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, Active-controlled, Multicenter Study to Evaluate the Long-term Safety and Efficacy of Combination of Solifenacin Succinate with Mirabegron Compared to Solifenacin Succinate and Mirabegron Monotherapy in Patients with Overactive Bladder

Investigators/Coordinating Investigators:

[redacted] United States

[redacted] Germany

Study Center(s): This multinational, multicenter study was conducted at 251 sites in 32 countries worldwide within 6 geographic regions (North America, Latin America, Western Europe, Eastern Europe, Asia and Southern Hemisphere).

Publication Based on the Study: None

Study Period: The study comprised a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, active-controlled, 12-month treatment period and then by a 2-week follow-up (FU) period

Study Initiation Date (Date of First Enrollment): 17 Mar 2014

Study Completion Date (Date of Last Evaluation): 08 Sep 2016

Phase of Development: 3

Objectives:

The primary objective of this study was:

- To evaluate the safety and tolerability of long-term combination treatment with solifenacin (5 mg) and mirabegron (50 mg) compared to solifenacin and mirabegron monotherapy.

The secondary objectives of this study were:

- To evaluate the efficacy of long-term combination treatment with solifenacin and mirabegron; and
- To evaluate patient-reported outcomes (PROs) during long-term combination treatment with solifenacin and mirabegron.

Methodology: The study comprised a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, active-controlled, 12-month treatment period and then by a 2-week FU period. Patients visited the clinic at screening (visit 1); at the end of the placebo run-in period (visit 2); after 1, 3, 6, 9 and 12 months of double-blind treatment (visits 3, 4, 5, 6 and 7); and 2 weeks after end of treatment (EoT), for a FU visit (visit 8).

Randomization was stratified by sex, age group (< 65 years, ≥ 65 years) and geographic region (North America, Latin America, Western Europe, Eastern Europe, Asia, Southern Hemisphere).

Number of Patients (Planned, Enrolled and Analyzed): A total of 2400 patients were planned to be enrolled, of which 1800 were to be randomized in a 4:1:1 ratio to the treatment groups: combination 5 + 50 mg therapy, and the 2 monotherapy groups (solifenacin 5 mg and mirabegron 50 mg). A total of 2084 female and male patients were screened, of which 2063 patients received placebo run-in medication.

Of the 1829 patients who were randomized into the study (i.e., in the randomized analysis set [RAS]), 99.5% (1819) of patients received double-blind study drug [Figure 1]. Of these patients, 99.2% (1814) were included in the safety analysis set (SAF) and 98.1% (1794) were included in the full analysis set (FAS).

Diagnosis and Main Criteria for Inclusion: Female and male patients ≥ 18 years of age with symptoms of "wet" overactive bladder (OAB)—that is, patients with urinary frequency and urgency with incontinence) for ≥ 3 months—were eligible for screening. Patients who recorded on average ≥ 8 micturition episodes per 24 h, on average ≥ 1 urgency episode per 24 h and ≥ 3 incontinence episodes over the 7-day micturition electronic diary (eDiary) at visit 2 were eligible for randomization to the double-blind treatment part of the study.

Medications prohibited between visit 1/screening and visit 8/FU included drugs used for the treatment of OAB other than the study drugs (including intravesical treatment) and drugs that influenced efficacy, masked safety signals or were Cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic margin. Patients had to stop taking prohibited medications ≥ 2 weeks prior to the start of the placebo run-in period. The therapeutic efficacy of some drugs could be counteracted by study drugs. This did not apply to drugs used only topically (i.e., including inhaled, intranasal, dermal, intradermal, ophthalmic, otic and intra-articular drugs).

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

Solifenacin succinate formulation was supplied as 5 mg tablets. Mirabegron oral controlled absorption system (OCAS) formulation was supplied as 50 mg tablets. Throughout the study, patients took 2 tablets orally, once daily, in the morning. The 3 treatment groups with batch numbers are summarized below:

Combination therapy group (solifenacin 5 mg + mirabegron 50 mg) (batch numbers [redacted])

• Solifenacin succinate 5 mg

• Mirabegron OCAS 50 mg

Solifenacin succinate 5 mg monotherapy group (batch numbers [redacted])

• Solifenacin succinate 5 mg

• Placebo to match mirabegron OCAS 50 mg

Mirabegron OCAS 50 mg monotherapy group (batch numbers [redacted])

• Mirabegron OCAS 50 mg

• Placebo to match solifenacin succinate 5 mg

Duration of Treatment: The treatment duration was 12 months (365 days).

Reference Product, Dose and Mode of Administration, Batch Numbers: Placebo was supplied to all patients for the 2-week run-in period. Patients were blinded during this run-in phase and during the treatment phase. As before, patients were to take 2 tablets orally per day throughout the study. The placebo tablets were, with respect to appearance and shape, indistinguishable from the corresponding active treatment tablets.

Placebo run-in medication [redacted]

• Placebo to match solifenacin succinate 5 mg

• Placebo to match mirabegron OCAS 50 mg

Criteria for Evaluation:

Efficacy: The primary efficacy variables were the change from baseline to end of treatment (EoT) in mean number of incontinence episodes per 24 h and in mean number of micturitions per 24 h. Key secondary efficacy variables comprised the change from baseline to EoT in mean volume voided (MVV) per micturition, in Symptom Bother score as assessed by the OAB questionnaire (OAB-q), and in the patient's assessment of the treatment satisfaction–visual analogue scale (TS-VAS).

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

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

Statistical Methods:

Analysis Sets

There were 3 primary analysis sets of interest. The RAS comprised all randomized patients and was used to summarize the disposition of patients who were randomized to double-blind treatment. The FAS comprised all randomized patients who took ≥ 1 dose of double-blind study drug after randomization, reported ≥ 1 micturition measurement in the baseline eDiary and ≥ 1 micturition measurement postbaseline and reported ≥ 1 incontinence episode in the baseline eDiary. The FAS was regarded as the main analysis set for the primary and secondary efficacy variables. The SAF comprised all patients who received ≥ 1 dose of double-blind treatment. All safety analyses were performed on the SAF.

Efficacy

The change from baseline to EoT in mean number of incontinence episodes per 24 h was analyzed using a separate stratified rank analysis of covariance (ANCOVA) model for each pairwise treatment group difference of interest (combination 5 + 50 mg therapy vs each monotherapy component). The response variable for the stratified rank ANCOVA was standardized ranks on change from baseline to EoT value with baseline standardized ranks, sex, age group and previous study history (i.e., combination of study from which the patient rolled over and actual treatment received during previous study) as covariates, and with geographical region as a stratum. [redacted]

The stratified rank ANCOVA was utilized for hypothesis testing and calculating the pairwise P values. Least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for mean changes from baseline within a treatment group, as well as the difference between the combination 5 + 50 mg group and each of its monotherapy components, were derived from the corresponding ANCOVA model with treatment group (all 3 treatment groups in the model), sex, age group, previous study history and geographic region as factors, and with baseline value as a covariate.

The change from baseline in MVV, the change from baseline to EoT in mean number of micturitions per 24 h, the change from baseline in Symptom Bother score as assessed by the OAB-q, and the change from baseline in patient's assessment of TS-VAS were analyzed in an ANCOVA model with treatment group, sex, age group, geographic region and previous study history as factors, and with baseline value as a covariate.

Safety

All adverse events (AEs), including TEAEs, were coded using MedDRA v16.0 and summarized by number (%) of patients with the TEAE according to SOC and preferred term (PT); severity (i.e., mild, moderate, severe); and by relationship to study drug (i.e., not related, possibly related or probably related).

Vital signs variables (pulse rate, systolic blood pressure [SBP] and diastolic blood pressure [DBP]) were summarized with descriptive statistics (i.e., mean, SD, minimum, maximum, median, 90%, 95% and 99% percentiles) by treatment group and applicable visit. Change from baseline to each visit for each site-based and home-based vital signs variable was analyzed using an ANCOVA model with treatment group, age group, sex, previous study history and geographic regions as factors, and with baseline value as a covariate.

Clinical laboratory evaluations (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 for each visit.

Summary of Results/Conclusions:

Patient Disposition and Demographics:

The study was conducted at 251 sites in 32 countries. The majority of patients were from Eastern Europe (55.1%), with 20.7% from North America, 12.4% from Western Europe, 7.6% from Asia, 3.8% from the Southern Hemisphere and 0.4% from Latin America [Table 2].

The majority of patients were female (79.9%) and White (87.1%). The overall mean age at screening was 58.5 years (range 19 to 86 years) with 34.2% of patients aged ≥ 65 years, 9.4% aged ≥ 75 years and 0.3% aged ≥ 85 years. About 9.4% of all enrolled patients were ≥ 75 years of age, which fell short of the intent to have at least 10% of all patients distributed within this age group [Table 2].

Overall, the discontinuation rate from the double-blind treatment period was low (11.2%) with no relevant differences among treatment groups. In total, 88.8% (1624) of patients in the RAS completed the study. The majority of premature treatment discontinuations (n = 102) was due to patient choice, with the highest rate of 8.9% (27/305) of patients reported in the solifenacin 5 mg group compared to 5.9% (18/306) patients in the mirabegron 50 mg group and 4.7% (57/1218) patients in the combination 5 + 50 mg group. The lowest rate of discontinuation due to lack of efficacy was in the combination 5 + 50 mg group (1.1%) compared to 2.6% in the mirabegron 50 mg group and 1.3% in the solifenacin 5 mg group [Table 1].

Efficacy Results:

Efficacy was a secondary objective of this study.

For the first primary efficacy endpoint of mean number of incontinence episodes at EoT, combination 5 + 50 mg was statistically significantly superior respectively to mirabegron 50 mg (-0.45 episodes, P < 0.001) and solifenacin 5 mg (-0.13 episodes, P = 0.002) in the difference in change from baseline. For the second primary efficacy endpoint of mean number of micturitions per 24 h at EoT, combination 5 + 50 mg was statistically significantly superior respectively to mirabegron 50 mg (-0.48 episodes, P < 0.001) and solifenacin 5 mg (-0.42 episodes, P = 0.004) in the difference in change from baseline [Table 3].

For the key secondary efficacy endpoint of MVV per micturition at EoT, combination 5 + 50 mg was statistically significantly superior respectively to mirabegron 50 mg (15.84 mL, P < 0.001) and solifenacin 5 mg (12.77 mL, P < 0.001) in the difference in change from baseline.

For the key secondary efficacy endpoints of OAB-q Symptom Bother score and TS-VAS, combination 5 + 50 mg was statistically significantly superior respectively to mirabegron 50 mg (OAB-q: -7.55, P < 0.001; TS-VAS: 0.55, P < 0.001) and solifenacin 5 mg (OAB-q: -4.60, P < 0.001; TS-VAS: 0.59, P < 0.001) in the difference in change from baseline to EoT for both endpoints.

The proportion of responders with zero incontinence episodes in the last 3 days prior to EoT was 58.8% in the combination 5 + 50 mg group, 47.8% in the mirabegron 50 mg group (treatment difference of 10.9% vs combination 5 + 50 mg) and 53.2% in the solifenacin 5 mg group (treatment difference of 5.6% vs combination 5 + 50 mg). The odds to achieve zero incontinence episodes at EoT were statistically significantly higher in the combination 5 + 50 mg group compared to mirabegron 50 mg (P < 0.001), but not compared to solifenacin 5 mg (P = 0.080).

Efficacy was demonstrated for all primary and key secondary efficacy variables, and the effect was maintained over the 12-month treatment period. [redacted] Furthermore, combination 5 + 50 mg therapy also showed clinically relevant and statistically significant improvements over its 2 monotherapy components in the treatment of most OAB symptoms; these objective outcomes translated into meaningful benefits for patients, which are supported by significant improvements in HRQL.

Safety Results:

All treatment arms investigated in this study appeared to be well tolerated with an acceptable safety profile. In general, combination 5 + 50 mg therapy demonstrated a similar safety profile to that expected for its 2 monotherapy components, with no new safety findings identified.

It should be noted that the 4:1:1 randomization used in this study also increased the chances to observe rare (background) events in the larger combination 5 + 50 mg group. As expected, the frequency of TEAEs in the combination 5 + 50 mg group was higher (49.4%) compared to the solifenacin 5 mg (44.2%) and mirabegron 50 mg (41.3%) monotherapy groups.

The frequency of TEAEs leading to permanent discontinuation of study drug was similar across treatment groups (range from 1.7% in solifenacin 5 mg to 2.1% in combination 5 + 50 mg and to 2.3% in mirabegron 50 mg).

The most frequently reported TEAEs in the combination 5 + 50 mg group were nasopharyngitis (3.6%), urinary tract infection (3.4%) and dry mouth (6.1%) Table 4. Drug-related TEAEs (by PT) with a frequency of ≥ 1% in any treatment group were dry mouth, constipation and hypertension

The frequency of serious TEAEs was low, with events ranging from 2.6% in both monotherapy groups to 4.2% in the combination 5 + 50 mg group. Only 1 patient had a serious TEAE that was considered treatment-related by the investigator [redacted]. Although there was a slight increase in incidence in serious TEAEs in the combination 5 + 50 mg group, there was no clustering around specific events Table 5.

Two patients died during or after the double blind treatment period: [redacted] Both cases were considered not related to study treatment by the investigator and sponsor.

Overall, 0.4% (5/1206) patients in the combination 5 + 50 mg group and 0.3% (1/305) patient in the mirabegron 50 mg group experienced a serious TEAE in the SOC Cardiac disorders Table 5. In all patients, relevant medical history confounded the event.

QTcF outliers in the combination 5 + 50 mg group did not show any additive or synergistic effects beyond those known from the monotherapy components.

Tachyarrhythmias (grouped as increased heart rate, tachycardia, atrial fibrillation and palpitations) were reported in a slightly higher frequency in the combination 5 + 50 mg group (i.e., 3.0% vs 1.0% in the solifenacin 5 mg group and vs 2.6% in the mirabegron 50 mg group). A total of 2 patients (both in the combination 5 + 50 mg group) were permanently discontinued from treatment due to tachyarrhythmia. Most tachyarrhythmias started after month 3 without a clear temporal pattern across treatment groups.

There were 12 serious TEAEs of cardiovascular or cerebrovascular nature: 10 events were reported for 0.7% (8/1206) patients in the combination 5 + 50 mg group and 0.3% [redacted] in the monotherapy groups. All these events were adjudicated by the cardiovascular IAC, and all adjudicated cardiovascular events were confounded by a history of cardiovascular disease on the basis of medical history and/or presence of other risk factors.

The frequency of urinary retention–related events appeared to be slightly increased in the combination 5 + 50 mg group (0.7%) vs both monotherapy groups (0.3%). Change from baseline in PVR was slightly higher in the combination 5 + 50 mg group compared to both monotherapy groups.

There were no concerns for hypersensitivity reactions, somnolence or laboratory data, including liver function tests. Furthermore, no new safety concerns were identified beyond what was already known for the monotherapies.

Adjudicated neoplasm events were reported in the mirabegron 50 mg monotherapy and in the combination 5 + 50 mg group at a similar frequency; no event was recorded in the solifenacin 5 mg group. Many events occurred in patients with advanced age. The type and frequency of events seem commensurate with the elderly age of the patient population; therefore, no conclusions can be drawn from these data.

Few patients (≤ 5.6% for any 1 parameter) met the criteria for potentially clinically significant (PCS) laboratory values, with no relevant differences across treatment groups. No Hy's Law cases were reported

Increases in pulse rate of about 1 bpm from baseline were observed in the mirabegron 50 mg and combination 5 + 50 mg groups compared to an increase of 0.32 bpm for the solifenacin 5 mg group. Changes from baseline in SBP were lower in the combination 5 + 50 mg group compared to both monotherapy groups. There were no relevant changes in DBP in any treatment group.

Compared to its 2 monotherapy components, combination 5 + 50 mg therapy was well tolerated and had an acceptable safety profile with no new safety findings identified.

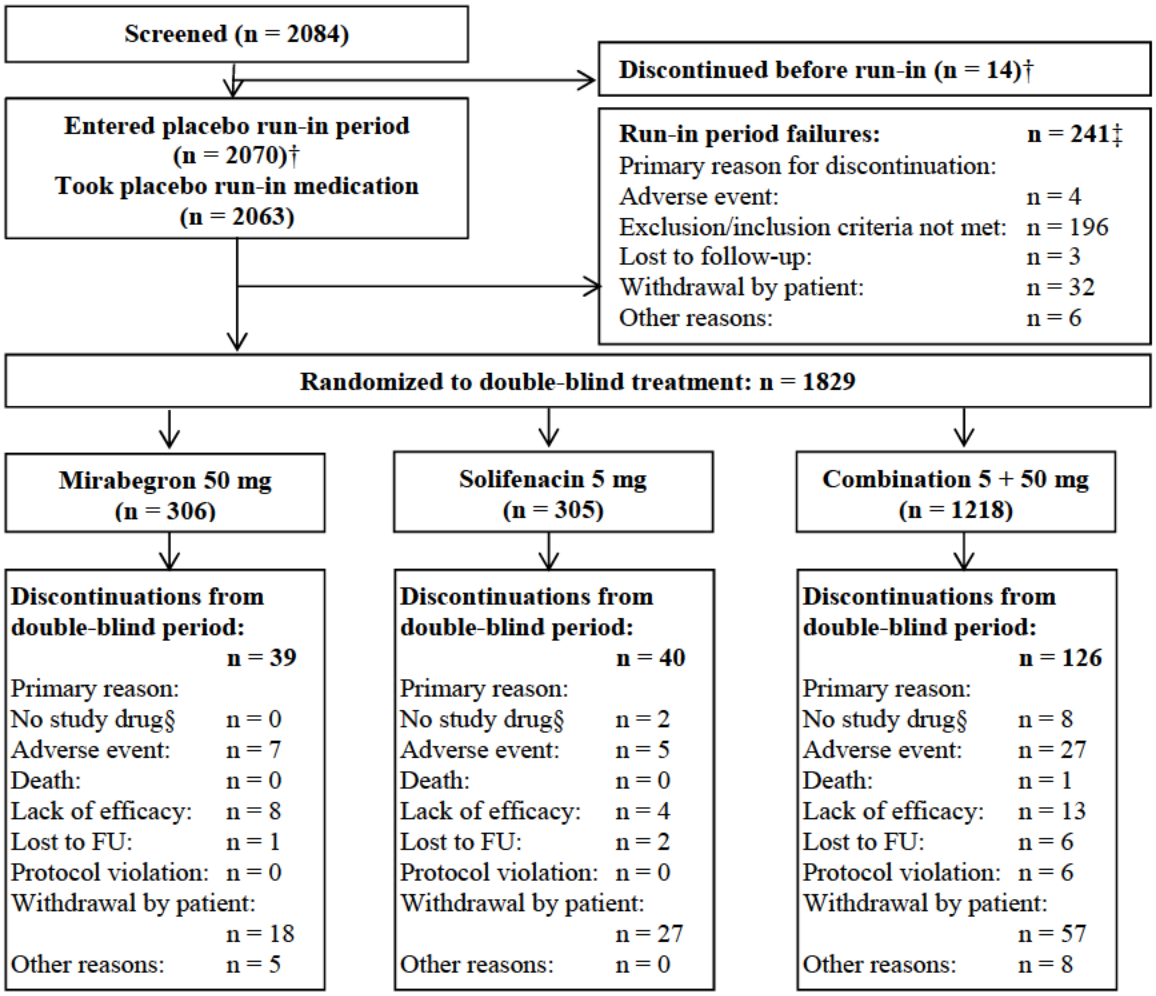
CONCLUSIONS:

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

- Combination therapy with solifenacin 5 mg + mirabegron 50 mg provided clear and clinically relevant improvements in efficacy compared to the respective monotherapies with effect sizes that were generally consistent over the 12-month treatment period.
- The improvements seen with combination 5 + 50 mg therapy compared to the respective monotherapies translated into significant improvements in HRQL and many responder rates, supporting the clinical relevance of the effect.
- Combination 5 + 50 mg therapy once daily for 12 months 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: 10 Feb 2017

Figure 1 Patient Disposition (SPAS, SPAS Excluding Screen Failure Subject, RAS)



FU: follow-up; RAS: randomized analysis set; SPAS: screening period analysis set.

†Including patients who were dispensed run-in study drug but did not take any. One patient should have been a screen failure but had been allocated a run-in kit by mistake and, therefore, was counted as having entered the placebo run-in period at the site and a run-in withdrawal reason was allocated. The patient was not counted as being discontinued before run-in but allocated in this row. The patient was not in the run-in period analysis set though as no run-in medication was actually dispensed.

‡Only the primary reason for run-in failure is collected.

§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

Table 1 Patients with Study Discontinuation by Treatment Group (RAS)

n (%) of Patients	Mirabegron 50 mg (n = 306)	Solifenacin 5 mg (n = 305)	Combination 5 + 50 mg (n = 1218)
Received ≥ 1 dose of study drug†			
Completed treatment	267 (87.3%)	265 (86.9%)	1092 (89.7%)
Discontinued from treatment	39 (12.7%)	40 (13.1%)	126 (10.3%)
Primary reason for discontinuation‡			
Randomized/registered but not received/dispensed study drug	0	2 (0.7%)	8 (0.7%)
Adverse event	7 (2.3%)	5 (1.6%)	27 (2.2%)
Death	0	0	1 (0.1%)
Lack of efficacy	8 (2.6%)	4 (1.3%)	13 (1.1%)
Lost to FU	1 (0.3%)	2 (0.7%)	6 (0.5%)
Protocol violation	0	0	6 (0.5%)
Withdrawal by patient	18 (5.9%)	27 (8.9%)	57 (4.7%)
Other	5 (1.6%)	0	8 (0.7%)

The RAS comprised all patients randomized to double-blind treatment.

FU: follow-up; RAS: randomized analysis set.

†Patients who did not complete the 12 months of double-blind treatment.

‡Only the primary reason for run-in failure is collected.

Source: Table 12.1.1.3.3

Table 2 Summary of Demographics and Baseline Characteristics (FAS)

Parameter Category/Statistics	Mirabegron 50 mg (n = 302)	Solifenacin 5 mg (n = 299)	Combination 5 + 50 mg (n = 1193)	Total (n = 1794)
Sex, n (%)				
Male	63 (20.9%)	58 (19.4%)	239 (20.0%)	360 (20.1%)
Female	239 (79.1%)	241 (80.6%)	954 (80.0%)	1434 (79.9%)
Age, y†				
Mean /Median	58.8 /61.0	58.8 /60.0	58.3 /60.0	58.5 /60.0
< 65	200 (66.2%)	196 (65.6%)	784 (65.7%)	1180 (65.8%)
≥ 65	102 (33.8%)	103 (34.4%)	409 (34.3%)	614 (34.2%)
< 75	273 (90.4%)	264 (88.3%)	1089 (91.3%)	1626 (90.6%)
≥ 75	29 (9.6%)	35 (11.7%)	104 (8.7%)	168 (9.4%)
≥ 85	0	4 (1.3%)	2 (0.2%)	6 (0.3%)
Race, n (%)				
White	262 (86.8%)	259 (86.6%)	1042 (87.3%)	1563 (87.1%)
Black or African American	5 (1.7%)	4 (1.3%)	27 (2.3%)	36 (2.0%)
Asian	31 (10.3%)	33 (11.0%)	118 (9.9%)	182 (10.1%)
Other‡	4 (1.3%)	3 (1.0%)	6 (0.5%)	13 (0.7%)
Ethnicity, n (%)				
Hispanic or Latino	13 (4.3%)	13 (4.3%)	50 (4.2%)	76 (4.2%)
Not Hispanic or Latino	289 (95.7%)	286 (95.7%)	1143 (95.8%)	1718 (95.8%)
Weight (kg)				
Mean (SD)	78.83 (17.44)	77.07 (15.61)	78.24 (17.29)	78.15 (17.05)
Median	78.00	75.00	76.00	76.00
Min - Max	39.3 - 151.0	45.0 - 136.8	43.0 - 179.4	39.3 - 179.4
Height (cm)				
Mean (SD)	165.22 (8.73)	164.41 (8.25)	165.31 (8.49)	165.15 (8.49)
Median	164.50	164.00	165.00	164.50
Min - Max	143.8 - 198.0	147.3 - 194.0	137.2 - 198.0	137.2 - 198.0
BMI (kg/m^2)				
Mean (SD)	28.81 (5.72)	28.49 (5.25)	28.61 (5.88)	28.62 (5.75)
Median	28.13	27.61	27.64	27.76
Min - Max	18.4 - 56.8	18.3 - 51.0	16.3 - 61.9	16.3 - 61.9
Geographic region				
North America	62 (20.5%)	60 (20.1%)	250 (21.0%)	372 (20.7%)
Latin America	1 (0.3%)	3 (1.0%)	4 (0.3%)	8 (0.4%)
Western Europe	37 (12.3%)	38 (12.7%)	147 (12.3%)	222 (12.4%)
Eastern Europe	167 (55.3%)	164 (54.8%)	657 (55.1%)	988 (55.1%)
Asia	22 (7.3%)	23 (7.7%)	91 (7.6%)	136 (7.6%)
Southern hemisphere	13 (4.3%)	11 (3.7%)	44 (3.7%)	68 (3.8%)

The FAS included all randomized patients who took ≥ 1 dose of double-blind study drug and who recorded > 1 micturition measurement in the baseline eDiary and ≥ 1 micturition measurement in a postbaseline eDiary and reported ≥ 1 incontinence episode in the baseline eDiary.

Footnotes continued on next page.

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

†Baseline refers to last nonmissing value prior to first dose of double-blind treatment. Age at baseline was calculated as (first double-blind treatment date – birth date)/365.25. If first double-blind treatment date was missing, then the dispense date at the randomization visit + 1 day was used instead. If birth date was partial or missing, then the age as recorded in the eCRF was used.

‡American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander are listed under the 'Other' race category.

Source: Table 12.1.2.1.3

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

Statistic		Mirabegron 50 mg (n = 302)	Solifenacin 5 mg (n = 299)	Combination 5 + 50 mg (n = 1193)
Change from Baseline to EoT in Mean Number of Incontinence Episodes per 24 h				
	n	301	297	1184
Baseline	Mean (SE)	3.15 (0.21)	3.11 (0.21)	3.04 (0.09)
EoT	Mean (SE)	1.52 (0.16)	1.19 (0.14)	1.02 (0.07)
Change from baseline	Mean (SE)	-1.63 (0.17)	-1.92 (0.18)	-2.02 (0.07)
Adjusted change from baseline†	Mean (SE)	-1.58 (0.11)	-1.90 (0.11)	-2.03 (0.05)
	95% 2-sided CIs	(-1.79, -1.37)	(-2.12, -1.69)	(-2.14, -1.93)
Adjusted difference vs mirabegron or solifenacin‡	Mean (SE)	-0.45 (0.12)	-0.13 (0.12)	NA
	95% 2-sided CIs	(-0.69, -0.21)	(-0.37, 0.11)	
	P value§	< 0.001*	0.002*	
Change from Baseline to EoT in Mean Number of Micturitions per 24 h				
	n	301	297	1184
Baseline	Mean (SE)	10.49 (0.14)	10.74 (0.16)	10.52 (0.08)
EoT	Mean (SE)	8.43 (0.16)	8.49 (0.15)	7.95 (0.08)
Change from baseline	Mean (SE)	-2.06 (0.15)	-2.25 (0.17)	-2.57 (0.07)
Adjusted change from baseline†	Mean (SE)	-2.10 (0.13)	-2.16 (0.13)	-2.58 (0.07)
	95% 2-sided CIs	(-2.36, -1.85)	(-2.42, -1.91)	(-2.71, -2.46)
Adjusted difference vs mirabegron or solifenacin‡	Mean (SE)	-0.48 (0.15)	-0.42 (0.15)	NA
	95% 2-sided CIs	(-0.77, -0.20)	(-0.71, -0.13)	
	P value¶	< 0.001*	0.004*	

The FAS included all randomized patients who took ≥ 1 dose of double-blind study drug and who recorded > 1 micturition measurement in the baseline eDiary and ≥ 1 micturition measurement in a postbaseline eDiary and reported ≥ 1 incontinence episode in the baseline eDiary.
ANCOVA: analysis of covariance; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; NA: not applicable.
†Adjusted change from baseline values as well as the 95% CIs were generated from the ANCOVA model with treatment group, sex, age group (< 65, ≥ 65 years), previous study history and geographic region as fixed factors and baseline value as a covariate.
‡Difference of the adjusted mean is calculated by subtracting the adjusted mean of the corresponding monotherapy group from the adjusted mean of the combination group based on the ANCOVA model described above.
§The 2-sided P value is for pairwise comparisons between the combination therapy group and the corresponding monotherapy group from the stratified rank ANCOVA.

Footnotes continued on next page.

¶The 2-sided P value is for pairwise comparisons between the combination therapy group and the corresponding monotherapy group from the ANCOVA model.
*Statistically significantly different compared to monotherapy at the 0.05 level.
Source: Tables 12.3.1.1.1 and 12.3.1.1.2

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

MedDRA (v16.0), SOC PT, n (%)	**Mirabegron 50 mg (n = 305)**	**Solifenacin 5 mg (n = 303)**	**Combination 5 + 50 mg (n = 1206)**
Overall	**86 (28.2%)**	**90 (29.7%)**	**381 (31.6%)**
Infections and infestations	**57 (18.7%)**	**54 (17.8%)**	**202 (16.7%)**
Nasopharyngitis	16 (5.2%)	15 (5.0%)	43 (3.6%)
Urinary tract infection	11 (3.6%)	12 (4.0%)	41 (3.4%)
Escherichia urinary tract infection	6 (2.0%)	3 (1.0%)	35 (2.9%)
Influenza	8 (2.6%)	9 (3.0%)	26 (2.2%)
Bronchitis	12 (3.9%)	5 (1.7%)	24 (2.0%)
Urinary tract infection bacterial	1 (0.3%)	1 (0.3%)	26 (2.2%)
Upper respiratory tract infection	5 (1.6%)	8 (2.6%)	11 (0.9%)
Cystitis	2 (0.7%)	5 (1.7%)	12 (1.0%)
Pharyngitis	1 (0.3%)	5 (1.7%)	10 (0.8%)
Sinusitis	4 (1.3%)	0	4 (0.3%)
Gastrointestinal disorders	**18 (5.9%)**	**26 (8.6%)**	**108 (9.0%)**
Dry mouth	12 (3.9%)	18 (5.9%)	74 (6.1%)
Constipation	3 (1.0%)	7 (2.3%)	40 (3.3%)
Diarrhoea	3 (1.0%)	4 (1.3%)	8 (0.7%)
Musculoskeletal and connective tissue disorders	**8 (2.6%)**	**9 (3.0%)**	**46 (3.8%)**
Back pain	6 (2.0%)	0	14 (1.2%)
Arthralgia	2 (0.7%)	2 (0.7%)	14 (1.2%)
Pain in extremity	3 (1.0%)	5 (1.7%)	9 (0.7%)
Osteoarthritis	1 (0.3%)	2 (0.7%)	13 (1.1%)
Nervous system disorders	**9 (3.0%)**	**5 (1.7%)**	**48 (4.0%)**
Headache	5 (1.6%)	5 (1.7%)	35 (2.9%)
Dizziness	4 (1.3%)	0	13 (1.1%)
Vascular disorders	**4 (1.3%)**	**4 (1.3%)**	**23 (1.9%)**
Hypertension	4 (1.3%)	4 (1.3%)	23 (1.9%)
Cardiac disorders	**5 (1.6%)**	**1 (0.3%)**	**23 (1.9%)**
Tachycardia	5 (1.6%)	1 (0.3%)	23 (1.9%)
Respiratory, thoracic and mediastinal disorders	**5 (1.6%)**	**4 (1.3%)**	**9 (0.7%)**
Cough	5 (1.6%)	4 (1.3%)	9 (0.7%)

The SAF comprised all randomized patients who received ≥ 1 dose of double-blind treatment.

TEAE refers to an AE that 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.

Footnotes continued on next page.

Sorting Order: based on Total group, descending in incidence by system organ class (SOC) and PT. In case of ties, alphabetical order by SOC and PT.

AE: adverse event; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.11

Table 5 Serious TEAEs in ≥ 2 patients in ≥ 1 Group (SAF)

MedDRA (v16.0), SOC PT, n (%)	**Mirabegron 50 mg (n = 305)**	**Solifenacin 5 mg (n = 303)**	**Combination 5 + 50 mg (n = 1206)**
Overall	8 (2.6%)	8 (2.6%)	51 (4.2%)
Infections and infestations	**2 (0.7%)**	**1 (0.3%)**	**8 (0.7%)**
Appendicitis	1 (0.3%)	0	2 (0.2%)
Pneumonia	1 (0.3%)	0	2 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (0.3%)**	**0**	**9 (0.7%)**
Basal cell carcinoma	0	0	3 (0.2%)
Gastrointestinal disorders	**1 (0.3%)**	**2 (0.7%)**	**6 (0.5%)**
Abdominal pain	1 (0.3%)	0	1 (0.1%)
Pancreatitis acute	0	1 (0.3%)	1 (0.1%)
Injury, poisoning and procedural complications	0	1 (0.3%)	8 (0.7%)
Clavicle fracture	0	0	2 (0.2%)
Cardiac disorders	**1 (0.3%)**	**0**	**5 (0.4%)**
Atrial fibrillation	1 (0.3%)	0	2 (0.2%)
Musculoskeletal and connective tissue disorders	**0**	**2 (0.7%)**	**4 (0.3%)**
Osteoarthritis	0	0	2 (0.2%)
Surgical and medical procedures	**2 (0.7%)**	**0**	**4 (0.3%)**
Cholecystectomy	0	0	2 (0.2%)
Nervous system disorders	**0**	**0**	**4 (0.3%)**
Reproductive system and breast disorders	**0**	**0**	**4 (0.3%)**
General disorders and administration site conditions	**1 (0.3%)**	**0**	**1 (0.1%)**
Hepatobiliary disorders	**0**	**0**	**2 (0.2%)**
Cholelithiasis	0	0	2 (0.2%)
Respiratory, thoracic and mediastinal disorders	**1 (0.3%)**	**0**	**1 (0.1%)**
Vascular disorders	**0**	**1 (0.3%)**	**1 (0.1%)**

The SAF comprised all randomized patients who received ≥ 1 dose of double-blind treatment.

TEAE refers to an AE that 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.

AE: adverse event; PT: preferred term; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.6