| | | |
|---|---|---|
| **Name of Sponsor/Company:** Astellas Pharma Europe B.V. | | |
| **Name of Finished Product:** Not applicable | | |
| **Name of Active Ingredient:** Solifenacin Succinate (YM905)/Mirabegron (YM178) | | |

## SYNOPSIS

**Title of Study:**

A Randomized, Double-blind, Parallel-group, Placebo- and Active-controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Combinations of Solifenacin Succinate and Mirabegron Compared to Solifenacin Succinate and Mirabegron Monotherapy in the Treatment of Overactive Bladder

**Coordinating Investigators:**

[redacted] Canada

[redacted] UK

**Study Centers:**

The study was conducted at 435 sites worldwide.

**Publication Based on the Study:**

Not applicable

**Study Period:**

***Study Initiation Date (Date of First Enrollment):***

05 Nov 2013

***Study Completion Date (Date of Last Evaluation):***

22 Oct 2015

**Phase of Development:**

Phase 3

**Objectives:**

***Primary objective***

- To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron (5 + 25 mg and 5 + 50 mg) compared to solifenacin (5 mg) and mirabegron (25 mg and 50 mg) monotherapy

***Secondary objectives***

- To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron (5 + 25 mg and 5 + 50 mg) compared to placebo
- To evaluate the safety and tolerability of 2 dose combinations of solifenacin and mirabegron (5 + 25 mg and 5 + 50 mg) compared to solifenacin (5 mg) and mirabegron (25 mg and 50 mg) monotherapy and compared to placebo

- To evaluate the patient-reported outcomes of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapy and placebo
- To investigate the population pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of 2 dose combinations of solifenacin and mirabegron with mirabegron and solifenacin monotherapies

**Methodology:**

This was a multinational, multicenter, randomized, double-blind, parallel-group, placebo- and active- controlled phase 3 study. The study comprised a single-blind, 4-week placebo run-in period followed by a randomized, double-blind, placebo- and active- controlled, 12-week treatment period followed by a 2-week follow-up period during which the patient took placebo (single-blind placebo run-out period). Patients visited the clinic at screening (visit 1), at the end of the placebo run-in period (visit 2, baseline), after 4, 8 and 12 weeks of double-blind treatment (visit 3, 4 and 5) and 2 weeks after end of double-blind treatment, for a follow-up visit (visit 6). Patients were not allowed to take any active OAB treatment during the study other than study drugs.

A subset of eligible patients at selected sites was randomized to participate in an ambulatory blood pressure monitoring (ABPM) substudy. These patients had to pass additional ABPM-specific eligibility criteria and visited the clinic additionally on the days following the visits during which the ABPM device was fitted (visits 2 [was repeated if recording was invalid], 3, 4 [only in case of invalid recording at visit 3] and 5).

Patients who were eligible at screening (visit 1) entered a 4-week placebo run-in period for washout, micturition diary training and baseline micturition diary (last 7 days before randomization). Patients not participating in the ABPM substudy were also asked to complete vital signs measurements at home for 5 consecutive days prior to the next visit. Patients who were eligible at baseline/randomization (visit 2) were randomized in a 2:2:1:1:1:1 ratio of the following treatments: 1) solifenacin 5 mg + mirabegron 25 mg (combination 5 + 25 mg), 2) solifenacin 5 mg + mirabegron 50 mg (combination 5 + 50 mg), 3) placebo, 4) solifenacin 5 mg, 5) mirabegron 25 mg or 6) mirabegron 50 mg. Randomization was stratified by sex, age group (< 65, ≥ 65 years), previous OAB treatment (yes/no), geographic region and participation in the ABPM substudy (yes/no).

**Number of Patients (Planned, Enrolled and Analyzed):**

A total of 6991 patients were screened of which 6275 patients received placebo run-in medication. Of the 3527 patients who were randomized into the study (randomized analysis set [RAS]), 3494 (99.1%) received double-blind study drug Figure 1. Of these, 3398 (96.3%) patients were included in the safety analysis set (SAF) and 3308 (93.8%) were included in the full analysis set (FAS).

A total of 953 patients at 104 selected sites were randomized to the ABPM substudy and 715 patients were included in the ambulatory blood pressure monitoring analysis set (ABPMAS).

**Diagnosis and Main Criteria for Inclusion:**

Male or female patients, aged 18 years or older with symptoms of "wet" OAB (urinary frequency and urgency with incontinence) for ≥ 3 months prior to screening were eligible to participate. At randomization, patients had to have on average ≥ 8 micturitions/24 h (excluding incontinence episodes), ≥ 3 incontinence episodes and on average ≥ 1 urgency episode (grade 3 or 4 on the Patient Perception of Intensity of Urgency Scale [PPIUS])/24 h over the 7-day micturition diary period.

Medications prohibited between screening and follow-up included drugs used for the treatment of OAB other than the study drugs, other drugs that could influence efficacy, mask safety signals or were cytochrome P450

2D6 substrates with a narrow therapeutic margin and drugs for which the therapeutic efficacy could be counteracted by the study drugs.

**Test Products, Dose and Mode of Administration, Batch Numbers:**

Combination of 5 mg solifenacin + 25 mg mirabegron (+mirabegron 50 mg placebo) once daily orally (group 1) (batch numbers [redacted]).

Combination of 5 mg solifenacin + 50 mg mirabegron (+mirabegron 25 mg placebo) once daily orally (group 2) ((batch numbers [redacted]).

**Duration of Treatment:**

The study consisted of a 4-week, single-blind, run-in period during which patients received placebo (solifenacin 5 mg placebo, mirabegron 50 mg placebo, mirabegron 25 mg placebo, batch numbers [redacted]). Eligible patients were randomized to receive 12 weeks double-blind treatment. Following completion of the treatment period, patients entered the single-blind, 2-week follow-up period during which patients received placebo (solifenacin 5 mg placebo, mirabegron 50 mg placebo, mirabegron 25 mg placebo, batch numbers [redacted]). For the double-blind treatment period, patients were assigned to 1 of 6 groups (groups 1 and 2, see above).

- Group 3: solifenacin placebo, mirabegron 25 mg placebo, mirabegron 50 mg placebo (batch numbers [redacted])
- Group 4: solifenacin 5 mg, mirabegron 25 mg placebo, mirabegron 50 mg placebo (batch numbers [redacted])
- Group 5: mirabegron 25 mg, solifenacin placebo, mirabegron 50 mg placebo (batch numbers [redacted])
- Group 6: mirabegron 50 mg, solifenacin placebo, mirabegron 25 mg placebo (batch numbers [redacted])

**Reference Products, Dose and Mode of Administration, Batch Numbers:**

Mirabegron 25 mg and 50 mg oral controlled absorption system (OCAS) modified release tablets.

Solifenacin 5 mg tablets (see above for batch numbers).

Matching placebo of mirabegron OCAS 25 mg and 50 mg tablets (see above for batch numbers).

Matching placebo of solifenacin succinate 5 mg tablets (see above for batch numbers).

**Criteria for Evaluation:**

*Coprimary efficacy variables* (derived from the 7-day micturition diary)

- Change from baseline to end of treatment (EoT) in mean number of incontinence episodes/24 h
- Change from baseline to EoT in mean number of micturitions/24 h

*Key secondary efficacy variables*

- Change from baseline to EoT in mean volume voided per micturition based on the 7-day micturition diary
- Change from baseline to EoT in overactive bladder questionnaire (OAB-q) Symptom Bother score
- Change from baseline to EoT in treatment satisfaction - visual analogue scale (TS-VAS)

Other secondary efficacy variables included responders for zero incontinence episodes (3-day diary), micturition frequency normalization, change from baseline to EoT in mean number of urgency episodes (grade 3 or 4)/24 h and change from baseline to EoT in mean number of nocturia episodes/24 h. The analysis of patient-reported outcomes variables included changes from baseline in health-related quality of life (HRQL) Total score (including subscales), patient perception of bladder condition (PPBC) score and Patient's global impression of change (PGIC) scale, as well as responder analyses for patients with ≥ 10-point improvement in OAB-q Symptom Bother score, in the proportion of patients with a ≥ 1-point or ≥ 2-point improvement from baseline in PPBC.

*Safety variables*

Safety assessments comprised the incidence and severity of treatment-emergent adverse events (TEAEs) (including TEAEs of special interest and common antimuscarinic side effects), neoplasm and cardiovascular events, vital signs, safety laboratory tests (hematology, biochemistry and urinalysis), electrocardiogram (ECG) parameters and post-void residual (PVR) volume.

Additional safety variables for the ABPM substudy were the change from baseline in mean 24-h, mean daytime and mean nighttime systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate; and the change from baseline in mean SBP, DBP and pulse rate in the $t_{max}$ window (4 to 6 h postdose)

**Statistical Methods:**

All statistical comparisons were made using 2-sided tests at the 0.05 significance level unless specifically stated otherwise. All null-hypotheses were "no treatment difference"; all alternative hypotheses were "treatment difference". Adjustment for multiple testing was only performed for coprimary and key secondary variables.

***Analysis Sets***

Analysis sets of interest were the FAS comprising all randomized patients who took ≥ 1 dose of double-blind study drug after randomization, recorded ≥ 1 micturition measurement in the baseline diary and ≥ 1 micturition measurement postbaseline and reported ≥ 1 incontinence episode in the baseline diary; the SAF comprising all randomized patients who received ≥ 1 dose of double-blind treatment; and the ABPMAS comprising all patients in the SAF for whom ≥ 1 ABPM variable could be calculated at baseline and postbaseline visit Table 1. The FAS was regarded as the main analysis set for the primary and secondary efficacy variables. All safety analyses were performed on the SAF, except for vital signs variables based on ABPM which were analyzed using ABPMAS.

***Efficacy***

Coprimary Variables: Change from baseline to EoT in mean number of incontinence episodes/24 h was analyzed using a separate stratified rank analysis of covariance (ANCOVA) model for each pairwise treatment group difference of interest (combination treatment vs each monotherapy component). The response variable was the standardized ranks on change from baseline to EoT value, with baseline standardized ranks, sex, age group (< 65, ≥ 65 years) and previous OAB treatment as covariates and geographical region as a stratum. Standardized ranks within each geographical region were derived across the 2 pairwise treatment groups of interest for the covariate baseline and the response variable change from baseline.

The stratified rank ANCOVA was utilized for hypothesis testing and calculating P values for the comparisons of combination vs each monotherapy component. Least Squares (LS) mean estimates and 2-sided 95% confidence

intervals (CIs) for mean changes from baseline within each treatment group, as well as for the difference in mean change from baseline between each combination group and each of its monotherapy components were derived from the corresponding ANCOVA model with treatment group (all 6 treatment groups in the model), sex, age group (< 65, ≥ 65 years), previous OAB treatment and geographic region as fixed factors and baseline value as a covariate.

Change from baseline to EoT in mean number of micturitions/24 h was analyzed using an ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB treatment and geographic region as fixed factors and baseline value as a covariate.

Because there were 2 coprimary endpoints, key secondary endpoints and because 2 combination treatment groups were compared vs their monotherapy components, the type 1 error was controlled at the 1-sided 0.025 level by using a sequential Bonferroni-based testing procedure following the graphical approach by Bretz et al (2009) Figure 2. However, to reduce complexity mean volume voided was the only key secondary variable included in the testing procedure. It should be noted that each of these hypothesis tests comprised 2 subtests for the comparisons versus solifenacin and mirabegron monotherapies. The null hypotheses corresponding to both tests need to be rejected in order to proceed.

The sequential Bonferroni-based testing procedure started at $H_{11}$ which was tested at 1-sided 0.025. If $H_{11}$ was rejected, $H_{21}$ was tested (at 1-sided 0.025). If $H_{21}$ was rejected, the α was split: 50% for the key secondary variable of mean volume voided for the 5 + 50 mg combination ($H_{31}$) and 50% for the coprimary variable of mean number of incontinence episodes for the 5 + 25 mg combination ($H_{12}$). The power to test $H_{31}$ was more than 99% at the 1-sided 0.0125 significance level. If $H_{31}$ was rejected, 100% of the local significance level was shifted to the coprimary endpoint of mean number of incontinence episodes for the 5 + 25 mg combination ($H_{12}$). If $H_{12}$ was rejected, $H_{22}$ was tested at the remaining significance level (1-sided 0.025 or 0.0125, depending on whether $H_{31}$ was rejected). In the last step, $H_{32}$ was tested if $H_{22}$ was rejected at the remaining significance level. The study was considered a success if both coprimary endpoints were met for a given dose level.

Key secondary variables (see under 'Criteria for Evaluation') were analyzed using an ANCOVA model as described above for the coprimary variable of mean number of micturitions/24 h. Mean volume voided per micturition was included in the testing procedure described above. For the other 2 key secondary efficacy variables, the effect of the combination therapy groups was compared to each of its monotherapy components at a 2-sided 0.05 significance for those combination groups for which both null-hypotheses for mean volume voided were rejected.

Change from baseline in mean number of urgency episodes (grade 3 or 4)/24 h was analyzed using the same model as mean number of micturitions/24 h. Responder analyses were performed using a logistic regression model with treatment, age group (< 65, ≥ 65 years), sex, previous OAB treatment (yes/no) and geographic region as factors and baseline value as covariate (if applicable). Differences between combination therapy, monotherapies and placebo, 2-sided 95% CIs, odds ratios and P values were calculated. Preplanned subgroup analyses were performed using an ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB treatment (yes/no), geographic region, and the subgroup (unless already included in the model) as factors, a subgroup-by-treatment interaction, and the baseline value as covariate. If the P value for the interaction was < 0.10, further evaluation was performed to assess whether the interaction was qualitative or quantitative in nature.

***Safety***

AEs were coded using MedDRA v16.0 and summarized by severity (i.e., mild, moderate, severe) and by relationship to study drug (i.e., not related, possibly, probably related). Vital signs parameters were summarized with descriptive statistics by treatment group and visit and also analyzed using ANCOVA and repeated measures models. Clinical laboratory tests (hematology, biochemistry and urinalysis), 12-lead ECG, QT interval corrected using Fridericia's correction formula (QTcF interval) and PVR volume were summarized descriptively by treatment group and visit.

**Summary of Results/Conclusions:**

**Demographics:**

The study was conducted at 435 sites in 42 countries. The majority of patients in the FAS were from Eastern Europe (44.0%), with 26.2% from North America and 12.8% each from Asia and Western Europe [Table 2].

In general, all treatment arms in the FAS were similar with respect to demographics and baseline characteristics [Table 2]. The majority of patients were female (77.0%). Most patients were White (79.7%), 15.1% were Asian and 3.3% Black or African American. Of the patients, 6.2% were Hispanic or Latino. The overall mean age at baseline was 57.4 years (range 18 to 86) with 33.0% of patients aged ≥ 65 years, 8.0% aged ≥ 75 years and 0.3% aged ≥ 85 years. The mean BMI across all treatment groups was 28.52 kg/m$^2$. Mean number of incontinence episodes/24 h ranged from 3.16 to 3.58, mean number of micturitions/24 h ranged from 10.73 to 11.19) and mean volume voided per micturition ranged from 151.94 to 159.32 mL (7-day micturition diary).

The demographics in the ABPM substudy were generally comparable to the main study, although only 1.8% Asian patients were included. The demographic and baseline characteristics were consistent across treatment groups in the SAF and per protocol analysis set (PPS) and were similar to the FAS.

**Efficacy Results:**

The primary objective was not met as the 5 + 50 mg combination group showed superiority to solifenacin 5 mg, but failed to demonstrate superiority to mirabegron 50 mg for the coprimary efficacy endpoint change from baseline to EoT in mean number of incontinence episodes/24 h [Table 3]. According to the prespecified testing procedure no hypothesis testing could be performed for the other coprimary endpoint (change from baseline to EoT in mean number of micturitions/24 h), the key secondary endpoints, or for the 5 + 25 mg group.

Clear improvements in efficacy of combination therapy were, however, observed when comparing with monotherapy for the coprimary variable of mean number of micturitions and key secondary variables of mean volume voided (except for the 5 + 25 mg combination vs solifenacin 5 mg) [Table 4], OAB-q Symptom Bother [Table 5] and TS-VAS (only vs mirabegron) [Table 6] with nominal P values < 0.05. The effect sizes of combination treatment vs placebo in general were similar to the sum of the effect sizes observed in the monotherapy groups vs placebo, indicating that combination therapy has an additive effect for many parameters.

In responder analyses at EoT, statistically significant odds ratios in favor of both combinations vs the monotherapy components were demonstrated for the proportion of patients with zero incontinence episodes [Table 7] and the proportion of patients achieving micturition frequency normalization [Table 8].

Combination 5 + 50 mg was statistically significantly superior to both monotherapy components at EoT and at most other timepoints for urgency episodes [Table 9] and nocturia [Table 10] with effect sizes that appeared to

be additive. Combination 5 + 25 mg was statistically significantly superior to mirabegron 25 mg for the same variables, except for nocturia.

Patient reported outcome variables demonstrated that combination treatment had a positive effect on patients' quality of life, thereby demonstrating the clinical relevance of the improvements in micturition diary parameters.

- For the HRQL Total score and subscale scores, both combinations were superior over the monotherapy components at EoT, apart from the Social score for combination 5 + 50 mg vs mirabegron.
- For the PPBC score at EOT, differences were statistically significant in favor of both combinations vs the monotherapies.
- For the PGIC scale, the proportion of patients reporting that their bladder symptoms had very much improved at EoT was higher in the combination groups compared with the monotherapies.
- There were statistically significant differences at EoT in favor of combination vs monotherapy in the proportion of responders with ≥ 10-point improvement in OAB-q Symptom Bother score, in the proportion of patients with a ≥ 1-point improvement from baseline in PPBC (except for combination 5 + 25 mg vs solifenacin 5 mg for both analyses) and in the proportion of patients with major (≥ 2 points) improvement from baseline in PPBC.

Combination 5 + 25 mg was not statistically significantly better than solifenacin 5 mg on many endpoints. In general, the effect size of combination 5 + 25 mg vs monotherapies was lower compared to that of combination 5 + 50 mg.

Most effects of combination therapy became statistically better than monotherapy at week 4, with limited or no meaningful further improvement over time in comparison to monotherapies.

A substantially greater effect of both combinations was observed in the prespecified analysis of patients who received previous OAB treatment in comparison to the treatment effect sizes observed in the treatment-naïve patients, with nominal 95% CIs excluding zero for the comparisons of combination vs each monotherapy [Table 11 through Table 16].

**Safety Results:**

Combination therapy with solifenacin + mirabegron demonstrated a similar safety profile to that expected of its 2 monotherapy components, with no new safety findings identified Table 17 (frequently reported TEAEs) and Table 18 (serious TEAEs). All treatment arms investigated in this study appeared to be well-tolerated with an acceptable safety profile.

A similar percentage of patients discontinued from all groups, including placebo, monotherapy and combination; the main reason was withdrawal of consent; discontinuation due to AE was also similar across groups.

TEAEs of special interest in the combination therapy groups were observed at a frequency similar to, or, for some events, slightly higher than observed with monotherapies.

- Hypersensitivity, glaucoma, somnolence and blurred vision had a similar reporting frequency in the combination groups compared to monotherapy groups or placebo, while UTI had a slightly higher frequency in the 5 + 25 mg combination group compared to the other groups.

- The antimuscarinic side effects of dry mouth, constipation, and dyspepsia had a slightly higher reporting frequency in the combination groups compared to the monotherapy groups and placebo.
- Events indicative of urinary retention were reported slightly more frequently in the combination groups compared to monotherapy and placebo. Consistent with these findings, PVR was slightly increased in the combination groups compared to solifenacin 5 mg and the mirabegron monotherapy groups. More patients in the combination groups experienced a shift towards higher PVR categories.
- The frequency of increased blood pressure was similar between the placebo and the mirabegron monotherapy groups, and slightly higher for solifenacin 5 mg. The frequency in the combination groups was slightly higher than with mirabegron monotherapy but lower than with solifenacin.
- Sixteen serious potential cardiovascular events were reported, of which 13 events occurred in the combination groups. These cases were all reviewed by the blinded IAC who adjudicated 5 cases as noncardiovascular events, 8 as non-APTC/MACE cardiovascular events and 3 as APTC/MACE events. All adjudicated cardiovascular events, except 1 case of atrial flutter, were confounded by a history of cardiovascular disease on the basis of medical history and/or the presence of other risk factors.
- Although the frequency of serious cardiovascular events and atrial fibrillation appears to be somewhat higher in the combination groups, no firm conclusions can be drawn from this, due to the low number of patients affected and the significant confounders present in the vast majority of cases. A cardiovascular effect likely to signal risk was not observed in the ABPM data (see below), which showed high variability and no consistent difference in vital signs in combination groups compared to monotherapies, nor in monotherapies compared to placebo.

For the mean 24-h SBP, DBP and pulse rate measurements based on ABPM, differences between mirabegron monotherapy and placebo appeared to be mostly absent or generally consistent with results from previous studies, except for the apparent decrease in SBP and DBP in the mirabegron 25 mg group. The mean 24-h vital sign values do not point to an increase in combination groups compared to monotherapies. It should be noted that variability in the ABPM data was high (and for mean 24-h SBP higher than expected) compared to the potential effect sizes and many comparisons may reflect random variability, as no consistent patterns across parameters, doses or timepoints could be observed for either mirabegron monotherapy, solifenacin monotherapy or combination treatment. Outlier analyses did not identify relevant differences between combination and monotherapy, nor between monotherapy and placebo, indicating that any differences in the observed mean changes do not result in potentially important changes in a small subset of patients.

Although between 4 to 6 h after dosing a circa 2 mmHg mean increase in SBP and a circa 3 bpm mean increase in pulse rate for mirabegron 50 mg relative to placebo were observed, no general pattern of differences with other treatment groups around this time of pharmacokinetic $t_{max}$ could be discerned. Compared with baseline there was a decrease in SBP of 1.94 mmHg and an increase in pulse rate of 3.41 bpm for mirabegron 50 mg; the observed increase in SBP vs placebo was caused by the larger decrease in SBP of 4.40 mmHg in the placebo group. There was no clear dose-response for mirabegron or a consistent effect on both SBP and pulse rate visible in monotherapy and combination therapy groups.

In summary, data from the ABPM substudy as a whole did not show any clear or consistent trend for a drug effect of mirabegron or solifenacin vs placebo, or of combination vs monotherapy, with the exception of a possible effect around $t_{max}$. Since the differences between 4 to 6 h after dosing did not translate into a mean 24-h increase, nor during daytime or during nighttime, this effect, even if it was a true effect, was considered clinically not relevant. Differences in mean 24-h SBP, DBP and pulse rate, where apparent, were generally of a

similar magnitude as the observed difference between mirabegron and placebo in the mirabegron monotherapy phase 3 studies using home-measurements according to the method of Verberk et al (2006).

For site-based SBP, DBP and pulse rate, no relevant differences were observed between active treatment groups and placebo as well as between combination and monotherapy. Pulse rate showed slight increases for mirabegron 50 mg, combination 5 + 50 mg and 5 + 25 mg compared to placebo, which are consistent with the results from previous mirabegron monotherapy phase 3 studies. The differences in the combination groups compared to placebo were of similar magnitude or smaller than those for the mirabegron 50 mg group.

There were no concerns for ECGs and laboratory data, including QTcF interval and liver function tests.

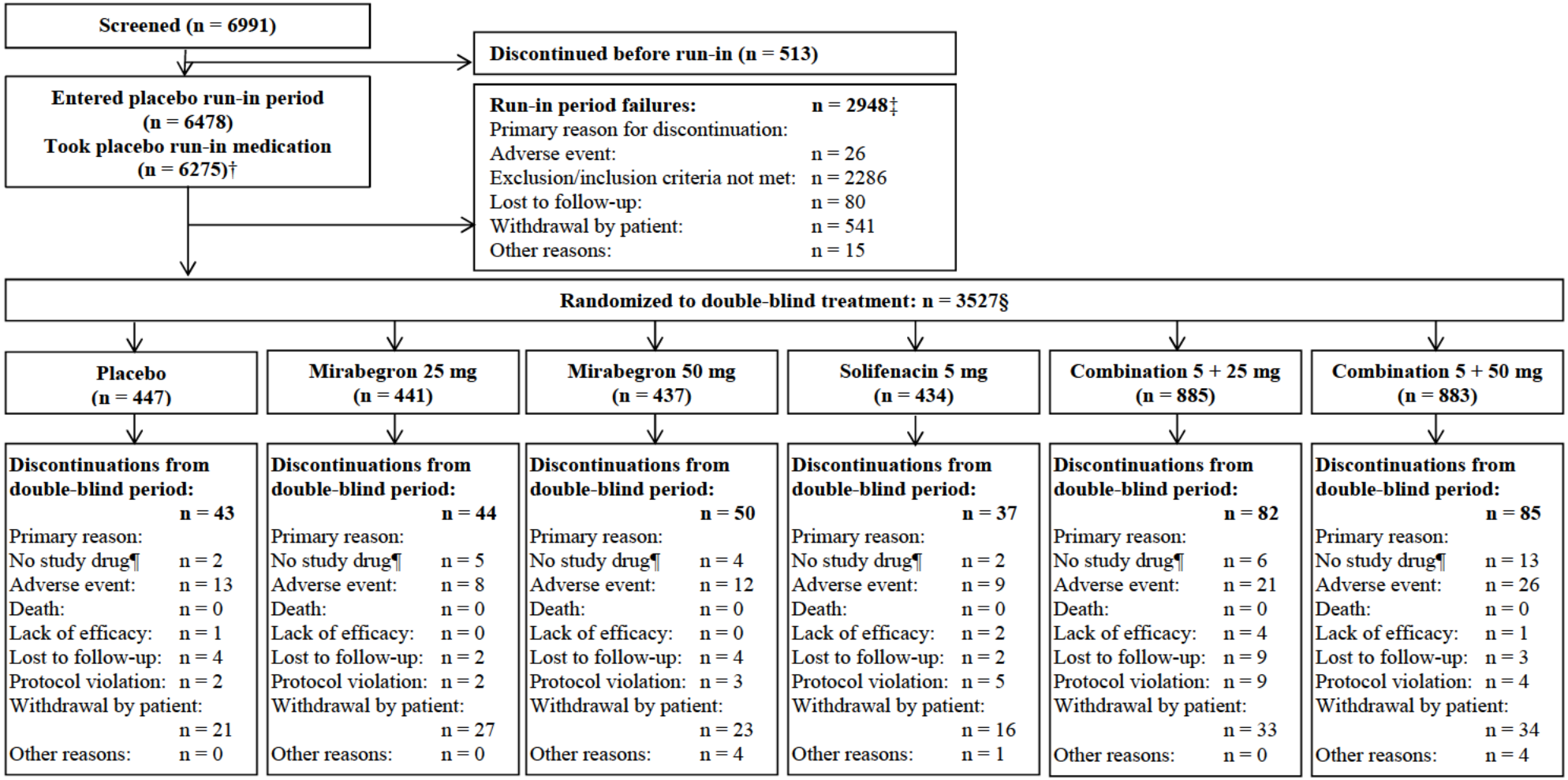
**CONCLUSIONS:**

Based on the results of this study, it is concluded that:

- Combination therapy with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg provided clear and clinically relevant improvements in efficacy compared to the respective monotherapies with effect sizes generally consistent with an additive effect. However, the primary objective was not met although it approached statistical significance (P = 0.052 for one of the coprimary endpoints).
- In general, the effect size with combination 5 + 50 mg was larger and more pronounced than with combination 5 + 25 mg with no obvious differences in safety profile.
- The improvements seen with combination therapy compared to monotherapy translated into significant improvements in HRQL and responder rates such as for zero incontinence, supporting the clinical relevance of the effect.
- Solifenacin + mirabegron combination therapy once daily for 12 weeks had an acceptable safety profile without new safety concerns in comparison to its monotherapy components and was well tolerated, similar to the monotherapies.

**Date of Report:** 5 Jul 2016

**Figure 1 Patient Disposition**




† Excludes 1 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 randomized.
‡ Excludes 4 patients who did not have end of run-in page provided.
§ Includes 1 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 randomized.
¶ Randomized/registered but never received/dispensed study drug.
Source: Tables 12.1.1.1.1, 12.1.1.3.2, 12.1.1.3.3 (randomized analysis set)

**Figure 2** **Graphical Representation of the Testing Procedure for the Coprimary and Key Secondary Efficacy Variables Based on the Micturition Diary**

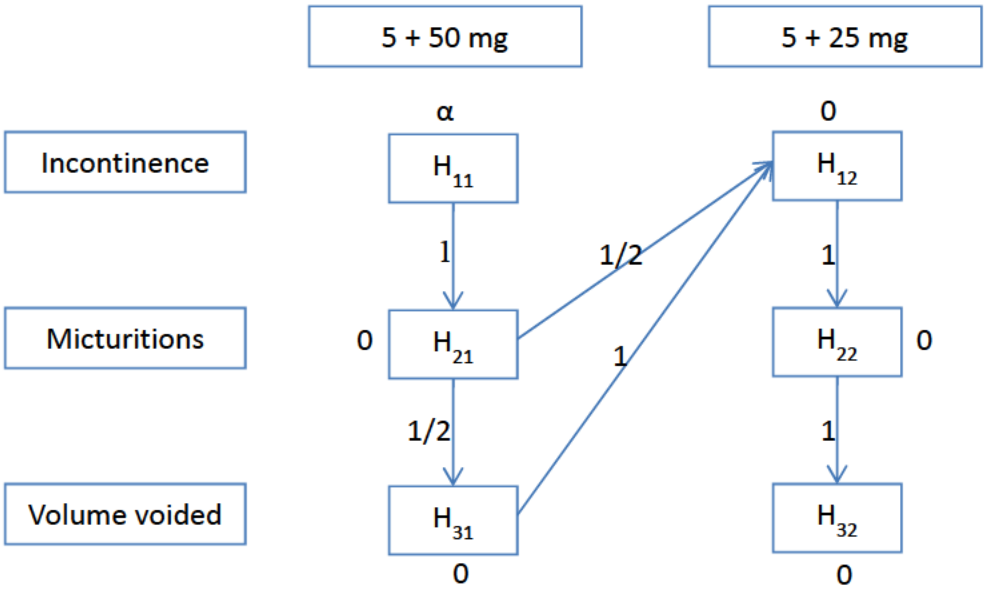


**Table 1 Analysis Sets by Treatment Group**

| Analysis Set, n | Placebo | M 25 mg | M 50 mg | S 5 mg | C 5 + 25 mg | C 5 + 50 mg | Total |
|---|---|---|---|---|---|---|---|
| RAS | 447 | 441 | 437 | 434 | 885 | 883 | 3527 |
| SAF† | 429 (96.0%) | 423 (95.9%) | 422 (96.6%) | 423 (97.5%) | 853 (96.4%) | 848 (96.0%) | 3398 (96.3%) |
| FAS† | 418 (93.5%) | 410 (93.0%) | 411 (94.1%) | 415 (95.6%) | 827 (93.4%) | 827 (93.7%) | 3308 (93.8%) |
| PPS† | 328 (73.4%) | 333 (75.5%) | 330 (75.5%) | 346 (79.7%) | 667 (75.4%) | 665 (75.3%) | 2669 (75.7%) |
| ABPMAS | 92 (20.6%) | 85 (19.3%) | 87 (19.9%) | 86 (19.8%) | 176 (19.9%) | 189 (21.4%) | 715 (20.3%) |

Percentages are calculated relative to the RAS.

RAS: randomized analysis set, all patients randomized to double-blind treatment.

SAF: safety analysis set, all randomized patients who took ≥ 1 dose of double-blind treatment.

FAS: full analysis set, all SAF patients who recorded ≥ 1 micturition and ≥ 1 incontinence episode in the baseline diary and ≥ 1 micturition postbaseline.

PPS: per protocol analysis set, all FAS patients who did not meet criteria for exclusion from PPS.

ABPMAS: ambulatory blood pressure monitoring analysis set, all SAF patients for whom ≥ 1 ambulatory blood pressure monitoring (ABPM) variable could be calculated at baseline and a postbaseline visit.

C: solifenacin + mirabegron combination therapy; M: mirabegron; S: solifenacin.

† Excluding patients from site [redacted] (this site did not participate in the ABPM substudy).

Source: Table 12.1.1.2

**Table 2 Summary of Demographics and Baseline Characteristics for Patients (FAS)**

| Parameter Category/ Statistics | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) | Total (n = 3308) |
|---|---|---|---|---|---|---|---|
| Sex, n | | | | | | | |
| Female | 318 (76.1%) | 317 (77.3%) | 314 (76.4%) | 323 (77.8%) | 639 (77.3%) | 635 (76.8%) | 2546 (77.0%) |
| Male | 100 (23.9%) | 93 (22.7%) | 97 (23.6%) | 92 (22.2%) | 188 (22.7%) | 192 (23.2%) | 762 (23.0%) |
| Race, n | | | | | | | |
| White | 336 (80.4%) | 318 (77.6%) | 326 (79.3%) | 327 (78.8%) | 660 (79.8%) | 668 (80.8%) | 2635 (79.7%) |
| Black or African American | 13 (3.1%) | 17 (4.1%) | 7 (1.7%) | 13 (3.1%) | 32 (3.9%) | 27 (3.3%) | 109 (3.3%) |
| Asian | 60 (14.4%) | 69 (16.8%) | 68 (16.5%) | 66 (15.9%) | 121 (14.6%) | 116 (14.0%) | 500 (15.1%) |
| Other | 5 (1.2%) | 4 (1.0%) | 6 (1.5%) | 6 (1.4%) | 14 (1.7%) | 11 (1.3%) | 46 (1.4%) |
| Unknown | 4 (1.0%) | 2 (0.5%) | 4 (1.0%) | 3 (0.7%) | 0 | 5 (0.6%) | 18 (0.5%) |
| Ethnicity, n | | | | | | | |
| Not Hispanic | 387 (92.6%) | 394 (96.1%) | 382 (92.9%) | 387 (93.3%) | 770 (93.1%) | 764 (92.4%) | 3084 (93.2%) |
| Hispanic | 27 (6.5%) | 14 (3.4%) | 25 (6.1%) | 25 (6.0%) | 57 (6.9%) | 58 (7.0%) | 206 (6.2%) |
| Unknown | 4 (1.0%) | 2 (0.5%) | 4 (1.0%) | 3 (0.7%) | 0 | 5 (0.6%) | 18 (0.5%) |
| Geographic region, n | | | | | | | |
| Asia | 55 (13.2%) | 56 (13.7%) | 54 (13.1%) | 51 (12.3%) | 106 (12.8%) | 100 (12.1%) | 422 (12.8%) |
| Eastern Europe | 183 (43.8%) | 178 (43.4%) | 180 (43.8%) | 184 (44.3%) | 365 (44.1%) | 366 (44.3%) | 1456 (44.0%) |
| Latin America | 3 (0.7%) | 3 (0.7%) | 4 (1.0%) | 7 (1.7%) | 10 (1.2%) | 10 (1.2%) | 37 (1.1%) |
| North America | 108 (25.8%) | 108 (26.3%) | 110 (26.8%) | 108 (26.0%) | 216 (26.1%) | 218 (26.4%) | 868 (26.2%) |
| Southern hemisphere | 16 (3.8%) | 12 (2.9%) | 9 (2.2%) | 13 (3.1%) | 26 (3.1%) | 26 (3.1%) | 102 (3.1%) |
| Western Europe | 53 (12.7%) | 53 (12.9%) | 54 (13.1%) | 52 (12.5%) | 104 (12.6%) | 107 (12.9%) | 423 (12.8%) |
| Age (y), mean/median | 57.9/60.0 | 56.9/58.0 | 56.8/58.0 | 58.1/60.0 | 57.1/59.0 | 57.6/60.0 | 57.4/59.0 |
| ≥ 65, n | 141 (33.7%) | 135 (32.9%) | 128 (31.1%) | 135 (32.5%) | 273 (33.0%) | 279 (33.7%) | 1091 (33.0%) |
| ≥ 75, n | 36 (8.6%) | 30 (7.3%) | 32 (7.8%) | 33 (8.0%) | 66 (8.0%) | 69 (8.3%) | 266 (8.0%) |
| ≥ 85, n | 0 | 1 (0.2%) | 1 (0.2%) | 1 (0.2%) | 1 (0.1%) | 6 (0.7%) | 10 (0.3%) |
| Weight (kg) | | | | | | | |
| Mean (SD) | 78.77 (18.30) | 77.09 (20.04) | 77.01 (17.20) | 77.98 (17.77) | 77.87 (17.45) | 77.84 (17.56) | 77.79 (17.93) |
| Median | 75.75 | 75.00 | 75.80 | 75.00 | 77.00 | 75.50 | 75.80 |
| Min - Max | 45.1 - 150.0 | 37.4 - 205.0 | 37.5 - 184.5 | 43.0 - 150.5 | 42.0 - 165.5 | 42.5 - 145.1 | 37.4 - 205.0 |
| Height (cm) | | | | † | | | ‡ |
| Mean (SD) | 165.36 (8.85) | 165.24 (8.77) | 165.09 (8.78) | 165.26 (8.48) | 164.81 (8.88) | 164.75 (8.58) | 165.01 (8.72) |
| Median | 165.00 | 164.25 | 164.00 | 165.00 | 164.00 | 164.00 | 164.00 |
| Min - Max | 147.0 - 196.0 | 143.9 - 198.0 | 147.3 - 192.0 | 144.8 - 190.5 | 135.0 - 198.0 | 142.2 - 192.0 | 135.0 - 198.0 |
| BMI ($kg/m^2$) | | | | † | | | ‡ |
| Mean (SD) | 28.76 (6.11) | 28.17 (6.73) | 28.23 (5.92) | 28.51 (5.92) | 28.63 (5.88) | 28.62 (5.87) | 28.52 (6.03) |
| Median | 27.85 | 26.90 | 27.34 | 27.49 | 27.95 | 27.64 | 27.60 |
| Min - Max | 17.6 - 54.1 | 17.0 - 61.0 | 16.7 - 72.1 | 17.6 - 52.0 | 16.8 - 57.1 | 15.4 - 53.1 | 15.4 - 72.1 |

The full analysis set (FAS) included all randomized patients who took ≥ 1 dose of double-blind treatment and who recorded ≥ 1 micturition and ≥ 1 incontinence episode in the baseline diary and ≥ 1 micturition postbaseline. American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander are listed under the 'Other' race category.

BMI: body mass index (weight [kg]/height [$m^2$]); C: solifenacin + mirabegron combination therapy; M: mirabegron; Max: maximum; Min: minimum; S: solifenacin.

† Based on n = 414.

‡ Based on n = 3307.

Source: Table 12.1.2.1.2

**Table 3 Coprimary Endpoints of Change from Baseline to EoT in Mean Number of Incontinence Episodes/24 h and in Mean Number of Micturitions/24 h (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **Change from Baseline to EoT in Mean Number of Incontinence Episodes/24 h** | | | | | | | |
| | n | 412 | 409 | 406 | 413 | 823 | 816 |
| Baseline | Mean (SE) | 3.40 (0.17) | 3.42 (0.17) | 3.16 (0.17) | 3.59 (0.17) | 3.21 (0.11) | 3.15 (0.11) |
| EoT | Mean (SE) | 2.01 (0.16) | 1.66 (0.14) | 1.47 (0.14) | 1.66 (0.14) | 1.20 (0.08) | 1.23 (0.09) |
| Change from baseline | Mean (SE) | -1.40 (0.12) | -1.76 (0.14) | -1.69 (0.11) | -1.93 (0.13) | -2.01 (0.09) | -1.92 (0.08) |
| Adj. change from baseline† | Mean (SE) | -1.34 (0.10) | -1.70 (0.10) | -1.76 (0.10) | -1.79 (0.10) | -2.04 (0.07) | -1.98 (0.07) |
| | 95% 2-sided CI | (-1.53, -1.14) | (-1.90, -1.51) | (-1.95, -1.56) | (-1.98, -1.59) | (-2.18, -1.90) | (-2.12, -1.85) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.25 (0.12) | -0.20 (0.12) |
| | 95% 2-sided CI | | | | | (-0.49, -0.01) | (-0.44, 0.04) |
| | P value§ | | | | | 0.072 | 0.033 |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.34 (0.12) | -0.23 (0.12) |
| | 95% 2-sided CI | | | | | (-0.58, -0.10) | (-0.47, 0.01) |
| | P value | | | | | 0.001 | 0.052 |
| Adj. difference vs placebo‡¶ | Mean (SE) | NA | -0.37 (0.14) | -0.42 (0.14) | -0.45 (0.14) | -0.70 (0.12) | -0.65 (0.12) |
| | 95% 2-sided CI | | (-0.64, -0.09) | (-0.70, -0.14) | (-0.73, -0.17) | (-0.94, -0.46) | (-0.89, -0.41) |
| | P value§ | | 0.028 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| **Change from Baseline to EoT in Mean Number of Micturitions/24 h** | | | | | | | |
| | n | 412 | 409 | 406 | 413 | 823 | 816 |
| Baseline | Mean (SE) | 10.97 (0.14) | 10.81 (0.13) | 11.19 (0.16) | 10.74 (0.12) | 10.72 (0.10) | 10.72 (0.08) |
| EoT | Mean (SE) | 9.29 (0.16) | 8.81 (0.13) | 9.05 (0.19) | 8.57 (0.14) | 8.26 (0.11) | 8.16 (0.09) |
| Change from baseline | Mean (SE) | -1.67 (0.13) | -2.00 (0.13) | -2.14 (0.14) | -2.17 (0.12) | -2.46 (0.08) | -2.55 (0.08) |
| Adj. change from baseline† | Mean (SE) | -1.64 (0.12) | -2.00 (0.12) | -2.03 (0.12) | -2.20 (0.12) | -2.49 (0.08) | -2.59 (0.08) |
| | 95% 2-sided CI | (-1.86, -1.41) | (-2.23, -1.78) | (-2.26, -1.80) | (-2.42, -1.97) | (-2.65, -2.33) | (-2.75, -2.43) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.29 (0.14) | -0.39 (0.14) |
| | 95% 2-sided CI | | | | | (-0.57, -0.01) | (-0.67, -0.11) |
| | P value†† | | | | | 0.040 | 0.006 |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.48 (0.14) | -0.56 (0.14) |
| | 95% 2-sided CI | | | | | (-0.76, -0.21) | (-0.84, -0.28) |
| | P value†† | | | | | 0.001 | < 0.001 |
| Adj. difference vs placebo‡¶ | Mean (SE) | NA | -0.36 (0.16) | -0.39 (0.16) | -0.56 (0.16) | -0.85 (0.14) | -0.95 (0.14) |
| | 95% 2-sided CI | | (-0.69, -0.04) | (-0.71, -0.07) | (-0.88, -0.24) | (-1.13, -0.57) | (-1.23, -0.67) |
| | P value†† | | 0.026 | 0.016 | 0.001 | < 0.001 | < 0.001 |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the stratified rank ANCOVA.

¶ Secondary analysis.

†† The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA.

* Statistically significantly superior compared to monotherapy at the 0.05 level with multiplicity adjustment.

Source: Tables 12.3.1.1.1, 12.3.1.1.2

**Table 4 Change from Baseline to EoT in Mean Volume Voided Per Micturition (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| | n | 413 | 407 | 408 | 411 | 821 | 821 |
| Baseline | Mean (SE) | 157.82 (2.89) | 152.46 (3.02) | 155.35 (3.01) | 151.86 (2.91) | 159.19 (2.03) | 153.83 (2.08) |
| EoT | Mean (SE) | 166.22 (3.20) | 166.01 (3.34) | 177.14 (3.35) | 183.09 (3.68) | 193.80 (2.84) | 193.68 (2.96) |
| Change from baseline | Mean (SE) | 8.41 (2.20) | 13.55 (2.53) | 21.79 (2.18) | 31.23 (2.47) | 34.61 (1.91) | 39.85 (2.03) |
| Adj. change from baseline† | Mean (SE) | 8.44 (2.55) | 13.32 (2.57) | 21.99 (2.57) | 30.99 (2.56) | 34.84 (1.81) | 39.73 (1.81) |
| | 95% 2-sided CI | (3.44, 13.44) | (8.29, 18.36) | (16.96, 27.03) | (25.97, 36.00) | (31.29, 38.39) | (36.19, 43.28) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | 3.85 (3.13) | 8.75 (3.13) |
| | 95% 2-sided CI | | | | | (-2.29, 10.00) | (2.61, 14.89) |
| | P value | | | | | 0.219 | 0.005 |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 21.52 (3.14) | 17.74 (3.14) |
| | 95% 2-sided CI | | | | | (15.35, 27.68) | (11.58, 23.90) |
| | P value | | | | | < 0.001 | < 0.001 |
| Adj. difference vs placebo‡¶ | Mean (SE) | NA | 4.88 (3.62) | 13.55 (3.62) | 22.54 (3.61) | 26.40 (3.13) | 31.29 (3.13) |
| | 95% 2-sided CI | | (-2.22, 11.98) | (6.46, 20.65) | (15.46, 29.63) | (20.27, 32.53) | (25.16, 37.42) |
| | P value | | 0.178 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

Mean volume voided is presented as mL.

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above. The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA.

¶ Secondary analysis.

* Statistically significantly superior compared to monotherapy at the 0.05 level with multiplicity adjustment.

Source: Table 12.3.2.1.1

**Table 5 Change from Baseline to EoT in OAB-q Symptom Bother Score (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| | n | 400 | 392 | 398 | 399 | 800 | 795 |
| Baseline | Mean (SE) | 61.25 (0.95) | 60.64 (0.99) | 61.02 (0.92) | 64.49 (0.99) | 62.33 (0.72) | 61.18 (0.69) |
| EoT | Mean (SE) | 42.04 (1.13) | 37.36 (1.12) | 35.38 (1.08) | 36.58 (1.12) | 30.95 (0.75) | 29.31 (0.77) |
| Change from baseline | Mean (SE) | -19.21 (1.14) | -23.28 (1.17) | -25.64 (1.11) | -27.91 (1.05) | -31.39 (0.82) | -31.87 (0.83) |
| Adj. change from baseline† | Mean (SE) | -19.45 (0.98) | -23.93 (0.99) | -26.14 (0.98) | -26.44 (0.98) | -31.06 (0.69) | -32.24 (0.70) |
| | 95% 2-sided CI | (-21.38, -17.53) | (-25.88, -21.99) | (-28.07, -24.21) | (-28.37, -24.51) | (-32.42, -29.70) | (-33.61, -30.88) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -4.63 (1.20) | -5.80 (1.21) |
| | 95% 2-sided CI | | | | | (-6.98, -2.27) | (-8.17, -3.44) |
| | P value | | | | | <0.001 | <0.001 |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -7.13 (1.21) | -6.10 (1.20) |
| | 95% 2-sided CI | | | | | (-9.50, -4.76) | (-8.46, -3.74 ) |
| | P value | | | | | <0.001 | <0.001 |
| Adj. difference vs placebo‡¶ | Mean (SE) | NA | -4.48 (1.39) | -6.69 (1.39) | -6.98 (1.39) | -11.61 (1.20) | -12.79 (1.20) |
| | 95% 2-sided CI | | -(7.21, -1.75) | (-9.42, -3.97) | (-9.71, -4.26) | (-13.97, -9.25) | (-15.15, -10.43) |
| | P value | | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB-q: overactive bladder questionnaire; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above. The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA.

¶ Secondary analysis.

Source: Table 12.3.2.1.2

**Table 6 Change from Baseline to EoT in TS-VAS (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| | n | 399 | 391 | 398 | 399 | 798 | 794 |
| Baseline | Mean (SE) | 5.22 (0.19) | 5.28 (0.18) | 5.20 (0.18) | 5.21 (0.18) | 5.35 (0.13) | 5.33 (0.13) |
| EoT | Mean (SE) | 6.69 (0.15) | 7.44 (0.13) | 7.44 (0.13) | 7.55 (0.12) | 7.83 (0.08) | 7.86 (0.08) |
| Change from baseline | Mean (SE) | 1.47 (0.18) | 2.16 (0.17) | 2.23 (0.17) | 2.34 (0.18) | 2.48 (0.12) | 2.52 (0.13) |
| Adj. change from baseline† | Mean (SE) | 1.42 (0.11) | 2.16 (0.11) | 2.18 (0.11) | 2.28 (0.11) | 2.53 (0.08) | 2.55 (0.08) |
| | 95% 2-sided CI | (1.20, 1.64) | (1.93, 2.38) | (1.96, 2.40) | (2.06, 2.50) | (2.37, 2.69) | (2.40, 2.71) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | 0.25 (0.14) | 0.27 (0.14) |
| | 95% 2-sided CI | | | | | (-0.03, 0.52) | (0.00, 0.55) |
| | P value | | | | | 0.077 | 0.050 |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 0.37 (0.14) | 0.37 (0.14) |
| | 95% 2-sided CI | | | | | (0.10, 0.65) | (0.10, 0.65) |
| | P value | | | | | 0.008 | 0.007 |
| Adj. difference vs placebo‡¶ | Mean (SE) | NA | 0.74 (0.16) | 0.76 (0.16) | 0.86 (0.16) | 1.11 (0.14) | 1.14 (0.14) |
| | 95% 2-sided CI | | (0.42, 1.05) | (0.45, 1.08) | (0.55, 1.18) | (0.84, 1.38) | (0.86, 1.41) |
| | P value | | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin; TS-VAS: treatment satisfaction - visual analogue scale.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above. The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA. $P < 0.05$ indicates statistical significance at the 0.05 level.

¶ Secondary analysis.

Source: Table 12.3.2.1.3

**Table 7 Responders for Zero Incontinence Episodes/24 h at EoT Using Only the Last 3 Diary Days (FAS)**

| Statistic | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|
| n | 412 | 409 | 406 | 413 | 823 | 816 |
| Responders (%) † | 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% 2-sided CI (%) | | | | | (1.9%, 13.7%) | (3.5%, 15.2%) |
| Odds ratio vs S ¶ | NA | | | | 1.31 | 1.40 |
| 95% 2-sided CI for odds ratio | | | | | (1.02, 1.69) | (1.09, 1.81) |
| P value | | | | | 0.035* | 0.009* |
| Difference vs M (at same dose) ‡ | NA | | | | 10.1% | 5.9% |
| 95% 2-sided CI (%) | | | | | (4.2%, 15.9%) | (0.0%, 11.8%) |
| Odds ratio vs M (at same dose) ¶ | NA | | | | 1.50 | 1.34 |
| 95% 2-sided CI for odds ratio | | | | | (1.16, 1.93) | (1.04, 1.73) |
| P value | | | | | 0.002* | 0.023* |
| Difference vs placebo ‡ | NA | 3.0% | 8.7% | 5.2% | 13.0% | 14.6% |
| 95% 2-sided 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% 2-sided CI for odds ratio | | (0.87, 1.57) | (1.04, 1.87) | (0.99, 1.79) | (1.36, 2.26) | (1.45, 2.42) |
| P value | | 0.300 | 0.027* | 0.055 | < 0.001* | < 0.001* |

C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin.

† A responder is defined as a patient with zero incontinence episodes/24 h during the last 3 diary days prior to EoT.

‡ Differences of proportions are between combination/active therapy group and corresponding monotherapy/placebo group.

¶ Odds ratio and P value are from a logistic regression model including treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as factors and baseline value as a covariate. The 2-sided P value is for the pairwise comparisons between the combination/active therapy group and the corresponding monotherapy/placebo group from the same logistic regression model.

* $P < 0.05$ indicates statistical significance compared to monotherapy/placebo at the 0.05 level (without multiplicity adjustment).

Source: Table 12.3.3.18

**Table 8 Responders for Micturition Frequency Normalization at EoT (FAS)**

| Statistic | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|
| n | 412 | 409 | 406 | 413 | 823 | 816 |
| Responders (%) † | 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% 2-sided CI (%) | | | | | (0.4%, 12.1%) | (1.6%, 13.4%) |
| Odds ratio vs S § | NA | | | | 1.30 | 1.43 |
| 95% 2-sided CI for odds ratio | | | | | (1.01, 1.67) | (1.11, 1.84) |
| P value | | | | | 0.044* | 0.006* |
| Difference vs M (at same dose) ‡ | NA | | | | 9.2% | 12.4% |
| 95% 2-sided CI (%) | | | | | (3.3%, 15.1%) | (6.6%, 18.3%) |
| Odds ratio vs M (at same dose) § | NA | | | | 1.47 | 1.60 |
| 95% 2-sided CI for odds ratio | | | | | (1.13, 1.90) | (1.23, 2.08) |
| P value | | | | | 0.004* | <0.001* |
| Difference vs placebo ‡ | NA | 11.0% | 9.1% | 14.0% | 20.2% | 21.5% |
| 95% 2-sided 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% 2-sided CI for odds ratio | | (1.22, 2.25) | (1.23, 2.27) | (1.38, 2.54) | (1.86, 3.18) | (2.04, 3.49) |
| P value | | 0.001* | 0.001* | < 0.001* | < 0.001* | < 0.001* |

C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin.

† A responder is defined as a patient who had ≥ 8 micturitions/24 h at baseline and < 8 micturitions/24 h at EoT.

‡ Differences of proportions are between combination/active therapy group and corresponding monotherapy/placebo group.

§ Odds ratio and P value are from a logistic regression model including treatment group, sex, age group (<65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as factors and baseline value as covariate. The 2-sided P value is for the pairwise comparisons between the combination/active therapy group and the corresponding monotherapy/placebo group from the same logistic regression model.

* P < 0.05 indicates statistical significance compared to monotherapy/placebo at the 0.05 level (without multiplicity adjustment).

Source: Table 12.3.3.19

**Table 9 Change from Baseline in Mean Number of Urgency Episodes (Grade 3 or 4)/24 h (PPIUS Scale) (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| | n | 411 | 409 | 406 | 413 | 823 | 816 |
| Baseline | Mean (SE) | 6.51 (0.20) | 6.22 (0.19) | 6.46 (0.24) | 6.44 (0.19) | 6.21 (0.13) | 6.23 (0.13) |
| EoT | Mean (SE) | 4.36 (0.20) | 3.53 (0.17) | 3.77 (0.25) | 3.33 (0.18) | 2.87 (0.12) | 2.76 (0.11) |
| Change from baseline | Mean (SE) | -2.15 (0.19) | -2.69 (0.18) | -2.70 (0.19) | -3.11 (0.17) | -3.34 (0.12) | -3.47 (0.12) |
| Adj. change from baseline† | Mean (SE) | -2.06 (0.15) | -2.74 (0.15) | -2.63 (0.15) | -3.05 (0.15) | -3.38 (0.11) | -3.51 (0.11) |
| | 95% 2-sided CI | (-2.36, -1.77) | (-3.03, -2.44) | (-2.93, -2.33) | (-3.35, -2.76) | (-3.59, -3.17) | (-3.72, -3.30) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.33 (0.18) | -0.45 (0.18) |
| | 95% 2-sided CI | | | | | (-0.69, 0.03) | (-0.82, -0.09) |
| | P value | | | | | 0.074 | 0.014* |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.65 (0.18) | -0.87 (0.19) |
| | 95% 2-sided CI | | | | | (-1.01, -0.28) | (-1.24, -0.51) |
| | P value | | | | | < 0.001* | < 0.001* |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.67 (0.21) | -0.57 (0.21) | -0.99 (0.21) | -1.32 (0.18) | -1.44 (0.18) |
| | 95% 2-sided CI | | (-1.09, -0.26) | (-0.99, -0.15) | (-1.41, -0.57) | (-1.68, -0.96) | (-1.81, -1.08) |
| | P value | | 0.002* | 0.008* | < 0.001* | < 0.001* | < 0.001* |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; PPIUS: patient perception of intensity of urgency scale; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above. The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA model described above.

* $P < 0.05$ indicates statistically significantly different compared to monotherapy/placebo at the 0.05 level (without multiplicity adjustment).

Source: Table 12.3.3.9

**Table 10 Change from Baseline to EoT in Mean Number of Nocturia Episodes/24 h (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| | n | 363 | 344 | 353 | 350 | 708 | 697 |
| Baseline | Mean (SE) | 1.57 (0.06) | 1.53 (0.06) | 1.60 (0.06) | 1.60 (0.05) | 1.56 (0.04) | 1.52 (0.04) |
| EoT | Mean (SE) | 1.30 (0.06) | 1.15 (0.05) | 1.19 (0.06) | 1.19 (0.05) | 1.08 (0.03) | 0.98 (0.03) |
| Change from baseline | Mean (SE) | -0.27 (0.05) | -0.38 (0.05) | -0.41 (0.05) | -0.41 (0.05) | -0.48 (0.03) | -0.54 (0.03) |
| Adj. change from baseline† | Mean (SE) | -0.27 (0.04) | -0.40 (0.04) | -0.39 (0.04) | -0.39 (0.04) | -0.48 (0.03) | -0.56 (0.03) |
| | 95% 2-sided CI | (-0.35, -0.20) | (-0.48, -0.32) | (-0.47, -0.31) | (-0.47, -0.31) | (-0.53, -0.42) | (-0.61, -0.50) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.09 (0.05) | -0.17 (0.05) |
| | 95% 2-sided CI | | | | | (-0.19, 0.01) | (-0.26, -0.07) |
| | P value | | | | | 0.065 | 0.001* |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.08 (0.05) | -0.17 (0.05) |
| | 95% 2-sided CI | | | | | (-0.18, 0.02) | (-0.26, -0.07) |
| | P value | | | | | 0.100 | 0.001* |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.12 (0.06) | -0.12 (0.06) | -0.11 (0.06) | -0.20 (0.05) | -0.28 (0.05) |
| | 95% 2-sided CI | | (-0.23, -0.01) | (-0.22, -0.01) | (-0.22, 0.00) | (-0.30, -0.11) | (-0.38, -0.19) |
| | P value | | 0.029* | 0.040* | 0.042* | < 0.001* | < 0.001* |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous overactive bladder medication (yes, no) and geographic region as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above. The 2-sided P value is for pairwise comparisons between the combination/active group and the corresponding monotherapy/placebo group from the ANCOVA model described above.

* P < 0.05 indicates statistically significantly different from monotherapy/placebo at the 0.05 level (without multiplicity adjustment).

Source: Table 12.3.3.10

**Table 11 Change from Baseline to EoT in Mean Number of Incontinence Episodes/24 h by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 214 | 216 | 219 | 214 | 446 | 440 |
| Baseline | Mean (SE) | 3.53 (0.25) | 3.19 (0.22) | 3.11 (0.24) | 3.34 (0.25) | 3.13 (0.15) | 2.98 (0.15) |
| EoT | Mean (SE) | 2.11 (0.24) | 1.70 (0.20) | 1.40 (0.21) | 1.43 (0.19) | 1.31 (0.12) | 1.21 (0.14) |
| Change from baseline | Mean (SE) | -1.42 (0.16) | -1.49 (0.16) | -1.71 (0.15) | -1.91 (0.19) | -1.82 (0.12) | -1.77 (0.11) |
| Adj. change from baseline† | Mean (SE) | -1.33 (0.14) | -1.55 (0.14) | -1.82 (0.14) | -1.91 (0.14) | -1.90 (0.10) | -1.92 (0.10) |
| | 95% 2-sided CI | (-1.60, -1.06) | (-1.82, -1.28) | (-2.08, -1.55) | (-2.18, -1.64) | (-2.09, -1.71) | (-2.11, -1.73) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | 0.01 (0.17) | -0.01 (0.17) |
| | 95% 2-sided CI | | | | | (-0.32, 0.34) | (-0.34, 0.32) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.35 (0.17) | -0.11 (0.17) |
| | 95% 2-sided CI | | | | | (-0.68, -0.02) | (-0.44, 0.22) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.22 (0.20) | -0.48 (0.19) | -0.58 (0.20) | -0.57 (0.17) | -0.59 (0.17) |
| | 95% 2-sided CI | | (-0.60, 0.17) | (-0.86, -0.10) | (-0.96, -0.19) | (-0.90, -0.24) | (-0.92, -0.26) |
| **Previous OAB Medication (Interaction P value = 0.162)§** | | | | | | | |
| | n | 198 | 193 | 187 | 199 | 377 | 376 |
| Baseline | Mean (SE) | 3.27 (0.22) | 3.67 (0.26) | 3.22 (0.24) | 3.87 (0.24) | 3.31 (0.16) | 3.36 (0.16) |
| EoT | Mean (SE) | 1.90 (0.20) | 1.61 (0.18) | 1.55 (0.18) | 1.92 (0.21) | 1.07 (0.11) | 1.25 (0.13) |
| Change from baseline | Mean (SE) | -1.37 (0.17) | -2.07 (0.22) | -1.67 (0.18) | -1.95 (0.16) | -2.24 (0.13) | -2.11 (0.13) |
| Adj. change from baseline† | Mean (SE) | -1.35 (0.14) | -1.88 (0.15) | -1.69 (0.15) | -1.66 (0.14) | -2.21 (0.10) | -2.05 (0.10) |
| | 95% 2-sided CI | (-1.63, -1.07) | (-2.16, -1.59) | (-1.98, -1.40) | (-1.94, -1.38) | (-2.41, -2.00) | (-2.26, -1.85) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.54 (0.18) | -0.39 (0.18) |
| | 95% 2-sided CI | | | | | (-0.89, -0.19) | (-0.74, -0.04) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.33 (0.18) | -0.37 (0.18) |
| | 95% 2-sided CI | | | | | (-0.68, 0.02) | (-0.72, -0.01) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.53 (0.20) | -0.34 (0.21) | -0.32 (0.20) | -0.86 (0.18) | -0.71 (0.18) |
| | 95% 2-sided CI | | (-0.93, -0.13) | (-0.74, 0.07) | (-0.71, 0.08) | (-1.21, -0.51) | (-1.05, -0.36) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.1.4.11

**Table 12 Change from Baseline to EoT in Mean Number of Micturitions/24 h by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 214 | 216 | 219 | 214 | 446 | 440 |
| Baseline | Mean (SE) | 10.92 (0.19) | 10.91 (0.18) | 11.42 (0.23) | 10.79 (0.17) | 10.65 (0.14) | 10.63 (0.11) |
| EoT | Mean (SE) | 8.91 (0.22) | 8.52 (0.19) | 8.91 (0.27) | 8.40 (0.20) | 8.10 (0.15) | 8.04 (0.12) |
| Change from baseline | Mean (SE) | -2.01 (0.17) | -2.39 (0.20) | -2.52 (0.22) | -2.39 (0.20) | -2.55 (0.11) | -2.59 (0.12) |
| Adj. change from baseline† | Mean (SE) | -1.99 (0.16) | -2.35 (0.16) | -2.32 (0.16) | -2.41 (0.16) | -2.60 (0.11) | -2.65 (0.11) |
| | 95% 2-sided CI | (-2.30, -1.68) | (-2.66, -2.04) | (-2.64, -2.01) | (-2.72, -2.10) | (-2.82, -2.38) | (-2.87, -2.43) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.19 (0.19) | -0.24 (0.19) |
| | 95% 2-sided CI | | | | | (-0.57, 0.19) | (-0.62, 0.14) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.25 (0.19) | -0.32 (0.19) |
| | 95% 2-sided CI | | | | | (-0.63, 0.13) | (-0.70, 0.06) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.36 (0.23) | -0.33 (0.22) | -0.42 (0.23) | -0.61 (0.19) | -0.66 (0.19) |
| | 95% 2-sided CI | | (-0.80, 0.08) | (-0.78, 0.11) | (-0.86, 0.02) | (-0.99, -0.23) | (-1.04, -0.28) |
| **Previous OAB Medication (Interaction P value = 0.110)§** | | | | | | | |
| | n | 198 | 193 | 187 | 199 | 377 | 376 |
| Baseline | Mean (SE) | 11.01 (0.21) | 10.70 (0.18) | 10.92 (0.23) | 10.67 (0.17) | 10.81 (0.14) | 10.81 (0.12) |
| EoT | Mean (SE) | 9.71 (0.22) | 9.13 (0.19) | 9.21 (0.28) | 8.75 (0.18) | 8.46 (0.15) | 8.30 (0.13) |
| Change from baseline | Mean (SE) | -1.31 (0.18) | -1.57 (0.17) | -1.70 (0.15) | -1.92 (0.14) | -2.35 (0.13) | -2.52 (0.11) |
| Adj. change from baseline† | Mean (SE) | -1.24 (0.17) | -1.61 (0.17) | -1.69 (0.17) | -1.95 (0.17) | -2.36 (0.12) | -2.52 (0.12) |
| | 95% 2-sided CI | (-1.57, -0.92) | (-1.94, -1.28) | (-2.03, -1.36) | (-2.28, -1.63) | (-2.59, -2.12) | (-2.76, -2.28) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -0.40 (0.20) | -0.57 (0.21) |
| | 95% 2-sided CI | | | | | (-0.81, 0.00) | (-0.97, -0.17) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.75 (0.21) | -0.83 (0.21) |
| | 95% 2-sided CI | | | | | (-1.15, -0.34) | (-1.24, -0.42) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.37 (0.24) | -0.45 (0.24) | -0.71 (0.23) | -1.11 (0.21) | -1.28 (0.21) |
| | 95% 2-sided CI | | (-0.83, 0.10) | (-0.92, 0.02) | (-1.17, -0.25) | (-1.51, -0.71) | (-1.68, -0.87) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.1.5.11

**Table 13 Change from Baseline to EoT in Mean Volume Voided per Micturition by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 219 | 216 | 221 | 215 | 448 | 446 |
| Baseline | Mean (SE) | 154.97 (4.11) | 145.76 (4.10) | 148.49 (4.12) | 146.97 (3.93) | 157.60 (2.80) | 152.88 (3.03) |
| EoT | Mean (SE) | 166.08 (4.52) | 159.42 (4.57) | 171.02 (4.71) | 179.78 (5.40) | 190.49 (3.91) | 186.94 (4.07) |
| Change from baseline | Mean (SE) | 11.11 (3.33) | 13.66 (3.88) | 22.53 (3.06) | 32.81 (3.55) | 32.89 (2.66) | 34.05 (2.72) |
| Adj. change from baseline† | Mean (SE) | 12.05 (3.50) | 13.89 (3.53) | 23.02 (3.49) | 33.20 (3.54) | 33.79 (2.45) | 34.68 (2.46) |
| | 95% 2-sided CI | (5.18, 18.92) | (6.96, 20.81) | (16.18, 29.86) | (26.26, 40.14) | (28.98, 38.60) | (29.86, 39.50) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | 0.59 (4.30) | 1.48 (4.30) |
| | 95% 2-sided CI | | | | | (-7.84, 9.02) | (-6.95, 9.91) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 19.90 (4.29) | 11.66 (4.26) |
| | 95% 2-sided CI | | | | | (11.49, 28.32) | (3.31, 20.02) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | 1.83 (4.97) | 10.96 (4.94) | 21.15 (4.97) | 21.74 (4.27) | 22.63 (4.27) |
| | 95% 2-sided CI | | (-7.91, 11.57) | (1.28, 20.65) | (11.40, 30.90) | (13.36, 30.11) | (14.25, 31.00) |
| **Previous OAB Medication (Interaction P value = 0.030)§** | | | | | | | |
| | n | 194 | 191 | 187 | 196 | 373 | 375 |
| Baseline | Mean (SE) | 161.03 (4.05) | 160.04 (4.41) | 163.46 (4.35) | 157.21 (4.30) | 161.10 (2.95) | 154.96 (2.79) |
| EoT | Mean (SE) | 166.39 (4.54) | 173.47 (4.84) | 184.37 (4.69) | 186.71 (4.94) | 197.79 (4.13) | 201.70 (4.26) |
| Change from baseline | Mean (SE) | 5.36 (2.79) | 13.43 (3.14) | 20.91 (3.09) | 29.50 (3.44) | 36.68 (2.73) | 46.74 (3.02) |
| Adj. change from baseline† | Mean (SE) | 4.38 (3.72) | 12.72 (3.75) | 20.78 (3.79) | 28.60 (3.70) | 36.07 (2.69) | 45.73 (2.68) |
| | 95% 2-sided CI | (-2.92, 11.68) | (5.37, 20.08) | (13.34, 28.21) | (21.34, 35.86) | (30.80, 41.34) | (40.47, 50.99) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | 7.46 (4.57) | 17.13 (4.56) |
| | 95% 2-sided CI | | | | | (-1.50, 16.42) | (8.18, 26.08) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 23.34 (4.61) | 24.95 (4.64) |
| | 95% 2-sided CI | | | | | (14.31, 32.37) | (15.86, 34.04) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | 8.34 (5.28) | 16.40 (5.31) | 24.23 (5.24) | 31.69 (4.58) | 41.35 (4.58) |
| | 95% 2-sided CI | | (-2.00, 18.69) | (6.00, 26.80) | (13.94, 34.51) | (22.70, 40.67) | (32.37, 50.33) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.2.5.11

**Table 14 Change from Baseline to EoT in Symptom Bother Score by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 212 | 206 | 217 | 211 | 436 | 426 |
| Baseline | Mean (SE) | 61.90 (1.30) | 58.99 (1.36) | 60.25 (1.19) | 63.48 (1.42) | 62.09 (0.99) | 59.44 (0.92) |
| EoT | Mean (SE) | 38.99 (1.54) | 33.75 (1.49) | 31.16 (1.38) | 35.74 (1.52) | 30.70 (1.03) | 28.16 (1.01) |
| Change from baseline | Mean (SE) | -22.91 (1.62) | -25.24 (1.58) | -29.09 (1.49) | -27.74 (1.48) | -31.39 (1.12) | -31.29 (1.13) |
| Adj. change from baseline† | Mean (SE) | -23.30 (1.35) | -27.05 (1.37) | -30.23 (1.33) | -27.24 (1.35) | -31.59 (0.94) | -32.98 (0.95) |
| | 95% 2-sided CI | (-25.94, -20.66) | (-29.73, -24.37) | (-32.84, -27.62) | (-29.89, -24.60) | (-33.43, -29.75) | (-34.84, -31.11) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -4.35 (1.64) | -5.73 (1.65) |
| | 95% 2-sided CI | | | | | (-7.57, -1.13) | (-8.97, -2.50) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -4.54 (1.66) | -2.75 (1.63) |
| | 95% 2-sided CI | | | | | (-7.79, -1.29) | (-5.95, 0.45) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -3.75 (1.92) | -6.93 (1.89) | -3.94 (1.90) | -8.29 (1.64) | -9.68 (1.65) |
| | 95% 2-sided CI | | (-7.51, 0.01) | (-10.64, -3.22) | (-7.68, -0.21) | (-11.50, -5.08) | (-12.90, -6.45) |
| **Previous OAB Medication (Interaction P value = 0.001)§** | | | | | | | |
| | n | 188 | 186 | 181 | 188 | 364 | 369 |
| Baseline | Mean (SE) | 60.52 (1.40) | 62.47 (1.44) | 61.93 (1.43) | 65.63 (1.38) | 62.62 (1.03) | 63.18 (1.03) |
| EoT | Mean (SE) | 45.49 (1.64) | 41.36 (1.65) | 40.43 (1.62) | 37.51 (1.66) | 31.24 (1.08) | 30.63 (1.17) |
| Change from baseline | Mean (SE) | -15.03 (1.54) | -21.11 (1.72) | -21.51 (1.61) | -28.11 (1.49) | -31.38 (1.20) | -32.55 (1.22) |
| Adj. change from baseline† | Mean (SE) | -15.06 (1.43) | -20.39 (1.44) | -21.33 (1.46) | -25.47 (1.43) | -30.51 (1.03) | -31.39 (1.02) |
| | 95% 2-sided CI | -17.87, -12.26) | (-23.21, -17.58) | (-24.18, -18.47) | (-28.28, -22.67) | (-32.52, -28.49) | (-33.39, -29.38) |
| Adj. difference vs S‡ | Mean (SE) | NA | | | | -5.03 (1.76) | -5.91 (1.75) |
| | 95% 2-sided CI | | | | | (-8.48, -1.58) | (-9.35, -2.47) |
| Adj. difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -10.11 (1.76) | -10.06 (1.78) |
| | 95% 2-sided CI | | | | | (-13.57, -6.66) | (-13.54, -6.58) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -5.33 (2.02) | -6.26 (2.04) | -10.41 (2.02) | -15.44 (1.76) | -16.32 (1.75) |
| | 95% 2-sided CI | | (-9.30, -1.36) | (-10.26, -2.26) | (-14.37, -6.45) | (-18.89, -12.00) | (-19.76, -12.88) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.2.6.11

**Table 15 Change from Baseline to EoT in TS-VAS by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 211 | 206 | 217 | 211 | 435 | 425 |
| Baseline | Mean (SE) | 5.38 (0.25) | 5.24 (0.25) | 5.35 (0.24) | 5.33 (0.25) | 5.51 (0.17) | 5.38 (0.18) |
| EoT | Mean (SE) | 6.85 (0.21) | 7.66 (0.17) | 7.71 (0.15) | 7.71 (0.16) | 7.84 (0.10) | 7.93 (0.11) |
| Change from baseline | Mean (SE) | 1.47 (0.25) | 2.42 (0.24) | 2.36 (0.23) | 2.38 (0.27) | 2.33 (0.16) | 2.56 (0.17) |
| Adj. change from baseline† | Mean (SE) | 1.57 (0.16) | 2.41 (0.16) | 2.43 (0.15) | 2.42 (0.16) | 2.52 (0.11) | 2.64 (0.11) |
| | 95% 2-sided CI | (1.26, 1.88) | (2.10, 2.72) | (2.13, 2.74) | (2.12, 2.73) | (2.30, 2.73) | (2.42, 2.86) |
| Difference vs S‡ | Mean (SE) | NA | | | | 0.09 (0.19) | 0.22 (0.19) |
| | 95% 2-sided CI | | | | | (-0.28, 0.46) | (-0.16, 0.59) |
| Difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 0.11 (0.19) | 0.21 (0.19) |
| | 95% 2-sided CI | | | | | (-0.27, 0.48) | (-0.16, 0.58) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | 0.84 (0.22) | 0.86 (0.22) | 0.86 (0.22) | 0.95 (0.19) | 1.07 (0.19) |
| | 95% 2-sided CI | | (0.40, 1.27) | (0.43, 1.29) | (0.42, 1.29) | (0.57, 1.32) | (0.70, 1.45) |
| **Previous OAB Medication (Interaction P value = 0.244)§** | | | | | | | |
| | n | 188 | 185 | 181 | 188 | 363 | 369 |
| Baseline | Mean (SE) | 5.04 (0.28) | 5.33 (0.26) | 5.03 (0.27) | 5.07 (0.27) | 5.16 (0.20) | 5.28 (0.19) |
| EoT | Mean (SE) | 6.50 (0.23) | 7.20 (0.21) | 7.10 (0.21) | 7.36 (0.18) | 7.82 (0.11) | 7.76 (0.12) |
| Change from baseline | Mean (SE) | 1.46 (0.27) | 1.86 (0.24) | 2.08 (0.26) | 2.29 (0.26) | 2.66 (0.19) | 2.48 (0.19) |
| Adj. change from baseline† | Mean (SE) | 1.25 (0.17) | 1.87 (0.17) | 1.88 (0.17) | 2.12 (0.17) | 2.55 (0.12) | 2.46 (0.12) |
| | 95% 2-sided CI | (0.92, 1.57) | (1.54, 2.20) | (1.55, 2.21) | (1.79, 2.44) | (2.31, 2.78) | (2.22, 2.69) |
| Difference vs S‡ | Mean (SE) | NA | | | | 0.43 (0.20) | 0.34 (0.20) |
| | 95% 2-sided CI | | | | | (0.03, 0.83) | (-0.06, 0.74) |
| Difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | 0.68 (0.20) | 0.57 (0.21) |
| | 95% 2-sided CI | | | | | (0.28, 1.08) | (0.17, 0.98) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | 0.63 (0.23) | 0.64 (0.24) | 0.87 (0.23) | 1.30 (0.20) | 1.21 (0.20) |
| | 95% 2-sided CI | | (0.17, 1.09) | (0.17, 1.10) | (0.41, 1.33) | (0.90, 1.70) | (0.81, 1.61) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin; TS-VAS: treatment satisfaction - visual analogue scale.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.2.7.11

**Table 16 Change from Baseline to EoT in Mean Number of Urgency Episodes (Grade 3 or 4)/24 h by Use of Previous OAB Medication (FAS)**

| Statistic | | Placebo (n = 418) | M 25 mg (n = 410) | M 50 mg (n = 411) | S 5 mg (n = 415) | C 5 + 25 mg (n = 827) | C 5 + 50 mg (n = 827) |
|---|---|---|---|---|---|---|---|
| **No Previous OAB Medication** | | | | | | | |
| | n | 214 | 216 | 219 | 214 | 446 | 440 |
| Baseline | Mean (SE) | 6.80 (0.31) | 6.06 (0.25) | 6.87 (0.36) | 6.56 (0.28) | 6.18 (0.18) | 6.04 (0.18) |
| EoT | Mean (SE) | 4.11 (0.30) | 3.02 (0.23) | 3.58 (0.35) | 3.01 (0.25) | 2.94 (0.17) | 2.53 (0.15) |
| Change from baseline | Mean (SE) | -2.70 (0.27) | -3.04 (0.24) | -3.28 (0.29) | -3.55 (0.27) | -3.24 (0.17) | -3.51 (0.18) |
| Adj. change from baseline† | Mean (SE) | -2.48 (0.21) | -3.16 (0.21) | -3.03 (0.21) | -3.44 (0.21) | -3.30 (0.14) | -3.64 (0.15) |
| | 95% 2-sided CI | (-2.88, -2.07) | (-3.56, -2.75) | (-3.44, -2.63) | (-3.85, -3.03) | (-3.58, -3.01) | (-3.93, -3.35) |
| Difference vs S‡ | Mean (SE) | NA | | | | 0.14 (0.25) | -0.20 (0.25) |
| | 95% 2-sided CI | | | | | (-0.36, 0.64) | (-0.70, 0.30) |
| Difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -0.14 (0.25) | -0.61 (0.25) |
| | 95% 2-sided CI | | | | | (-0.64, 0.35) | (-1.10, -0.11) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.68 (0.29) | -0.56 (0.29) | -0.96 (0.29) | -0.82 (0.25) | -1.16 (0.25) |
| | 95% 2-sided CI | | (-1.26, -0.10) | (-1.13, 0.02) | (-1.54, -0.38) | (-1.32, -0.32) | (-1.66, -0.67) |
| **Previous OAB Medication (Interaction P value = 0.004)§** | | | | | | | |
| | n | 197 | 193 | 187 | 199 | 377 | 376 |
| Baseline | Mean (SE) | 6.18 (0.25) | 6.40 (0.29) | 5.99 (0.31) | 6.30 (0.25) | 6.25 (0.18) | 6.45 (0.18) |
| EoT | Mean (SE) | 4.63 (0.26) | 4.10 (0.26) | 3.98 (0.35) | 3.67 (0.25) | 2.79 (0.16) | 3.03 (0.16) |
| Change from baseline | Mean (SE) | -1.55 (0.24) | -2.30 (0.26) | -2.01 (0.21) | -2.64 (0.21) | -3.46 (0.17) | -3.42 (0.17) |
| Adj. change from baseline† | Mean (SE) | -1.60 (0.22) | -2.26 (0.22) | -2.17 (0.22) | -2.63 (0.22) | -3.49 (0.16) | -3.36 (0.16) |
| | 95% 2-sided CI | (-2.03, -1.17) | (-2.69, -1.83) | (-2.61, -1.73) | (-3.05, -2.20) | (-3.80, -3.18) | (-3.67, -3.05) |
| Difference vs S‡ | Mean (SE) | NA | | | | -0.86 (0.27) | -0.73 (0.27) |
| | 95% 2-sided CI | | | | | (-1.39, -0.34) | (-1.25, -0.21) |
| Difference vs M (at the same dose)‡ | Mean (SE) | NA | | | | -1.23 (0.27) | -1.19 (0.27) |
| | 95% 2-sided CI | | | | | (-1.76, -0.70) | (-1.72, -0.65) |
| Adj. difference vs placebo‡ | Mean (SE) | NA | -0.66 (0.31) | -0.57 (0.31) | -1.03 (0.31) | -1.89 (0.27) | -1.76 (0.27) |
| | 95% 2-sided CI | | (-1.26, -0.05) | (-1.18, 0.04) | (-1.63, -0.42) | (-2.42, -1.36) | (-2.28, -1.23) |

Adj.: adjusted; ANCOVA: analysis of covariance; C: solifenacin + mirabegron combination therapy; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; M: mirabegron; NA: not applicable; OAB: overactive bladder; S: solifenacin.

† Adjusted change from baseline values as well as the 95% CIs from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous OAB medication (yes, no), geographic region and interaction between previous OAB medication (yes, no) and treatment group as fixed factors and baseline value as a covariate.

‡ Difference of the adjusted mean calculated by subtracting the adjusted mean of the corresponding monotherapy/placebo group from the adjusted mean of the combination/active group based on the ANCOVA model described above.

§ Interaction between previous OAB medication (yes, no) and treatment group. Interaction considered statistically significant if $P \leq 0.10$. ANCOVA model adjusted estimates of an entire subgroup level were not displayed if at least 1 subgroup-by-treatment stratum had $n < 10$.

Source: Table 12.3.3.25.11

**Table 17 Treatment-Emergent Adverse Events Reported by ≥ 1.0% of Patients in Any Treatment group (SAF)**

| MedDRA (v16.0)<br>System Organ Class<br>Preferred Term, n | Placebo<br>(n = 429) | M 25 mg<br>(n = 423) | M 50 mg<br>(n = 422) | S 5 mg<br>(n = 423) | C 5 + 25 mg<br>(n = 853) | C 5 + 50 mg<br>(n = 848) |
|---|---|---|---|---|---|---|
| **Gastrointestinal disorders** | **21 (4.9%)** | **25 (5.9%)** | **27 (6.4%)** | **33 (7.8%)** | **112 (13.1%)** | **102 (12.0%)** |
| Dry mouth | 8 (1.9%) | 17 (4.0%) | 14 (3.3%) | 25 (5.9%) | 72 (8.4%) | 60 (7.1%) |
| Constipation | 6 (1.4%) | 6 (1.4%) | 11 (2.6%) | 6 (1.4%) | 38 (4.5%) | 31 (3.7%) |
| Diarrhoea | 6 (1.4%) | 6 (1.4%) | 4 (0.9%) | 2 (0.5%) | 9 (1.1%) | 7 (0.8%) |
| Dyspepsia | 3 (0.7%) | 1 (0.2%) | 1 (0.2%) | 1 (0.2%) | 10 (1.2%) | 16 (1.9%) |
| **Infections and infestations** | **43 (10.0%)** | **32 (7.6%)** | **40 (9.5%)** | **45 (10.6%)** | **88 (10.3%)** | **69 (8.1%)** |
| Urinary tract infection | 13 (3.0%) | 8 (1.9%) | 8 (1.9%) | 9 (2.1%) | 31 (3.6%) | 15 (1.8%) |
| Nasopharyngitis | 8 (1.9%) | 13 (3.1%) | 14 (3.3%) | 12 (2.8%) | 14 (1.6%) | 15 (1.8%) |
| Escherichia urinary tract infection | 5 (1.2%) | 4 (0.9%) | 4 (0.9%) | 10 (2.4%) | 16 (1.9%) | 14 (1.7%) |
| Influenza | 6 (1.4%) | 3 (0.7%) | 2 (0.5%) | 4 (0.9%) | 7 (0.8%) | 11 (1.3%) |
| Upper respiratory tract infection | 3 (0.7%) | 2 (0.5%) | 5 (1.2%) | 9 (2.1%) | 6 (0.7%) | 7 (0.8%) |
| Bronchitis | 6 (1.4%) | 3 (0.7%) | 2 (0.5%) | 1 (0.2%) | 11 (1.3%) | 4 (0.5%) |
| Sinusitis | 5 (1.2%) | 1 (0.2%) | 2 (0.5%) | 1 (0.2%) | 5 (0.6%) | 2 (0.2%) |
| Pharyngitis | 1 (0.2%) | 1 (0.2%) | 5 (1.2%) | 2 (0.5%) | 2 (0.2%) | 3 (0.4%) |
| **Nervous system disorders** | **13 (3.0%)** | **12 (2.8%)** | **10 (2.4%)** | **10 (2.4%)** | **28 (3.3%)** | **13 (1.5%)** |
| Headache | 11 (2.6%) | 9 (2.1%) | 6 (1.4%) | 7 (1.7%) | 17 (2.0%) | 12 (1.4%) |
| Dizziness | 2 (0.5%) | 3 (0.7%) | 6 (1.4%) | 3 (0.7%) | 12 (1.4%) | 1 (0.1%) |
| **Musculoskeletal and connective tissue disorders** | **7 (1.6%)** | **8 (1.9%)** | **9 (2.1%)** | **8 (1.9%)** | **12 (1.4%)** | **24 (2.8%)** |
| Back pain | 4 (0.9%) | 4 (0.9%) | 6 (1.4%) | 4 (0.9%) | 8 (0.9%) | 12 (1.4%) |
| Arthralgia | 4 (0.9%) | 4 (0.9%) | 3 (0.7%) | 4 (0.9%) | 5 (0.6%) | 12 (1.4%) |
| **Cardiac disorders** | **3 (0.7%)** | **5 (1.2%)** | **6 (1.4%)** | **2 (0.5%)** | **17 (2.0%)** | **11 (1.3%)** |
| Tachycardia | 3 (0.7%) | 5 (1.2%) | 6 (1.4%) | 2 (0.5%) | 17 (2.0%) | 11 (1.3%) |
| **Vascular disorders** | **5 (1.2%)** | **3 (0.7%)** | **6 (1.4%)** | **8 (1.9%)** | **11 (1.3%)** | **11 (1.3%)** |
| Hypertension | 5 (1.2%) | 3 (0.7%) | 6 (1.4%) | 8 (1.9%) | 11 (1.3%) | 11 (1.3%) |
| **General disorders and administration site conditions** | **4 (0.9%)** | **5 (1.2%)** | **1 (0.2%)** | **2 (0.5%)** | **7 (0.8%)** | **5 (0.6%)** |
| Oedema peripheral | 4 (0.9%) | 5 (1.2%) | 1 (0.2%) | 2 (0.5%) | 7 (0.8%) | 5 (0.6%) |
| **Renal and urinary disorders** | **1 (0.2%)** | **2 (0.5%)** | **2 (0.5%)** | **0** | **7 (0.8%)** | **9 (1.1%)** |
| Dysuria | 1 (0.2%) | 2 (0.5%) | 2 (0.5%) | 0 | 7 (0.8%) | 9 (1.1%) |

The safety analysis set (SAF) comprised all randomized patients who received ≥ 1 dose of double-blind treatment. TEAE refers to an adverse event which started or worsened in the period from first double-blind medication intake until 14 days after the last double-blind medication intake. Serious TEAEs with a start date reported until 30 days after the last double-blind medication intake were also summarized as TEAEs.

C: solifenacin + mirabegron combination therapy; M: mirabegron; S: solifenacin; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.11.1

**Table 18 Serious Treatment-Emergent Adverse Events (SAF)**

| MedDRA (v16.0) System Organ Class Preferred Term, n | Placebo (n = 429) | M 25 mg (n = 423) | M 50 mg (n = 422) | S 5 mg (n = 423) | C 5 + 25 mg (n = 853) | C 5 + 50 mg (n = 848) |
|---|---|---|---|---|---|---|
| **Overall** | **8 (1.9%)** | **6 (1.4%)** | **5 (1.2%)** | **3 (0.7%)** | **12 (1.4%)** | **19 (2.2%)** |
| **Infections and infestations** | **2 (0.5%)** | **1 (0.2%)** | **1 (0.2%)** | **1 (0.2%)** | **1 (0.1%)** | **4 (0.5%)** |
| Appendicitis | 0 | 0 | 1 (0.2%) | 0 | 0 | 1 (0.1%) |
| Bronchitis | 1 (0.2%) | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Bronchopneumonia | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Pneumonia | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Post procedural infection | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Pyelonephritis | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| Pyelonephritis acute | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| Scrub typhus | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 |
| Septic shock | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| **Nervous system disorders** | **1 (0.2%)** | **0** | **1 (0.2%)** | **0** | **1 (0.1%)** | **3 (0.4%)** |
| Transient ischaemic attack | 0 | 0 | 0 | 0 | 1 (0.1%) | 1 (0.1%) |
| Cerebral haemorrhage | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Cerebrovascular disorder | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| Grand mal convulsion | 0 | 0 | 1 (0.2%) | 0 | 0 | 0 |
| Hydrocephalus | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Radiculopathy | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| Subarachnoid haemorrhage | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Cardiac disorders** | **1 (0.2%)** | **1 (0.2%)** | **0** | **0** | **1 (0.1%)** | **2 (0.2%)** |
| Cardiac failure | 0 | 0 | 0 | 0 | 1 (0.1%) | 1 (0.1%) |
| Angina pectoris | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| Atrial flutter | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Palpitations | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| Supraventricular tachycardia | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| **Injury, poisoning and procedural complications** | **0** | **1 (0.2%)** | **0** | **0** | **2 (0.2%)** | **2 (0.2%)** |
| Hip fracture | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Laceration | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Ligament rupture | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Lower limb fracture | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| Upper limb fracture | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| **Neoplasms benign, malignant and unspecified (incl. cysts and polyps)** | **1 (0.2%)** | **0** | **1 (0.2%)** | **1 (0.2%)** | **1 (0.1%)** | **1 (0.1%)** |
| Prostate cancer | 1 (0.2%) | 0 | 1 (0.2%) | 0 | 0 | 0 |
| Benign neoplasm of thyroid gland | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 |
| Plasma cell myeloma | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Squamous cell carcinoma | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Vascular disorders** | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) | 3 (0.4%) |
| Hypertensive crisis | 0 | 0 | 0 | 0 | 1 (0.1%) | 2 (0.2%) |
| Hypertension | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Hypovolaemic shock | 0 | 0 | 1 (0.2%) | 0 | 0 | 0 |

*Table continued on next page*

| MedDRA (v16.0)<br>System Organ Class<br>Preferred Term, n | Placebo<br>(n = 429) | M 25 mg<br>(n = 423) | M 50 mg<br>(n = 422) | S 5 mg<br>(n = 423) | C 5 + 25 mg<br>(n = 853) | C 5 + 50 mg<br>(n = 848) |
|---|---|---|---|---|---|---|
| **Gastrointestinal disorders** | **0** | **0** | **0** | **1 (0.2%)** | **1 (0.1%)** | **1 (0.1%)** |
| Diverticulum intestinal haemorrhagic | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 |
| Gastrointestinal haemorrhage | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Haemorrhoids | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Rectal haemorrhage | 0 | 0 | 0 | 1 (0.2%) | 0 | 0 |
| **Hepatobiliary disorders** | **1 (0.2%)** | **1 (0.2%)** | **1 (0.2%)** | **0** | **0** | **0** |
| Cholecystitis | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| Cholelithiasis | 0 | 0 | 1 (0.2%) | 0 | 0 | 0 |
| Hepatitis toxic | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | **0** | **0** | **0** | **0** | **1 (0.1%)** | **2 (0.2%)** |
| Intervertebral disc protrusion | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Rotator cuff syndrome | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| Spondylolisthesis | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Respiratory, thoracic and mediastinal disorders** | **0** | **0** | **0** | **0** | **2 (0.2%)** | **1 (0.1%)** |
| Apnoea | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Chronic obstructive pulmonary disease | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Hiccups | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Psychiatric disorders** | **0** | **1 (0.2%)** | **0** | **0** | **0** | **1 (0.1%)** |
| Depression | 0 | 1 (0.2%) | 0 | 0 | 0 | 1 (0.1%) |
| **Renal and urinary disorders** | **0** | **0** | **0** | **0** | **1 (0.1%)** | **1 (0.1%)** |
| Renal colic | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 |
| Urinary retention | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Ear and labyrinth disorders** | **0** | **1 (0.2%)** | **0** | **0** | **0** | **0** |
| Otorrhoea | 0 | 1 (0.2%) | 0 | 0 | 0 | 0 |
| **Immune system disorders** | **1 (0.2%)** | **0** | **0** | **0** | **0** | **0** |
| Hypersensitivity | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |
| **Reproductive system and breast disorders** | **0** | **0** | **0** | **0** | **0** | **1 (0.1%)** |
| Menorrhagia | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Skin and subcutaneous tissue disorders** | **0** | **0** | **0** | **0** | **0** | **1 (0.1%)** |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 1 (0.1%) |
| **Surgical and medical procedures** | **1 (0.2%)** | **0** | **0** | **0** | **0** | **0** |
| Renal stone removal | 1 (0.2%) | 0 | 0 | 0 | 0 | 0 |

The safety analysis set (SAF) comprised all randomized patients who received ≥ 1 dose of double-blind treatment. TEAE refers to an adverse event which started or worsened in the period from first double-blind medication intake until 14 days after the last double-blind medication intake. Serious TEAEs with a start date reported until 30 days after the last double-blind medication intake were also summarized. Includes serious TEAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms, if any upgrade was done.

C: solifenacin + mirabegron combination therapy; M: mirabegron; S: solifenacin; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.6