Name of Sponsor/Company: Astellas Pharma Europe Ltd		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Solifenacin Succinate (YM905)/Mirabegron (YM178)		

SYNOPSIS

Title of Study:

A Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Adding Mirabegron to Solifenacin in Incontinent OAB Patients who have Received Solifenacin for 4 Weeks and Warrant Additional Relief for their OAB Symptoms (905-EC-012)

Coordinating Investigators:

[redacted] UK

[redacted] USA

Study Centers:

The study was conducted at 281 sites in 36 countries in Europe, North America, the Middle East and Asia.

Publication Based on the Study:

Not applicable

Study Period:

Study Initiation Date (Date of First Enrollment):

10 July 2013

Study Completion Date (Date of Last Evaluation):

25 November 2014

Phase of Development:

Phase 3b

Objectives:

Primary objective

- To evaluate the efficacy of solifenacin 5 mg in combination with mirabegron 50 mg (referred to as combination therapy) vs solifenacin 5 mg monotherapy

Secondary objectives

- To evaluate the safety and tolerability of combination therapy vs solifenacin 5 mg and solifenacin 10 mg monotherapy
- To evaluate the efficacy of combination therapy vs solifenacin 10 mg monotherapy

Methodology:

This was a randomized, double-blind, parallel group, multicenter, phase 3b study. Patients were randomized within strata (at visit 3) to 1 of 3 treatment groups in a 1:1:1 ratio (combination therapy: solifenacin 5 mg: solifenacin 10 mg). Randomization was stratified by sex, age group (< 65, ≥ 65 years), 4-week incontinence episode reduction group (< 50%, ≥ 50%) and geographic region.

In the screening phase/run-in period, patients who met the inclusion/exclusion criteria began a wash-out period to remove the effects of any previous overactive bladder (OAB) medication and completed an electronic micturition diary for 2 weeks until visit 2. The last 3 days of diary entry immediately preceding visit 2 were used to confirm eligibility of the patient. Patients were asked to collect and measure their urine output for the 3 days prior to visit 2.

At visit 2, eligible patients were assigned to a 4-week single-blind solifenacin 5 mg once-daily run-in period. Patients completed a 3-day micturition diary, including measurement of their urine output for the 3 days prior to visit 3. At visit 3, patients still experiencing 1 or more incontinence episodes over the 3-day diary period were randomized to 12 weeks of double-blind treatment. Patients were randomized within strata to 1 of 3 treatment groups in a 1:1:1 ratio (combination therapy: solifenacin 5 mg: solifenacin 10 mg). During the first 4 weeks, patients in the combination therapy arm received mirabegron 25 mg and solifenacin 5 mg; at visit 4, the dose of mirabegron was increased from 25 to 50 mg per day. During the double-blind period, patients attended study visits for assessments of efficacy and safety after 4 (visit 4), 8 (visit 5) and 12 weeks (visit 6) of treatment. Patients then completed a 2-week, single-blind, follow-up (FU) period during which they received placebo. At the FU/End of study visit (visit 7), patients returned to the clinic for safety FU assessments.

Number of Patients (Planned, Enrolled and Analyzed):

A total of 3815 patients were screened of which 2401 patients received solifenacin 5 mg run-in medication. Of the 2174 patients who were randomized into the study (randomized analysis set [RAS]), 2172 (99.9%) received double-blind study drug (safety analysis set [SAF]) Table 1 and Figure 1. Of these 2110 (97.1%) patients were included in the full analysis set (FAS) (randomized patients who took at least 1 dose of double-blind study) and 1940 (89.2%) were included in the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion:

Male or female patients, aged 18 years or older with symptoms of OAB (urinary frequency and urgency with urgency incontinence) for ≥ 3 months prior to screening and symptoms of "wet" OAB (urinary frequency and urgency with incontinence or mixed incontinence with predominant urgency incontinence) with an average of ≥ 2 incontinence episodes/24 hours at the screening visit were eligible for inclusion. At run-in, patients had to have an average of ≥ 1 urgency (grade 3 or 4) episode (with or without incontinence) per 24 hours over 3-day micturition diary period, an average of ≥ 2 incontinence episodes/24 hours over 3-day micturition diary period and on average ≥ 8 micturitions/24 hours (excluding incontinence episodes) over the 3-day micturition diary period, and ≥ 1 incontinence episode over the 3-day micturition diary period and a desire to increase treatment for OAB symptoms at randomization.

Test Product, Dose and Mode of Administration, Batch Numbers:

Mirabegron was supplied as 25 mg brown film-coated oral controlled absorption system (OCAS) modified release tablets and 50 mg yellow film-coated oval OCAS modified release tablets (Batch numbers – see section below).

Solifenacin was provided as the marketed formulation as 5 mg and 10 mg tablets. All doses of solifenacin succinate were round, white, film-coated tablets (Batch number solifenacin 5 mg: [redacted]; solifenacin 5 mg placebo: [redacted]).

Duration of Treatment (or Duration of Study, if applicable):

The study consisted of a 4-week, single-blind, run-in period during which patients received solifenacin 5 mg once daily. Those patients still experiencing ≥ 1 incontinence episodes over a 3-day period were randomized to receive 12 weeks' double-blind treatment. For the first 4 weeks of the double-blind period, patients were assigned to 1 of 3 arms:

Arm 1: solifenacin 5 mg, mirabegron 25 mg, solifenacin 10 mg placebo (Batch numbers: [redacted]).

Arm 2: solifenacin 5 mg, mirabegron 25 mg placebo, solifenacin 10 mg placebo (Batch numbers: [redacted]).

Arm 3: solifenacin 5 mg placebo, mirabegron 25 mg placebo, solifenacin 10 mg (Batch numbers: [redacted]).

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

Arm 1: solifenacin 5 mg, mirabegron 50 mg, solifenacin 10 mg placebo (Batch numbers: [redacted]).

Arm 2: solifenacin 5 mg, mirabegron 50 mg placebo, solifenacin 10 mg placebo (Batch numbers: [redacted]).

Arm 3: solifenacin 5 mg placebo, mirabegron 50 mg placebo, solifenacin 10 mg (Batch numbers: [redacted]).

Reference Product, Dose and Mode of Administration, Batch Numbers:

Matching placebo of mirabegron OCAS 25 mg and 50 mg tablets were supplied (batch numbers as shown above).

Matching placebo of solifenacin succinate 5 mg and 10 mg tablets were supplied (batch numbers as shown above).

Criteria for Evaluation:

Primary efficacy variable

Change from baseline to end of treatment (EoT) in mean number of incontinence episodes per 24 hours during the 3-day diary period

Key secondary efficacy variables

- Change from baseline to EoT in mean number of micturitions per 24 hours
- Number of incontinence episodes reported during the 3-day diary at EoT

Other secondary efficacy variables

Variables derived from the Micturition Diary

- Change from baseline to EoT in mean number of incontinence episodes per 24 hours (week 4, 8, 12)
- Change from baseline to EoT in mean number of micturitions per 24 hours (week 4, 8, 12)
- Number of incontinence episodes reported during the EoT 3-day diary (week 4, 8, 12)
- Change from baseline in mean volume voided per micturition (week 4, 8, 12 and EoT)
- Change from baseline corrected micturition frequency (CMF) (EoT)
- Change from baseline in mean number of urgency incontinence episodes per 24 hours (week 4, 8, 12 and EoT)
- Number of urgency incontinence episodes at EoT reported during the 3-day diary (week 4, 8, 12 and EoT)
- Change from baseline in mean number of urgency episodes (grade 3 and/or 4) per 24 hours (patient perception of intensity of urgency scale [PPIUS] scale) (week 4, 8, 12 and EoT)
- Change from baseline in mean number of pads per 24 hours (week 4, 8, 12 and EoT)
- Number of pads used during the 3-day diary (week 4, 8, 12 and EoT)
- Change from baseline in mean number of nocturia episodes per 24 hours (week 4, 8, 12 and EoT)
- Number of nocturia episodes reported during the 3-day diary (week 4, 8, 12 and EoT)

Health Economic Outcomes Research variables

- Change from baseline in total European quality of life in 5 dimensions (EQ-5D) score and subscale scores (week 4, 8, 12 and EoT)
- Change from baseline in overactive bladder symptom and health-related quality of life questionnaire (OAB-q) symptom bother, health-related quality of life (HRQL) score and subscale scores (week 4, 8, 12 and EoT)
- Change from baseline in treatment satisfaction - visual analogue scale (TS-VAS) score (week 4, 8, 12 and EoT)
- Change from baseline in patient perception of bladder condition (PPBC) score (week 4, 8, 12 and EoT)
- Patient's global impression of change (PGIC) and clinician's global impression of change (CGIC) scales (week 12 and EoT)

Responder Variables

- Responders for at least a 50% decrease from baseline in mean number of incontinence episodes per 24 hours (week 4, 8, 12 and EoT)
- Responders for zero incontinence episodes per 24 hours (week 4, 8, 12 and EoT)
- Proportion of patients with a mean of at least 8 micturitions per 24 hours at baseline and less than 8 micturitions per 24 hours postbaseline (week 4, 8, 12 and EoT)
- Proportion of responders with at least a 10-point improvement from baseline in OAB-q symptom bother and HRQL scores (week 4, 8, 12 and EoT)
- Proportion of patients with at least a 1-point improvement from baseline in PPBC (week 4, 8, 12 and EoT)

- Proportion of patients with major (at least a 2-point) improvement from baseline in PPBC (week 4, 8, 12 and EoT)

Exploratory Variables

- Double responder: 50% reduction in mean number of incontinence episodes per 24 hours compared to baseline and minimal important difference (MID) reached (improvement by at least 10 points) on the symptom bother scale of the OAB-q
- Double responder: 50% reduction in mean number of incontinence episodes per 24 hours compared to baseline and MID reached (improvement by at least 10 points) on the HRQL Total score of the OAB-q
- Double responder: 50% reduction in mean number of incontinence episodes per 24 hours compared to baseline and at least 1-point improvement from baseline in PPBC
- Triple responder: 50% reduction in mean number of incontinence episodes per 24 hours compared to baseline, MID reached (improvement by at least 10 points) on the Symptom Bother scale of the OAB-q, and at least 1-point improvement from baseline in PPBC
- Triple responder: 50% reduction in mean number of incontinence episodes per 24 hours compared to baseline, MID reached (improvement by at least 10 points) on the HRQL Total score of the OAB-q, and at least 1-point improvement from baseline in PPBC

Safety variables

Safety assessments comprised the incidence and severity of single-blind run-in adverse events (AEs) and treatment-emergent adverse events (TEAEs) (including AEs of special interest and those of hepatic origin), pre-specified TEAEs considered related to solifenacin and mirabegron based on the summary of product characteristics (SmPC) for each monotherapy, neoplasm and CV events for Independent Adjudication Committee review, vital signs, safety laboratory tests (hematology, biochemistry and urinalysis), electrocardiogram (ECG) parameters and post-void residual (PVR) volume.

Statistical Methods:

Analysis Sets

There were 6 analysis sets: the screening period analysis set (SPAS) comprising all patients who signed the informed consent; the run-in period analysis set (RPAS) comprising all patients who took at least 1 dose of single blind study drug; the randomized analysis set (RAS) comprising all randomized patients; the full analysis set (FAS) comprising all RAS patients who took at least 1 dose of double-blind study drug after randomization, reported at least 1 micturition in the baseline diary and at least 1 micturition postbaseline and reported at least 1 incontinence episode in the baseline diary; the PPS comprising all patients of the FAS who did not meet criteria for exclusion from PPS; and the safety analysis set (SAF) comprising all randomized patients who received at least 1 dose of double-blind treatment [Table 1].

Efficacy

The primary efficacy variable was change from baseline in mean number of incontinence episodes per 24 hours. The primary analysis was performed on the FAS. The primary comparison of interest was for combination therapy vs solifenacin 5 mg. Change from baseline to EoT in mean number of incontinence episodes per 24 hours was analyzed using separate stratified rank analyses of covariance (ANCOVA) model for the pairwise

treatment group difference of combination therapy versus solifenacin 5 mg or combination therapy vs solifenacin 10 mg. The stratified rank ANCOVA was used for hypothesis testing and calculating P values for the comparisons between combination therapy and solifenacin 5 mg. Least squares (LS) mean estimates and 2-sided 95% CIs for mean changes from baseline within each treatment group, as well as the for the difference in mean change from baseline between combination therapy and solifenacin 5 mg were derived from the corresponding ANCOVA model with treatment group and randomization stratification factors as fixed factors and mean number of incontinence episodes per 24 hours at baseline as a covariate.

For the key secondary efficacy variables, change from baseline to EoT in mean number of micturitions per 24 hours was performed on the FAS and PPS and was analyzed using an ANCOVA model which included treatment group, randomization stratification factors (sex, age group: < 65 and ≥ 65 years, geographic region, and 4-week incontinence episode reduction group) as fixed factors and baseline number of micturitions per 24 hours as a covariate. As a secondary analysis, the same ANCOVA model was used for testing noninferiority of combination therapy versus solifenacin 10 mg. The noninferiority margin was set to -0.20 micturitions per 24 hours. If noninferiority was demonstrated, then the superiority of combination therapy versus solifenacin 10 mg was investigated. The number of incontinence episodes reported during the EoT 3-day diary was analyzed using a mixed effects Poisson regression (negative binomial) model. The same mixed effects Poisson regression (negative binomial) model was used for testing noninferiority of combination therapy versus solifenacin 10 mg.

Analysis for other secondary variables was performed on the FAS. The primary comparison of interest was combination therapy versus solifenacin 5 mg. For variables that were normally distributed the same ANCOVA model was applied as described for micturitions. Variables based on incontinence were analyzed using a stratified rank ANCOVA as well as through Poisson regression. Variables based on nocturia episodes and pads were analyzed using ANCOVA as well as through Poisson regression. For dichotomous variables (e.g., 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, 95% CIs, odds ratios, 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.

Exploratory variables were summarized by treatment group, along with the difference between combination therapy and solifenacin 5 mg and between combination therapy and solifenacin 10 mg, 2-sided 95% CIs, odds ratios, 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.

Safety

AEs were coded using MedDRA v16.0 and summarized by severity (i.e., mild, moderate, severe) and by worst relationship to study drug (i.e., not related, possibly, probably related). TEAEs of interest included selected TEAEs for mirabegron and/or solifenacin and TEAEs that could have increased in frequency due to the mechanisms of action of both compounds when administered as combination therapy (increased blood pressure, QT prolongation, increased heart rate/tachycardia/atrial fibrillation/palpitations, tachycardia, urinary tract infection, urinary retention, hypersensitivity reactions, glaucoma and antimuscarinic side effects). The number and percentage of patients who reported at least 1 AE considered to be related to mirabegron and/or solifenacin

were summarized by treatment group. AEs of special interest were identified using Standardized MedDRA queries and common antimuscarinic side effects were summarized by SOC and preferred term (PT) by treatment group together with 95% CI next to the absolute and relative frequency of patients. Serious TEAEs and TEAEs leading to permanent discontinuation of study drug were summarized by SOC and preferred term. Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate) were summarized with descriptive statistics. Sub-populations were defined and analyzed using an ANCOVA model: past history of hypertension, hypertensive at screening, no hypertension at screening, beta-blocker users and non beta-blocker users. Clinical laboratory tests (hematology, biochemistry and urinalysis) and 12-lead ECG, QT interval corrected using Fridericia's correction formula (QTcF interval) were summarized descriptively. PVR volume was summarized by treatment group and visit.

Summary of Results/Conclusions:

Demographics:

In general, all treatment arms in the FAS were similar with respect to demographics and baseline characteristics. The majority of patients were female (83.3%) and White (94.2%). The overall mean age at screening was 57.4 years (range 18 to 89) with 30.9% of patients aged ≥ 65 years and 8.9% aged ≥ 75 years. The mean body mass index (BMI) across all treatment groups was 29.0 kg/m^2 [Table 2].

The demographic and baseline characteristics were consistent across treatment groups in the SAF and the PPS populations and were similar to the FAS.

The study was conducted at 281 sites in 36 countries. The majority of patients were from Eastern Europe (45.7%), with 26.7% from Western Europe, 17.0% from North America, 10.5% from the Middle East and 0.1% from Asia.

Efficacy Results:

Combination (solifenacin 5 mg + mirabegron 50 mg) was superior to solifenacin 5 mg for the primary efficacy variable (change from baseline to EoT in mean number of incontinence episodes per 24 hours). The adjusted change from baseline to EoT was greater in the combination group (-1.80 episodes) compared with solifenacin 5 mg group (-1.53 episodes) and solifenacin 10 mg group (-1.67 episodes). In the combination group, the reduction was statistically significantly greater than in the solifenacin 5 mg group (P = 0.001) [Table 3]. Sensitivity analyses confirmed the robustness of the primary efficacy analysis (PPS).

For the key secondary efficacy variables, the primary comparison of interest was combination therapy versus solifenacin 5 mg. The change from baseline to EoT in mean number of micturitions per 24 hours was statistically significantly greater in the combination group (by -0.45) than in the solifenacin 5 mg group (P < 0.001) [Table 3]. Noninferiority and superiority of combination versus solifenacin 10 mg was also demonstrated (PPS). For the number of incontinence episodes during the 3-day diary at EoT, the reduction in number of incontinence episodes was 18 % larger in the combination group than in the solifenacin 5 mg group. The rate ratio of the combination versus solifenacin 5 mg was statistically significantly < 1 indicating that combination was superior to solifenacin 5 mg. Noninferiority of combination versus solifenacin 10 mg was also demonstrated (PPS). Sensitivity analyses confirmed the key secondary efficacy results.

With the exception of nocturia, analyses of the diary-based additional secondary efficacy variables showed the treatment differences between combination and solifenacin 5 mg and 10 mg were statistically significantly in favor of combination treatment at most timepoints.

HEOR variables demonstrated that combination treatment had a positive effect on patients' quality of life. For the OAB-q Symptom Bother score, OAB-q HRQL Total score, combination was superior over solifenacin 5 mg and 10 mg at EoT. There was a statistically significant difference in favor of combination versus solifenacin 5 mg and 10 mg for PPBC, and in favor of combination versus solifenacin 5 mg for the TS-VAS at EoT. For the OAB-q HRQL subscale scores, combination demonstrated superiority over solifenacin 5 mg for all subscales apart from 'sleep' and superiority over solifenacin 10 mg for all subscales at EoT. For both the PGIC and CGIC scales, the proportion of patients and clinicians reporting that bladder symptoms had very much improved was higher for the combination group compared to both solifenacin groups.

Responder variables showed statistically significant differences in favor of combination versus solifenacin 5 mg and 10 mg for zero incontinence episodes/24 hours, and versus solifenacin 5 mg for a 50% decrease in mean number of incontinence episodes/24 hours and the proportion of patients with a mean of ≥ 8 micturitions/24 hours at baseline and < 8 micturitions/24 hours postbaseline.

Exploratory variables demonstrated statistically significant differences in favor of combination versus solifenacin 5 mg and 10 mg in the proportion of responders with at least a 10-point improvement in OAB-q symptom bother score, in the OAB-q HRQL Total score and in the proportion of patients with a major improvement in PPBC, and versus solifenacin 5 mg for the proportion of patients with at least a 1-point improvement from baseline PPBC.

Subgroup analyses did not show any clear indication of treatment differences among the subgroups for the primary and key secondary efficacy endpoints. Exploratory analyses (double- and triple-responder analyses) demonstrated statistically significant improvements in favor of combination compared to solifenacin 5 mg for all variables and statistically significant improvements in favor of combination compared to solifenacin 10 mg for 3 of the 5 variables.

Safety Results:

Based on the overall results of the study, all 3 treatment arms appeared to be safe and well-tolerated. The AE profile in the combination group generally appeared to be consistent with the known profile of mirabegron and solifenacin. The incidence of TEAEs was lowest in the solifenacin 5 mg group (33.1%) compared to the combination (35.9%) and solifenacin 10 mg (39.4%) groups Table 4. No TEAEs were reported in any treatment group at an incidence of > 9.5%. TEAEs with an incidence (by PT) of ≥ 2.0% in any treatment group were: dry mouth, with a higher incidence for solifenacin 10 mg (9.5%) compared to combination (5.9%) and solifenacin 5 mg (5.6%); constipation, with similar incidences for combination (4.6%) and solifenacin 10 mg (4.7%) compared to solifenacin 5 mg (3.0%); and, edema peripheral with a higher incidence for solifenacin 5 mg (2.2%) compared to combination (0.8%) and solifenacin 10 mg (0.3%).

The incidence of treatment-related TEAEs (as judged by the investigator) was higher in the solifenacin 10 mg group (22.4%) compared to the combination (19.4%) and solifenacin 5 mg (17.2%) groups. The most commonly-reported treatment-related TEAEs were in the Gastrointestinal SOC and the majority was mild in severity (11.9%). The incidence of treatment-related dry mouth was higher in the solifenacin 10 mg group (9.3%) compared to combination (5.8%) and solifenacin 5 mg (5.5%) groups. Similarly for treatment-related

constipation, the highest incidence was in the solifenacin 10 mg group (4.5%) compared to combination (4.3%) and solifenacin 5 mg (2.9%) groups. Overall, severe treatment-related TEAEs were experienced by 1.5% of patients receiving combination, 0.5% of patients receiving solifenacin 5 mg and 1.3% of patients receiving solifenacin 10 mg.

The overall incidence of patients with treatment-emergent SAEs was 1.7% (1.8%, 1.4% and 2.1%; combination, solifenacin 5 mg, solifenacin 10 mg, respectively) Table 5; only 4 SAEs (0.2%) were considered treatment-related (as judged by the investigator). The overall incidence of patients who discontinued due to a TEAE was the same in all 3 treatment groups (1.5%).

Based on findings from previous studies, a number of specific AEs were identified as being of interest. Potentially these AEs could have increased in frequency due to the mechanisms of action for both compounds when administered as a combination therapy. Overall, the incidence of TEAEs of special interest was low for all treatment groups:

- TEAEs of increased blood pressure appeared to be similar for solifenacin 10 mg (1.8%) and combination (1.7%) and lower for solifenacin 5 mg (0.8%); TEAEs of QT prolongation were observed in 0.2% of patients overall: 0.1% for both combination and solifenacin 5 mg and 0.3% for solifenacin 10 mg; for cardiac disorders TEAEs, 10 patients reported palpitations, 6 patients (0.8%) in the combination group compared to 2 patients (0.3%) in each of the monotherapy groups and 3 patients reported a PT of tachycardia, 2 patients in the combination group and 1 patient in the solifenacin 5 mg group; low rates of UTIs were observed across the treatment groups: slightly more patients had UTIs in the solifenacin 10 mg group (2.8%) compared to the combination (2.3%) and solifenacin 5 mg (2.2%) groups; urinary retention (overall category) was reported in 14 patients in total: 7 patients (1.0%) in the solifenacin 10 mg group, 4 patients (0.6%) in the combination group and 3 patients (0.4%) in the solifenacin 5 mg group, with no acute retentions that required catheterization; hypersensitivity had a higher incidence in the combination group (1.5%) compared to the solifenacin 5 mg (0.8%) and solifenacin 10 mg (0.8%) groups (most were reported in the skin and subcutaneous tissue disorders SOC). There were no TEAEs of glaucoma.
- During the double-blind treatment phase, dry mouth was the most common antimuscarinic side effect: solifenacin 10 mg (9.7%), combination (5.9%) and solifenacin 5 mg group (5.6%); the incidence of blurred vision was similar 1.4% in the combination group and solifenacin 5 mg groups (1.4%) and lower in the solifenacin 10 mg group (0.7%); the incidence of constipation appeared to be similar in the combination (4.6%) and solifenacin 10 mg group (4.7%) and lower in the solifenacin 5 mg group (3.0%); the incidence of dyspepsia was similar in the combination group (0.8%) compared to the solifenacin 5 mg group (0.5%) and slightly higher in the solifenacin 10 mg group (1.1%).
- For the TEAEs considered related to solifenacin and mirabegron (based on the Summary of Product Characteristics for each monotherapy), there appeared to be a higher incidence of somnolence in the combination group (1.5%) compared to 1.0% for solifenacin 5 mg and 0.6% for solifenacin 10 mg; the incidence of diarrhea was higher in the combination group (1.7%) and similar in the solifenacin 5 mg (0.7%) and solifenacin 10 mg (0.8%) groups (with confounding factors for 7, 2 and 3 patients in the corresponding groups). Overall, the possibility of a slight additive effect of combination treatment for constipation and/or somnolence could not be excluded.

Changes in hematology and serum chemistry parameters, including renal parameters, were small and comparable across treatment groups. No Hy's Law cases were reported. Two patients in the combination group

had alanine aminotransferase values > 5x the upper limit of the normal range. Both started prior to combination therapy, had confounding factors of concomitant medication and were considered unrelated to treatment.

For vital signs, ECG and PVR in the combination group, there were no signs of additive/synergistic effects beyond those known from either monotherapy.

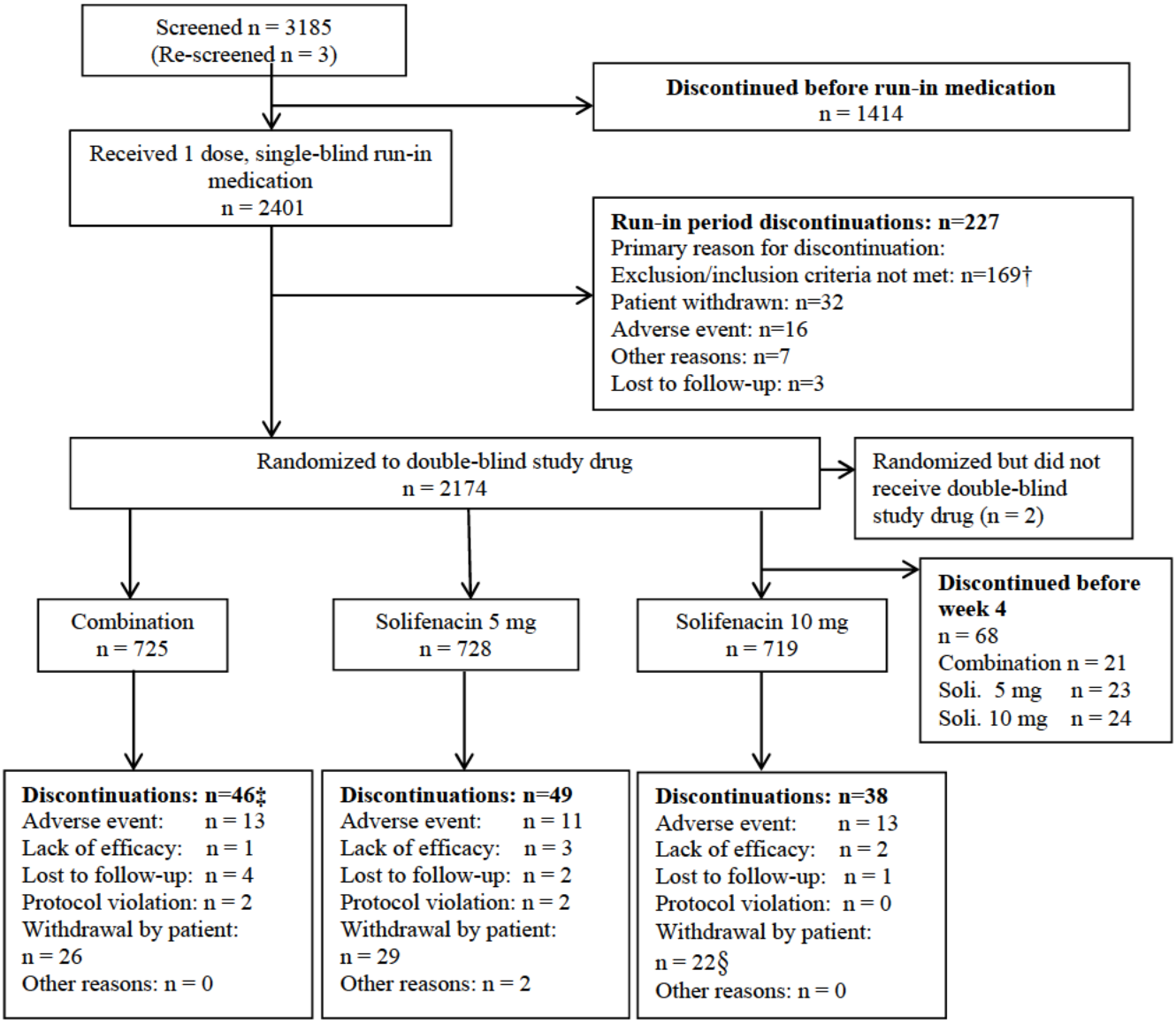
Overall, the study did not reveal any significant safety signals in patients who received combination during the double-blind treatment period. Combination was safe and well tolerated in this OAB patient population.

CONCLUSIONS:

- Add-on therapy with mirabegron provided additional benefit in incontinent patients with OAB with an insufficient response to solifenacin 5 mg when compared to either solifenacin 5 mg or solifenacin 10 mg.
- The improvements seen with combination treatment compared to solifenacin 5 mg and 10 mg monotherapy for several objective OAB outcome measures translated into significant improvements in HRQL.
- Add-on therapy of mirabegron once daily with solifenacin once daily for 12 weeks had an acceptable safety profile and was well tolerated.

Date of Report: 25 July 2015

Figure 1 Patient Disposition



DB: double-blind; Soli: Solifenacin.

† 116 patients did not comply with IC14 after the run-in period, that is, they did not experience at least 1 incontinence episode during the 3-day micturition diary period or did not wish to increase their treatment for OAB symptoms, and were subsequently not randomized.

‡ An additional 2 patients (both in the combination group) discontinued the study but had no EoT page and therefore the reason for discontinuation was not reported. Thus these 2 patients do not appear in the schema above.

§ Patient [redacted] is included as "withdrawal by patient" but is included in the safety section as a withdrawal due to an AE. Source: Tables 12.1.1.1.1, 12.1.1.1.2, 12.1.1.3.1 and 12.1.1.3.2.

Table 1 Patient Disposition

Analysis Set, n (%)	Combination (n = 727)	Solifenacin 5 mg (n = 728)	Solifenacin 10 mg (n = 719)	Total (n = 2174)
Randomized Analysis Set (RAS)	727 (100.0%)	728 (100.0%)	719 (100.0%)	2174 (100.0%)
Safety Analysis Set (SAF)	725 (99.7%)	728 (100.0%)	719 (100.0%)	2172 (99.9%)
Full Analysis Set (FAS)	707 (97.2%)	705 (96.8%)	698 (97.1%)	2110 (97.1%)
Per Protocol Set (PPS)	637 (87.6%)	655 (90.0%)	648 (90.1%)	1940 (89.2%)

Percentages are calculated relative to the RAS.

RAS: All patients randomized to double-blind treatment; SAF: All Randomized analysis set patients who took at least 1 dose of double-blind treatment; FAS: All Safety analysis set patients who recorded at least 1 micturition measurement in the baseline diary and at least 1 micturition measurement in a postbaseline diary and reported at least 1 incontinence episode in the baseline diary; PPS: Per protocol set, that is, all Full analysis set patients who had no major protocol violations.

Source: Table 12.1.1.2

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

Parameter Category/ Statistics	Combination (n = 707)	Solifenacin 5 mg (n = 705)	Solifenacin 10 mg (n = 698)	Total (n = 2110)
Sex, n (%)				
Female	588 (83.2%)	584 (82.8%)	585 (83.8%)	1757 (83.3%)
Male	119 (16.8%)	121 (17.2%)	113 (16.2%)	353 (16.7%)
Race, n (%)				
White	671 (94.9%)	656 (93.0%)	661 (94.7%)	1998 (94.2%)
Black or African American	19 (2.7%)	24 (3.4%)	26 (3.7%)	69 (3.3%)
Asian	13 (1.8%)	21 (3.0%)	9 (1.3%)	43 (2.0%)
Other	4 (0.6%)	4 (0.6%)	2 (0.3%)	10 (0.5%)
Ethnicity, n (%)				
Not Hispanic or Latino	666 (94.2%)	667 (94.6%)	662 (94.8%)	1995 (94.5%)
Hispanic or Latino	41 (5.8%)	38 (5.4%)	36 (5.2%)	115 (5.5%)
Age, mean/median	58.0/ 59.0	56.9/ 58.0	57.3/ 59.0	57.4/ 59.0
Age ≥ 65 years, n (%)	223 (31.5%)	214 (30.4%)	214 (30.7%)	651 (30.9%)
Age ≥ 75 years, n (%)	71 (10.0%)	64 (9.1%)	53 (7.6%)	188 (8.9%)
Weight (kg)				
Mean (SD)	78.5 (16.7)	78.6 (17.5)	78.0 (16.7)	78.4 (17.0)
Median	76.0	76.0	76.0	76.0
Min - Max	42 - 155	40 - 151	42 - 159	40 - 159
Height (cm)				
Mean (SD)	164.6 (8.3)	164.3 (8.0)	164.2 (7.5)	164.4 (7.9)
Median	164.0	164.0	164.0	164.0
Min - Max	135 - 195	144 -197	142 - 191	135 -197
BMI (kg/m^2)				
Mean (SD)	29.0 (5.9)	29.1 (6.3)	29.0 (6.0)	29.0 (6.1)
Median	27.7	28.1	28.2	28.1
Min - Max	18– 54	16– 57	16– 59	16– 59

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 postbaseline.

BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum

Source: Table 12.1.2.1.2

Table 3 Overview of Primary and Key Secondary Efficacy Results

Endpoint	Analysis	Combination vs Solifenacin 5 mg	Combination vs Solifenacin 10 mg
Primary Analysis			
Change from baseline to EoT in mean number of incontinence episodes per 24 hours (FAS)	**Adjusted Difference**		
	Mean (SE) 95% 2-sided CIs P value†	-0.26 (0.11) (-0.47, -0.05) 0.001	
Key Secondary Endpoints			
Change from baseline to EoT in mean number of micturitions per 24 hours (FAS)‡	**Adjusted Difference**		
	Mean (SE) 95% 2-sided CIs P value†	-0.45 (0.12) (-0.67, -0.22) < 0.001	-0.47 (0.12) (-0.70, -0.25)§ < 0.001
Number of incontinence episodes reported during the 3-day diary at EoT (FAS)¶	**Rate Ratio**		
	Mean (SE) 95% 2-sided CIs P value	0.82 (0.08) (0.71, 0.96) 0.014	0.89 (0.08) (0.76, 1.04)†† 0.134

ANCOVA: Analysis of covariance; EoT: End of treatment; FAS: Full Analysis Set; LS: Least squares.

† P values for pairwise comparisons are from the stratified rank ANCOVA model. $P < 0.05$ indicates superiority in favor of treatment group with the largest improvement.

‡ Means (LS means), 95% CIs for pairwise comparisons and P values are from the ANCOVA model with sex, age group (< 65, ≥ 65 years), geographic region, and 4-week incontinence episode reduction group as fixed factors and mean number of micturitions per 24 hours at baseline as a covariate.

§ Noninferiority is concluded if upper limit of 95% CI for difference of adjusted change from baseline between combination therapy and solifenacin 10 mg is < 0.20. If combination is noninferior to solifenacin 10 mg then superiority of combination will be concluded if upper limit of 95% CI between combination and solifenacin 10 mg is < 0.

¶ Results are from a Poisson regression model including treatment group, sex, age group (< 65, ≥ 65 years), geographic region, and 4-week incontinence episode reduction group, and log of (number of incontinence episodes reported during baseline).

†† Noninferiority is concluded if upper limit of 95% CI for rate ratio between combination therapy and solifenacin 10 mg is < 1.11. If combination is noninferior to solifenacin 10 mg then the superiority of combination versus solifenacin 10 mg will be concluded if upper limit of 95% CI between combination and solifenacin 10 mg < 1.

Source: Table 12.3.1.1.1, Table 12.3.2.1.1, Table 12.3.2.2.1

Table 4 TEAEs reported by ≥ 1.0% of Patients in Any Treatment group (SAF)

MedDRA (v16.0) System Organ Class Preferred Term, n (%)	Combination (n = 725)	Solifenacin 5 mg (n = 728)	Solifenacin 10 mg (n = 719)	Total (n = 2172)
Overall	260 (35.9%)	241 (33.1%)	283 (39.4%)	784 (36.1%)
Gastrointestinal disorders				
Dry mouth	43 (5.9%)	41 (5.6%)	68 (9.5%)	152 (7.0%)
Constipation	33 (4.6%)	22 (3.0%)	34 (4.7%)	89 (4.1%)
Diarrhoea	12 (1.7%)	5 (0.7%)	6 (0.8%)	23 (1.1%)
Nausea	9 (1.2%)	7 (1.0%)	4 (0.6%)	20 (0.9%)
Dyspepsia	6 (0.8%)	4 (0.5%)	8 (1.1%)	18 (0.8%)
Abdominal pain	5 (0.7%)	3 (0.4%)	7 (1.0%)	15 (0.7%)
Vomiting	2 (0.3%)	7 (1.0%)	6 (0.8%)	15 (0.7%)
Infections and infestations				
Nasopharyngitis	14 (1.9%)	13 (1.8%)	14 (1.9%)	41 (1.9%)
Urinary tract infection	7 (1.0%)	7 (1.0%)	12 (1.7%)	26 (1.2%)
Influenza	5 (0.7%)	8 (1.1%)	4 (0.6%)	17 (0.8%)
Nervous system disorders				
Headache	9 (1.2%)	13 (1.8%)	12 (1.7%)	34 (1.6%)
Dizziness	6 (0.8%)	11 (1.5%)	8 (1.1%)	25 (1.2%)
Somnolence	11 (1.5%)	7 (1.0%)	4 (0.6%)	22 (1.0%)
Musculoskeletal and connective tissue disorders				
Back pain	8 (1.1%)	7 (1.0%)	6 (0.8%)	21 (1.0%)
Renal and urinary disorders				
Hypertonic bladder	8 (1.1%)	5 (0.7%)	10 (1.4%)	23 (1.1%)
General disorders and admin. site conditions				
Oedema peripheral	6 (0.8%)	16 (2.2%)	2 (0.3%)	24 (1.1%)
Fatigue	3 (0.4%)	3 (0.4%)	8 (1.1%)	14 (0.6%)
Eye disorders				
Vision blurred	10 (1.4%)	10 (1.4%)	5 (0.7%)	25 (1.2%)
Vascular disorders				
Hypertension	8 (1.1%)	5 (0.7%)	6 (0.8%)	19 (0.9%)

The SAF comprised all randomized patients who received at least 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 30 days after the last double-blind medication intake.

Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level.

SAF: Safety Analysis Set; TEAE: Treatment-emergent adverse event.

Source: Table 12.6.1.2.5

Table 5 Summary of Serious Treatment-emergent Adverse Events (SAF)

MedDRA (v16.0) System Organ Class Preferred Term, n (%)	Combination (n = 725)	Solifenacin 5 mg (n = 728)	Solifenacin 10 mg (n = 719)	Total (n = 2172)
Overall	13 (1.8%)	10 (1.4%)	15 (2.1%)	38 (1.7%)
Infections and infestations	3 (0.4%)	1 (0.1%)	1 (0.1%)	5 (0.2%)
Appendicitis	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Encephalitis herpes	1 (0.1%)	0	0	1 (0.0%)
Pneumonia	1 (0.1%)	0	0	1 (0.0%)
Gastrointestinal disorders	1 (0.1%)	2 (0.3%)	1 (0.1%)	4 (0.2%)
Abdominal hernia	0	1 (0.1%)	0	1 (0.0%)
Abdominal pain	0	0	1 (0.1%)	1 (0.0%)
Inguinal hernia	0	1 (0.1%)	0	1 (0.0%)
Pancreatitis	1 (0.1%)	0	0	1 (0.0%)
General disorders and administration site conditions	2 (0.3%)	1 (0.1%)	1 (0.1%)	4 (0.2%)
Non-cardiac chest pain	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Adhesion	0	1 (0.1%)	0	1 (0.0%)
Pyrexia	1 (0.1%)	0	0	1 (0.0%)
Investigations	2 (0.3%)	0	2 (0.3%)	4 (0.2%)
Alanine aminotransferase increased	1 (0.1%)	0	0	1 (0.0%)
Arteriogram coronary normal	1 (0.1%)	0	0	1 (0.0%)
Arthroscopy	0	0	1 (0.1%)	1 (0.0%)
Aspartate aminotransferase increased	1 (0.1%)	0	0	1 (0.0%)
Colonoscopy	0	0	1 (0.1%)	1 (0.0%)
Gamma-glutamyltransferase increased	1 (0.1%)	0	0	1 (0.0%)
Cardiac disorders	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Acute myocardial infarction	0	0	1 (0.1%)	1 (0.0%)
Atrial fibrillation	0	1 (0.1%)	0	1 (0.0%)
Atrioventricular block complete	1 (0.1%)	0	0	1 (0.0%)
Hepatobiliary disorders	0	1 (0.1%)	2 (0.3%)	3 (0.1%)
Cholecystitis acute	0	1 (0.1%)	0	1 (0.0%)
Hepatic pain	0	0	1 (0.1%)	1 (0.0%)
Liver disorder	0	0	1 (0.1%)	1 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Back pain	0	1 (0.1%)	0	1 (0.0%)
Fracture pain	0	0	1 (0.1%)	1 (0.0%)
Mobility decreased	1 (0.1%)	0	0	1 (0.0%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.3%)	0	1 (0.1%)	3 (0.1%)
Adrenal adenoma	0	0	1 (0.1%)	1 (0.0%)
Anal cancer	1 (0.1%)	0	0	1 (0.0%)
Intraductal proliferative breast lesion	1 (0.1%)	0	0	1 (0.0%)
Injury, poisoning and procedural complications	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Femur fracture	0	0	1 (0.1%)	1 (0.0%)
Multiple fractures	1 (0.1%)	0	0	1 (0.0%)
Nervous system disorders	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Polyneuropathy	1 (0.1%)	0	0	1 (0.1%)
Transient ischaemic attack	0	0	1 (0.1%)	1 (0.1%)
Surgical medical procedures	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Joint resurfacing surgery	0	0	1 (0.1%)	1 (0.0%)
Skin neoplasm excision	0	1 (0.1%)	0	1 (0.0%)

Table continued on next page

MedDRA (v16.0) System Organ Class Preferred Term, n (%)	Combination (n = 725)	Solifenacin 5 mg (n = 728)	Solifenacin 10 mg (n = 719)	Total (n = 2172)
Vascular disorders	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hypertensive crisis	0	0	1 (0.1%)	1 (0.0%)
Thrombosis	0	1 (0.1%)	0	1 (0.0%)
Endocrine disorders	0	1 (0.1%)	0	1 (0.0%)
Goitre	0	1 (0.1%)	0	1 (0.0%)
Immune system disorders	1 (0.1%)	0	0	1 (0.0%)
Hypersensitivity	1 (0.1%)	0	0	1 (0.0%)
Reproductive system and breast disorders	0	1 (0.1%)	0	1 (0.0%)
Cervix haemorrhage uterine	0	1 (0.1%)	0	1 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.1%)	0	0	1 (0.0%)
Respiratory tract oedema	1 (0.1%)	0	0	1 (0.0%)
Skin and subcutaneous tissue disorders	0	0	1 (0.1%)	1 (0.0%)
Urticaria	0	0	1 (0.1%)	1 (0.0%)

The SAF consisted of all randomized patients who received at least 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 30 days after the last double-blind medication intake.

Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level.

SAF: Safety Analysis Set; TEAE: Treatment-emergent adverse event.

Source: Table 12.6.1.6.3