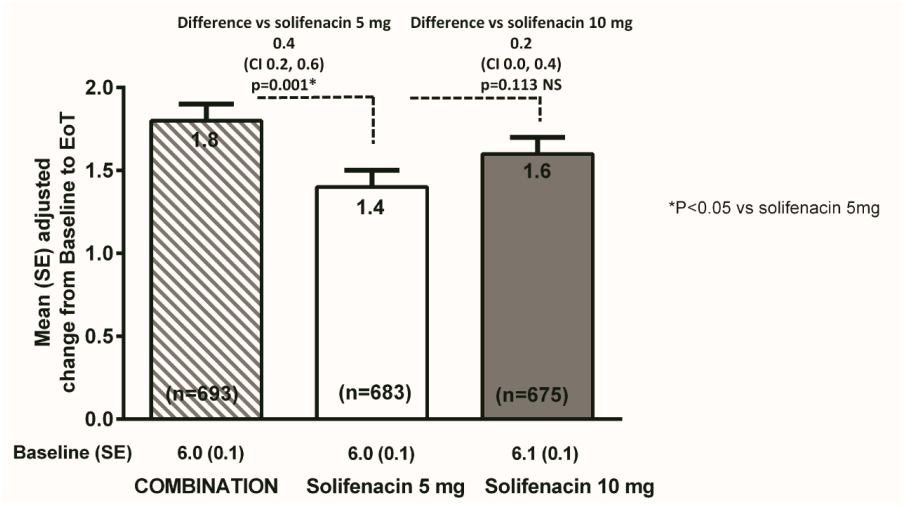


C. SOCIAL


Mean (SE) adjusted change from Baseline to EoT
30
20
10
0
Difference vs solifenacin 5 mg
1.86
(CI -0.15, 3.87)
p=0.069 NS
Difference vs solifenacin 10 mg
2.61
(CI 0.60, 4.63)
p=0.011†
19.16
17.30
16.55
(n=694)
(n=683)
(n=676)
†P<0.05 vs solifenacin 10 mg
Baseline (SE)
55.29 (0.93)
COMBINATION
56.00 (0.94)
Solifenacin 5 mg
55.85 (0.94)
Solifenacin 10 mg


Mean (SE) adjusted change from Baseline to EoT
30
20
10
0
Difference vs solifenacin 5 mg
2.48
(CI 0.81, 4.15)
p=0.004*
Difference vs solifenacin 10 mg
2.68
(CI 1.00, 4.35)
p=0.002†
14.39
11.91
11.72
(n=694)
(n=683)
(n=676)
*P<0.05 vs solifenacin 5 mg
†P<0.05 vs solifenacin 10 mg
Baseline (SE)
73.39 (0.92)
COMBINATION
72.90 (0.95)
Solifenacin 5 mg
74.67 (0.91)
Solifenacin 10 mg

D.


Difference vs solifenacin 5 mg
0.4
(CI 0.2, 0.6)
p=0.001*
Difference vs solifenacin 10 mg
0.2
(CI 0.0, 0.4)
p=0.113 NS
Mean (SE) adjusted change from Baseline to EoT
2.0
1.5
1.0
0.5
0.0
1.8
1.4
1.6
(n=693)
(n=683)
(n=675)
*P<0.05 vs solifenacin 5mg
Baseline (SE)
6.0 (0.1)
6.0 (0.1)
6.1 (0.1)
COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg

E.

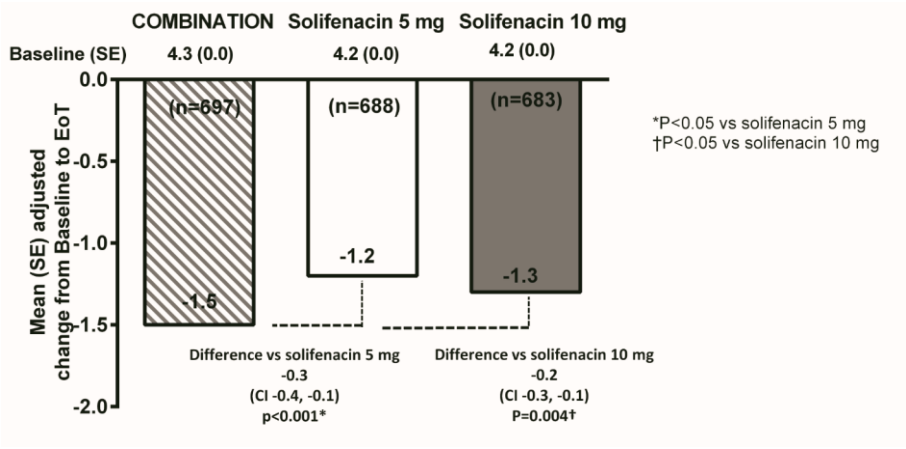
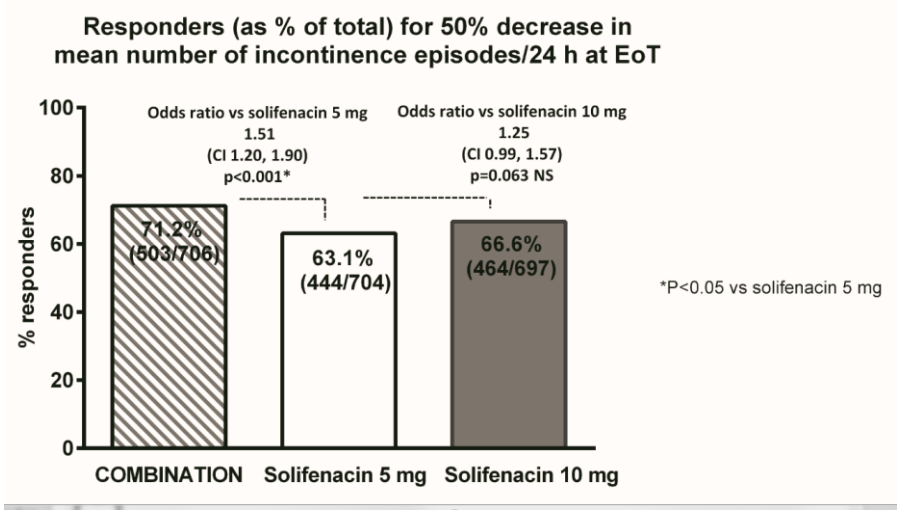
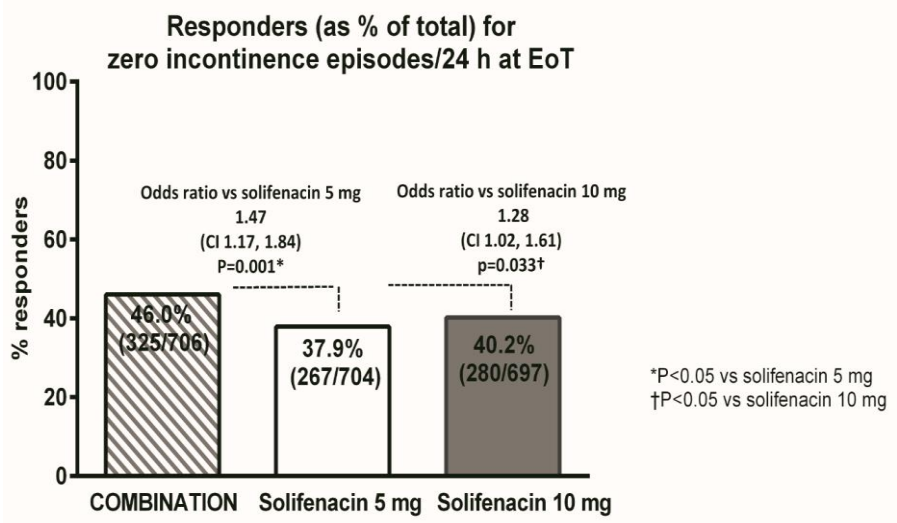

COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg
Baseline (SE)
4.3 (0.0)
4.2 (0.0)
4.2 (0.0)
Mean (SE) adjusted change from Baseline to EoT
0.0
-0.5
-1.0
-1.5
-2.0
(n=697)
(n=688)
(n=683)
-1.5
-1.2
-1.3
*P<0.05 vs solifenacin 5 mg
†P<0.05 vs solifenacin 10 mg
Difference vs solifenacin 5 mg
-0.3
(CI -0.4, -0.1)
p<0.001*
Difference vs solifenacin 10 mg
-0.2
(CI -0.3, -0.1)
P=0.004†

Figure 4. Proportion of responders at EoT with: *A*, ≥50% decrease from baseline in mean number of incontinence episodes/24 hours, *B*, zero incontinence episodes/24 hours, *C*, mean of ≥8 micturitions/24 hours at baseline and <8 micturitions/24 hours, *D*, ≥10-point improvements from baseline in OAB-q Symptom Bother score, *E*, ≥10-point improvements from baseline in HRQoL Total score, *F*, ≥1-point improvement in PPBC, *G*, ≥2-point improvement in PPBC.

A.

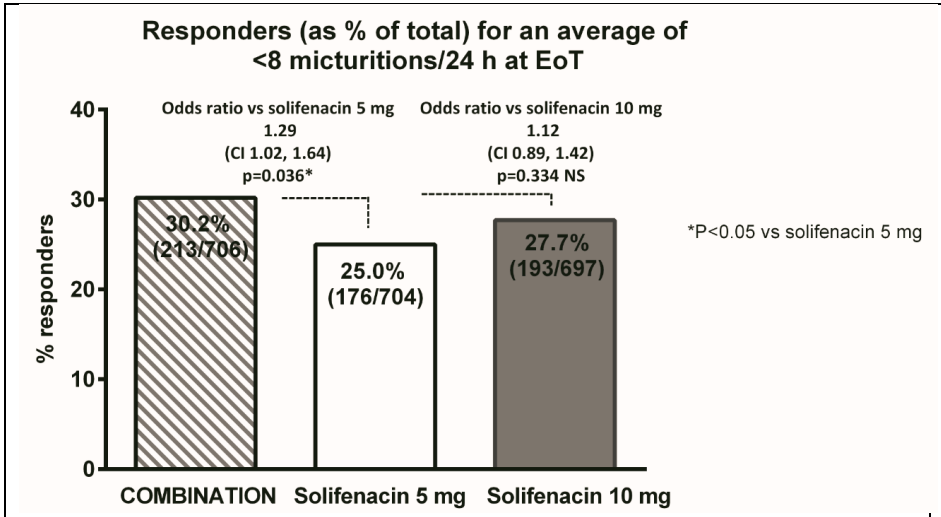


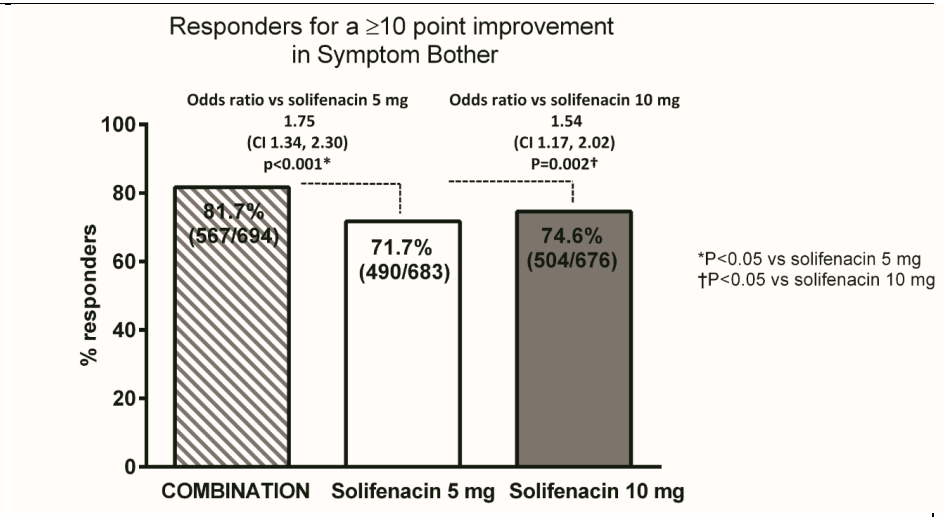
B.



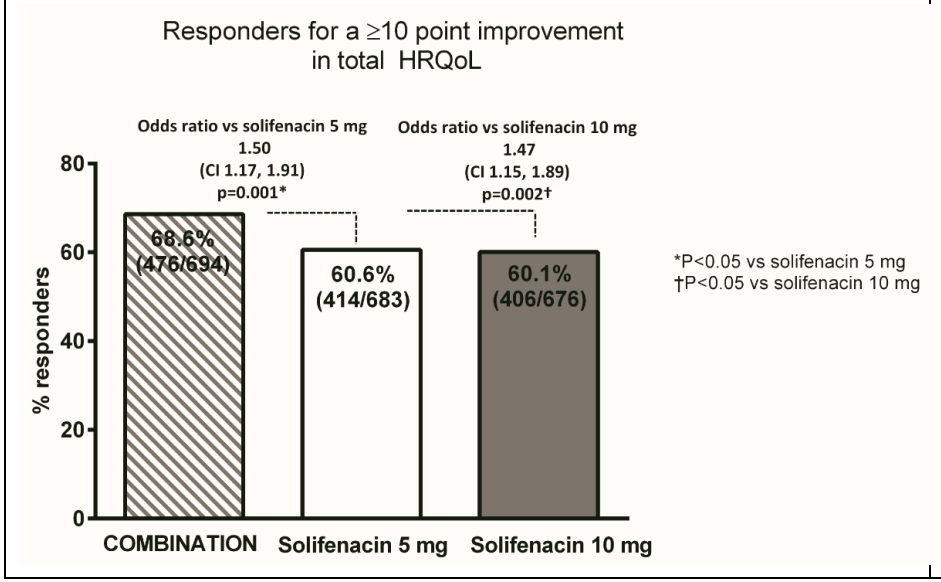
C.

D.

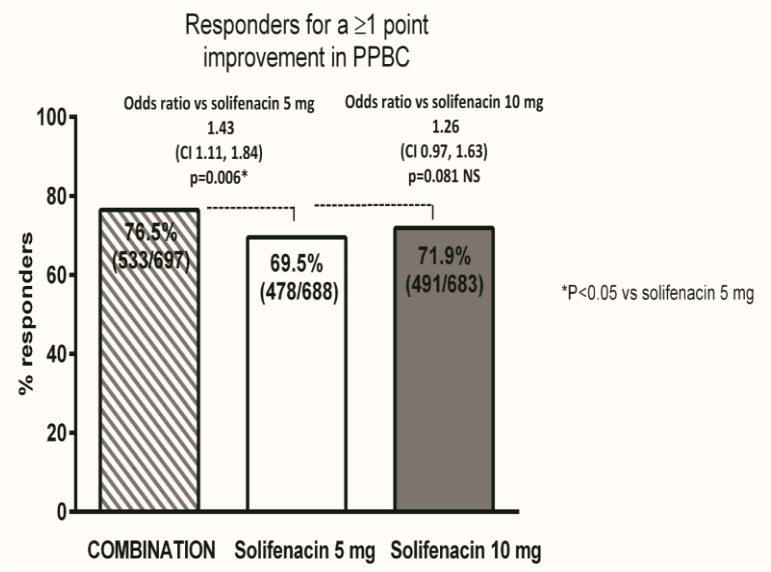

Responders (as % of total) for an average of <8 micturitions/24 h at EoT
Odds ratio vs solifenacin 5 mg
1.29
(CI 1.02, 1.64)
p=0.036*
Odds ratio vs solifenacin 10 mg
1.12
(CI 0.89, 1.42)
p=0.334 NS
% responders
30.2% (213/706)
25.0% (176/704)
27.7% (193/697)
COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg
*P<0.05 vs solifenacin 5 mg

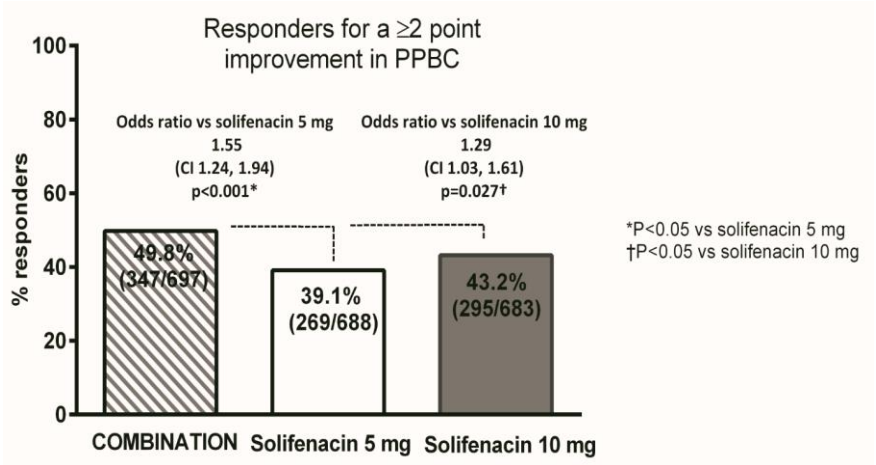

Responders for a ≥10 point improvement in Symptom Bother
Odds ratio vs solifenacin 5 mg
1.75
(CI 1.34, 2.30)
p<0.001*
Odds ratio vs solifenacin 10 mg
1.54
(CI 1.17, 2.02)
P=0.002†
% responders
81.7% (567/694)
71.7% (490/683)
74.6% (504/676)
COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg
*P<0.05 vs solifenacin 5 mg
†P<0.05 vs solifenacin 10 mg

E.


Responders for a ≥10 point improvement in total HRQoL
Odds ratio vs solifenacin 5 mg
1.50
(CI 1.17, 1.91)
p=0.001*
Odds ratio vs solifenacin 10 mg
1.47
(CI 1.15, 1.89)
p=0.002†
% responders
68.6% (476/694)
60.6% (414/683)
60.1% (406/676)
COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg
*P<0.05 vs solifenacin 5 mg
†P<0.05 vs solifenacin 10 mg

F.


Responders for a ≥1 point improvement in PPBC
Odds ratio vs solifenacin 5 mg
1.43
(CI 1.11, 1.84)
p=0.006*
Odds ratio vs solifenacin 10 mg
1.26
(CI 0.97, 1.63)
p=0.081 NS
% responders
76.5% (533/697)
69.5% (478/688)
71.9% (491/683)
COMBINATION
Solifenacin 5 mg
Solifenacin 10 mg
*P<0.05 vs solifenacin 5 mg

G.  Responders for a ≥2 point improvement in PPBC % responders 100 80 60 40 20 0 Odds ratio vs solifenacin 5 mg 1.55 (CI 1.24, 1.94) p<0.001* Odds ratio vs solifenacin 10 mg 1.29 (CI 1.03, 1.61) p=0.027† 49.8% (347/697) 39.1% (269/688) 43.2% (295/683) *P<0.05 vs solifenacin 5 mg †P<0.05 vs solifenacin 10 mg COMBINATION Solifenacin 5 mg Solifenacin 10 mg	

APPENDIX A (online supplementary)

A1. Key Inclusion and Exclusion Criteria

A2. Randomization and Blinding

A3. Sample Size Calculation and Statistical Analysis

Supplementary materials

A1. Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
Screening (Visit 1)	
Adult with OAB symptoms for ≥3 months Patient has symptoms of "wet" OAB (frequency and urgency with incontinence or mixed incontinence with predominant urgency incontinence)	Clinically significant Bladder Outlet Obstruction (BOO) Significant PVR volume (PVR >150 ml) Significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor Intravesical treatment in past 12 months Non-drug treatment including sacral nerve stimulation therapy (a bladder training program or pelvic floor exercises which began more than 30 days prior to study entry can be continued)
Run-in (Visit 2)	
During the 3-day micturition diary, patient experiences on average: ≥1 episode of urgency (grade 3 or 4)/24 hours with or without incontinence ≥2 incontinence episodes/24 hours	

≥8 micturitions/24 hours (excluding incontinence episodes)	
Randomization (Visit 3)	
Patient experiences ≥1 incontinence episode during the 3-day micturition diary period and wishes to increase their treatment for OAB symptoms	Patient has achieved 100% continence from Visit 2 to Visit 3 (no incontinence episodes are recorded in the 3-day diary administered for 3 days prior to Visit 3) Patient does not desire an increase in study medication Patient has an average total daily urine volume >3,000 ml as recorded in the micturition diary Severe uncontrolled hypertension (sitting average SBP ≥180 mmHg and/or DBP ≥110 mmHg) Clinically significant abnormal ECG

A2. Randomization and Blinding

Each patient number was assigned using interactive response technology once the patient had signed informed consent. Patients were randomized to 1 of 3 treatment groups in a 1:1:1 ratio stratified by sex, age group (<65, ≥65 years), 4-week incontinence episode reduction group (<50%, ≥50%), and geographic region (ie Eastern Europe, Western Europe, North America, Middle East and Asia).

To maintain blinding for the double-blind treatment period, active and placebo tablets were indistinguishable by using a double-dummy packaging system. Neither patient nor other study personnel were aware of the double-blind treatment given to any patient unless a medical emergency necessitated such disclosure. For the single-blinded run-in period, all patients received 1 active tablet of solifenacin 5 mg. For the single-blinded safety follow-up period, 1 placebo tablet was given.

For the first 4 weeks of the double-blind period, patients were assigned to 1 of 3 groups:

- Combination: solifenacin 5 mg, mirabegron 25 mg, solifenacin 10 mg placebo
- Solifenacin 5 mg: solifenacin 5 mg, mirabegron 25 mg placebo, solifenacin 10 mg placebo
- Solifenacin 10 mg: solifenacin 5 mg placebo, mirabegron 25 mg placebo, solifenacin 10 mg

For the last 8 weeks of the double-blind treatment period, the 25 mg mirabegron and matching placebo were replaced by a 50 mg mirabegron tablet and matching placebo tablet.

A3. Sample Size and Statistical Analysis

The sample size for this study was based on results of previous studies with mirabegron and solifenacin plus mirabegron combination[25] and mirabegron 50 mg vs placebo results.[26-28]

A total of 614 evaluable patients per treatment group provided 90% power to detect a reduction of 0.50 in the mean number of micturitions/24 hours for combination therapy vs solifenacin 5 mg monotherapy at a 2-sided significance level of 0.05, assuming a standard deviation of 2.7. A total of 610 patients provided 80% power for the analysis of mean number of incontinence episodes per 24 hours based on a (non-parametric) Wilcoxon rank sum test based on ordered categories derived from the results of the previous studies mentioned above. A total of 610 evaluable patients per treatment group provided 90% power to detect a reduction in the number of incontinence episodes reported during the 3-day diary period for combination therapy vs solifenacin 5 mg monotherapy of at least 20% at a 2-sided significance level of 0.05. This sample size was based on an analysis of Poisson regression, using an over-dispersion factor of 2.75 and an expected number of 4 incontinence episodes over a 3-day diary period for the solifenacin 5 mg monotherapy arm at EoT. Assuming a 15% dropout rate during the double-bind period, 724 patients were to be randomized to each arm. Using data from previous solifenacin studies it was assumed that 25% of incontinent patients would be continent after receiving 4 weeks of solifenacin 5 mg. Based on this rate of 25%, a total of approximately 2,896 patients were planned to enter the single-blind treatment period. Assuming a 15% screening failure rate, approximately 3,408 patients were to be screened in countries across Europe, North America, Middle East, North Africa and Asia Pacific to achieve approximately 2,172 randomized and 1,842 evaluable patients.

Demographic and other baseline characteristics were summarized using descriptive statistics for the continuous variables and numbers and percentages of patients for the categorical variables.

For dichotomous variables (eg proportion of patients with at least a 50% decrease in incontinence episodes, at least a 1-point improvement in PPBC), the number and proportion of responders were summarized by treatment group, along with the difference between combination therapy and solifenacin 5 mg and between combination therapy and solifenacin 10 mg, odds ratios, 95% CIs, and p values. These were calculated from a logistic regression model including treatment group, randomization stratification factors (sex, age group, geographic region and 4-week incontinence episode reduction group) and baseline measurement. Patients with missing outcome leading to missing response status were excluded.

The proportions of double and triple responders were summarized by treatment group, along with the difference between combination therapy and solifenacin 5 mg and between combination therapy and solifenacin 10 mg, odds ratios, 2-sided 95% CIs and p values. These were calculated from a logistic regression model including treatment group, randomization stratification factors (sex, age group (<65 and ≥65 years), geographic region and 4-week incontinence episode reduction group) and log transformation of the baseline measurement. Descriptive statistics for the exploratory variables at each study visit and EoT as well as the model statistics were tabulated by treatment group.

Changes and responders from baseline to weeks 4, 8 and 12 were only calculated if data from both baseline visit and the post baseline visit were available. Missing EoT data were imputed using the LOCF method. Patients with completely missing data were not

included in the analysis (so that the number of responders plus the number of nonresponders corresponded to the number of patients included in the by-week analyses).