Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Solifenacin Succinate (YM905)/Mirabegron (YM178)		
Name of Active Ingredient: Solifenacin Succinate /Mirabegron		

SYNOPSIS

Title of Study: A Randomized, Double-Blind, Factorial, Parallel-Group, Active and Placebo-Controlled, Multicenter Dose-Ranging Study to Evaluate the Efficacy, Safety and Tolerability of Six Dose Combinations of Solifenacin Succinate and Mirabegron Compared to Mirabegron and Solifenacin Succinate Monotherapies in the Treatment of Overactive Bladder

Investigators/Coordinating Investigator: [redacted]

Study Center(s): This multinational study was conducted at 141 sites in 20 countries.

Publication (reference): No publications based on the results of this study were available as of the time of finalization of this report.

Study Period: March 2011 to June 2012

Date of first enrollment (Study initiation date): 29 March 2011

Date of last evaluation (Study completion date): 28 June 2012

Phase of Development: Phase 2

Objectives: The primary objective of this study was to evaluate the efficacy of 4 combinations of solifenacin succinate (2.5 or 5 mg) plus mirabegron (25 or 50 mg) vs solifenacin succinate 5 mg monotherapy. The secondary objectives were to: 1) investigate the dose-response surface of combinations of solifenacin succinate (0, 2.5, 5 and 10 mg) and mirabegron (0, 25 and 50 mg) doses; 2) compare the safety and tolerability of 6 combinations of solifenacin succinate and mirabegron vs solifenacin succinate monotherapy, mirabegron monotherapy and placebo; and 3) investigate the population pharmacokinetics and the pharmacokinetic-pharmacodynamic relationship of 6 combinations of solifenacin succinate and mirabegron, and the mirabegron and solifenacin succinate monotherapies.

Methodology: This was a randomized, double-blind, factorial, parallel-group, active- and placebo-control, multicenter dose-ranging study to evaluate the efficacy, safety and tolerability of 6 dose combinations of solifenacin succinate and mirabegron compared to mirabegron and solifenacin succinate monotherapies in male and female patients with symptoms of overactive bladder (OAB) (urgency, urinary frequency and/or urgency incontinence) for at least 3 months. Patients were enrolled in a 2-week, single-blind, placebo run-in period. Eligible patients were randomized to 1 of 6 combination treatment groups, mirabegron or solifenacin monotherapy or placebo:

- Solifenacin succinate 2.5 mg + mirabegron 25 mg
- Solifenacin succinate 2.5 mg + mirabegron 50 mg
- Solifenacin succinate 5 mg + mirabegron 25 mg
- Solifenacin succinate 5 mg + mirabegron 50 mg
- Solifenacin succinate 10 mg + mirabegron 25 mg

- Solifenacin succinate 10 mg + mirabegron 50 mg
- Solifenacin succinate 2.5 mg
- Solifenacin succinate 5 mg
- Solifenacin succinate 10 mg
- Mirabegron 25 mg
- Mirabegron 50 mg
- Placebo

Number of Patients (planned, enrolled and analyzed): Approximately 1658 patients were planned to be enrolled, with 1326 randomized to ensure 1190 evaluable patients. A total of 1658 patients entered the placebo run-in period, 1306 patients were randomized into the study and 1278 patients were included in the Full Analysis Set (FAS).

Diagnosis and Main Criteria for Inclusion: Male and female patients at least 18 years of age with symptoms of OAB (urgency, urinary frequency and/or urgency incontinence) for at least 3 months who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied, were eligible for inclusion in this study.

Test Product, Dose and Mode of Administration, Batch Numbers: Solifenacin succinate was supplied as 2.5, 5 and 10 mg tablets. Mirabegron was supplied as 25 and 50 mg Oral Controlled Absorption System (OCAS) tablets.

Throughout the treatment phase, patients took 3 tablets to maintain the study blind: solifenacin succinate (2.5, 5 or 10 mg) or placebo, mirabegron 25 mg or placebo and mirabegron 50 mg or placebo. Medication (including placebo) was taken orally with a glass of water, with or without food, once daily in the morning. Study medication was to be swallowed whole (i.e., not chewed).

Lot numbers: solifenacin succinate: [redacted] and [redacted] mirabegron OCAS: [redacted] and [redacted]

Duration of Treatment (or Duration of Study, if applicable): Single-blind placebo/run-in period: 2 weeks and double-blind, placebo-controlled treatment period: 12 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers: Placebo tablets (placebo matching solifenacin succinate, placebo matching mirabegron 25 mg, and placebo matching mirabegron 50 mg) were taken in the same manner as the test products. Placebo tablets to match either solifenacin succinate or mirabegron were indistinguishable with respect to appearance and shape from the active mirabegron and solifenacin succinate tablets. Lot numbers: [redacted] and [redacted]

The mirabegron and solifenacin monotherapy arms were also comparators in this study. These test products are described above.

Criteria for Evaluation: During the study, patients were required to complete a patient diary, which was implemented on an electronic handheld device. This diary collected data on vital signs, micturition and incontinence.

The primary efficacy variable was the change from baseline to end of treatment in mean volume voided per micturition based on a 3-day micturition diary. Key secondary efficacy variables were change from baseline to end of treatment in mean number of micturitions per 24 h and change from baseline to end of treatment in mean

number of incontinence episodes per 24 h. Additional secondary efficacy variables derived from the 3-day micturition diary were:

- Change from baseline in mean volume voided after 2, 4, 8 and 12 weeks of treatment
- Change from baseline in mean number of micturitions per 24 h after 2, 4, 8 and 12 weeks of treatment
- Change from baseline in mean number of incontinence episodes per 24 h after 2, 4, 8 and 12 weeks of treatment
- Change from baseline in mean number of urgency incontinence episodes per 24 h after 2, 4, 8 and 12 weeks of treatment and at end of treatment
- Change from baseline in mean number of urgency episodes (grade 3 and/or 4) per 24 h (Patient Perception of Intensity of Urgency Scale [PPIUS]) after 2, 4, 8 and 12 weeks of treatment and at end of treatment
- Change from baseline in mean level of urgency after 2, 4, 8 and 12 weeks of treatment and at end of treatment
- Change from baseline in mean number of pads used per 24 h after 2, 4, 8 and 12 weeks of treatment and at end of treatment
- Change from baseline in mean number of nocturia episodes per 24 h after 2, 4, 8 and 12 weeks of treatment and at end of treatment

Furthermore, 2 responder analyses based on incontinence episodes and 1 responder analysis based on the number of micturitions were performed at weeks 2, 4, 8 and 12 and at end of treatment.

Additional secondary efficacy variables that were not derived from the 3-day micturition diary were the following:

- Change from baseline in Patient Perception of Bladder Condition (PPBC)
- Change from baseline in symptom bother and health-related quality of life (QoL) scores as assessed by the overactive bladder questionnaire (OAB-q)
- Change from baseline in scores as assessed by the Euro QoL-5 Dimensions (EQ-5D) questionnaire
- Change from baseline in scores as assessed by the Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) questionnaire
- Change from baseline in the patient's assessment of the Treatment Satisfaction–Visual Analog Scale (TS-VAS)

Responder analyses of changes from baseline in PPBC and OAB-q were also performed at week 12 and at end of treatment based on the following definitions:

- Improvement in PPBC: $\geq$ 1 point improvement from baseline
- Major improvement in PPBC: $\geq$ 2 points improvement from baseline
- Deterioration of PPBC: $\geq$ 1 point deterioration from baseline
- Responders in symptom bother and health related QoL scores as assessed by the OAB-q: $\geq$ 10 points improvement in OAB-q from baseline

Safety variables included frequency and severity of all adverse events (AEs), vital signs (sitting systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate), physical examination, laboratory tests (hematology, biochemistry, urinalysis), electrocardiogram (ECG) and post void residual (PVR) volume assessment.

Statistical Methods: Nine population sets were used for analyses in this study.

The Run-In Period Analysis Set consisted of all patients who took at least 1 dose of single-blind run-in study drug and was used to summarize the disposition of patients who entered the run-in period.

The Randomized Analysis Set consisted of all randomized patients and was used to summarize the disposition of patients who were randomized to double-blind treatment.

The FAS comprised all patients who met both of the following criteria: 1) took at least 1 dose of double-blind study medication after randomization and 2) had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 post-baseline visit. This population was used for summaries of demographic and baseline OAB characteristics and all efficacy analyses except for analyses on incontinence episodes or urgency incontinence episodes. A patient in the FAS must have had a baseline value > 0 for nocturia episodes, number of pads used and urgency episodes (severity of 3 or 4) to have been included in the efficacy analyses for those variables.

The population FAS-Incontinence comprised all patients who met the following criteria: 1) patients in the FAS and 2) reported at least 1 incontinence episode in the baseline diary. The FAS-Incontinence was utilized for summaries of demographic and baseline OAB characteristics of incontinent patients and efficacy analyses on incontinence and urgency incontinence episodes. Efficacy analyses on urgency incontinence episodes were performed on the subset of patients in the FAS-Incontinence set that had at least 1 urgency (grade 3 or 4) incontinence episode in the baseline diary.

The Per Protocol Set (PPS) included all patients who met both of the following criteria: 1) patients in the FAS and 2) completed the study without major violations of the protocol. The PPS was used for sensitivity analyses of the primary and key secondary efficacy variables and was regarded as secondary to the FAS.

The population PPS-Incontinence included all patients who met both of the following criteria: 1) patients in the FAS-Incontinence and 2) completed the study without major violations of the protocol. The PPS-Incontinence was used for sensitivity analysis of the key secondary variable of change from baseline in number of incontinence episodes per 24 h. In addition, demographic and baseline OAB characteristics were summarized using the PPS and PPS-Incontinence populations.

The Safety Analysis Set (SAF) consisted of all patients who received at least 1 dose of double-blind study medication and was used for summaries of the demographic and background characteristics and the safety data.

There were 2 analysis populations defined for pharmacokinetic parameters. The Pharmacokinetic Analysis Set (PKAS) consisted of all patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded.

The Full Profile PKAS subpopulation consisted of all patients in the PKAS who participated in the pharmacokinetic substudy, for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded. Both the PKAS and Full Profile PKAS were used for tabular and graphical summaries of the pharmacokinetic data.

Assuming a dropout rate of 20% during the screening period and a dropout rate of 10% after randomization, approximately 1658 patients had to be enrolled into the study to have 1326 patients randomized and 1190 evaluable patients, divided over 12 treatment arms.

Change from baseline to end of treatment in mean volume voided was analyzed using an analysis of covariance (ANCOVA) that included the 2 main factors mirabegron dose (0, 25 and 50 mg) and solifenacin succinate dose (0, 2.5, 5 and 10 mg) and their interaction, sex, age group and geographic region as fixed factors and the patient's mean volume voided per micturition at baseline as a covariate. The ANCOVA presented least squares (LS) mean estimates and 2-sided 95% CIs for mean changes from baseline within each treatment combination group. Differences of LS means between active treatment groups and placebo, as well as between combination treatment groups and solifenacin succinate 5 mg are presented together with 95% CIs and P values. The primary efficacy variable was analyzed using the FAS for subgroups including the following: use of previous OAB medication and incontinence at baseline. Subgroup analyses were performed using the same ANCOVA model as for the primary efficacy variable. Only patients from a particular subgroup level were included in each model to calculate LS means for each subgroup level within each treatment arm with 95% CIs. Adjustment for multiple testing was not performed.

The number of incontinence episodes during the micturition diary period at end of treatment was analyzed using a mixed effects Poisson regression model with the treatment groups, sex, age group, geographic region as factors and number at baseline as covariate. Rate ratios of the combination treatment groups vs solifenacin 5 mg as well as rate ratios of the active treatment groups vs placebo are presented together with 95% CIs and P values. The changes from baseline in the number of incontinence episodes and urgency incontinence episodes were also analyzed using a prespecified stratified rank ANCOVA model and the number of incontinence and urgency incontinence episodes during the 3-day diary period at end of treatment were analyzed using a prespecified Poisson regression model. Although the use of Poisson regression to analyze incontinence data was prespecified in the Statistical Analysis Plan (SAP), this document presents a mixed effects Poisson regression model which was not prespecified in the SAP and which is a generalization of the prespecified model.

All the additional secondary variables were analyzed using the same ANCOVA model used for the analysis of the primary efficacy variable.

All statistical comparisons were made using 2-sided tests at the 0.05 significance level unless specifically stated otherwise. Adjustment for multiple testing was not performed. All data processing, summarization, and analyses were performed using SAS® Version 9.1.3 in a UNIX environment.

Summary of Results/Conclusions:

Data is presented for individual treatment arms (placebo, monotherapy or combination), for pooled arms (mirabegron monotherapy, solifenacin monotherapy or all combination groups) and for the overall total (placebo plus monotherapy plus combination groups). The treatment groups are referred to in the text (and tables) as the following:

- placebo
- monotherapy treatment groups:
  - mirabegron 25 mg (M 25 mg)
  - mirabegron 50 mg (M 50 mg)

- solifenacin 2.5 mg (S 2.5 mg)
- solifenacin 5 mg (S 5 mg)
- solifenacin 10 mg (S 10 mg)

- combination treatment groups:
  - 2.5 + 25 combination (S 2.5 mg + M 25 mg)
  - 2.5 + 50 combination (S 2.5 mg + M 50 mg)
  - 5 + 25 combination (S 5 mg + M 25 mg)
  - 5 + 50 combination (S 5 mg + M 50 mg)
  - 10 + 25 combination (S 10 mg + M 25 mg)
  - 10 + 50 combination (S 10 mg + M 50 mg)
- pooled treatment groups:
  - mirabegron monotherapy groups (M total)
  - solifenacin monotherapy groups (S total)
  - all combination groups (C total)
- overall (grand total; i.e., placebo plus monotherapy groups plus combination treatment groups)

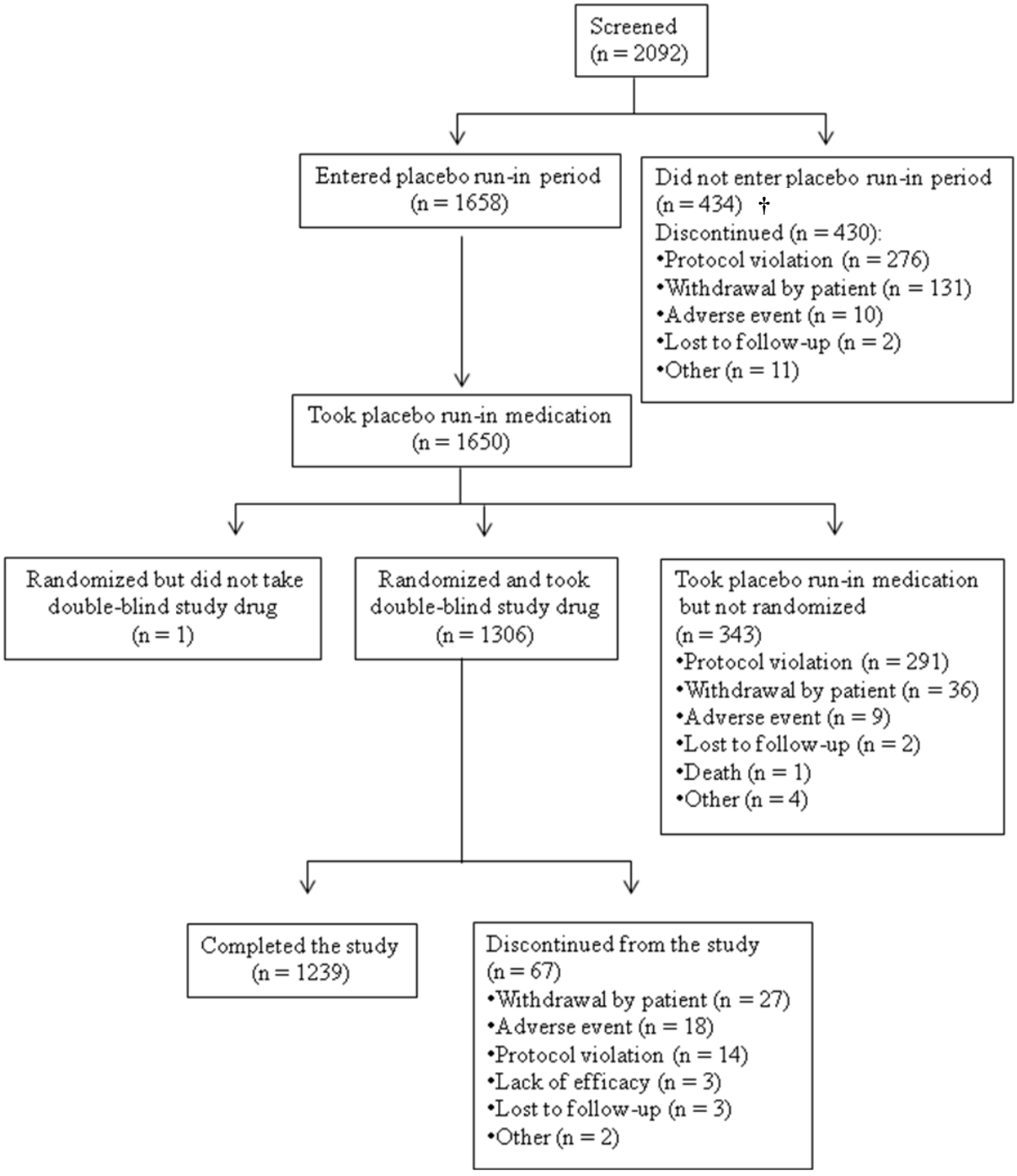
Population

A total of 2092 patients were screened, 1658 patients entered the placebo run-in period, 1650 patients took placebo run-in medication and 1306 patients were randomized into the study and received double-blind study drug [Figure 1, Table 1]. One patient (Patient No. [redacted]) was randomized to the mirabegron 50 mg treatment arm, but did not receive study drug. Of these 1306 patients, 1278 patients were included in the FAS.

Across all treatment arms, > 90% of patients completed the study [Table 2]. In each treatment group, the 3 most frequently cited primary reasons for discontinuation were withdrawal of consent, AE and protocol violation. The proportion of patients who permanently discontinued study drug due to an AE (primary reason) was approximately 1% to 2% for most groups. A higher proportion of patients discontinued due to an AE in the mirabegron 50 mg (2/78 [2.6%]), solifenacin 10 mg (2/78 [2.6%]), 5 + 25 combination (4/144 [2.8%]) and 10 + 50 combination (3/81 [3.7%]) groups. No patients in the placebo or solifenacin 2.5 mg groups discontinued the study due to an AE.

In general, all treatment arms were similar with respect to demographics and baseline characteristics and similar between the SAF and FAS [Table 3 and Table 4].

Figure 1 Patient Disposition



Source: Tables 12.1.1.1, 12.1.1.3.1, 12.1.1.3.2 and 12.1.1.3.4

† The primary reason for discontinuation was inadvertently not populated in the analysis datasets for 4 rescreened subjects which are thus not included below in the counts by reason. These are subjects [redacted] (all withdrawal by subject) and [redacted] (other, sponsor did not approve full rescreening of subject due to insufficient time prior to close of study randomization.

Table 1 Analysis Sets by Treatment Group

Population, n (%)	Placebo	M 25 mg	M 50 mg	S 2.5 mg	S 5 mg	S 10 mg	S 2.5 mg + M 25 mg	S 2.5 mg + M 50 mg	S 5 mg + M 25 mg	S 5 mg + M 50 mg	S 10 mg + M 25 mg	S 10 mg + M 50 mg	M Total	S Total	C Total	Grand Total
RAS†	81 (100)	78 (100)	79 (100)	79 (100)	156 (100)	78 (100)	149 (100)	149 (100)	144 (100)	152 (100)	81 (100)	81 (100)	157 (100)	313 (100)	756 (100)	1307 (100)
FAS‡	80 (98.8)	76 (97.4)	77 (97.5)	77 (97.5)	150 (96.2)	76 (97.4)	146 (98.0)	147 (98.7)	141 (97.9)	150 (98.7)	78 (96.3)	80 (98.8)	153 (97.5)	303 (96.8)	742 (98.1)	1278 (97.8)
FAS-Incontinence§	17 (21.0)	13 (16.7)	18 (22.8)	15 (19.0)	35 (22.4)	15 (19.2)	35 (23.5)	33 (22.1)	32 (22.2)	24 (15.8)	24 (29.6)	20 (24.7)	31 (19.7)	65 (20.8)	168 (22.2)	281 (21.5)
PPS¶	72 (88.9)	64 (82.1)	67 (84.8)	67 (84.8)	131 (84.0)	68 (87.2)	128 (85.9)	132 (88.6)	128 (88.9)	125 (82.2)	69 (85.2)	70 (86.4)	131 (83.4)	266 (85.0)	652 (86.2)	1121 (85.8)
PPS-Incontinence††	16 (19.8)	9 (11.5)	17 (21.5)	12 (15.2)	30 (19.2)	13 (16.7)	32 (21.5)	29 (19.5)	29 (20.1)	18 (11.8)	20 (24.7)	18 (22.2)	26 (16.6)	55 (17.6)	146 (19.3)	243 (18.6)
SAF‡‡	81 (100)	78 (100)	78 (98.7)	79 (100)	156 (100)	78 (100)	149 (100)	149 (100)	144 (100)	152 (100)	81 (100)	81 (100)	156 (99.4)	313 (100)	756 (100)	1306 (99.9)

The percentages are based on the number of patients randomized to double-blind treatment in each arm of the study and overall for monotherapy, combination therapy and total.

C: combination (solifenacin + mirabegron); FAS: Full Analysis Set; M: mirabegron; PPS: Per Protocol Set; RAS: Randomized Analysis Set; S: solifenacin; SAF: Safety Analysis Set

† RAS: all patients randomized to a double-blind treatment

‡ FAS: all patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit.

§ FAS-Incontinence: all FAS patients who had at least 1 baseline incontinence episode

¶ PPS: all FAS patients without a major protocol deviation

†† PPS-Incontinence: all FAS-Incontinence patients without a major protocol deviation

‡‡ SAF: all patients randomized to a double-blind treatment who took at least 1 dose of study drug

Source: Table 12.1.1.2.1

Table 2 Patients with Study Discontinuation by Treatment Group (SAF)

Parameter Category, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Discontinuation																
Yes	5 (6.2)	7 (9.1)	3 (3.8)	4 (5.1)	10 (6.4)	4 (5.1)	7 (4.7)	7 (4.7)	8 (5.6)	6 (3.9)	2 (2.5)	4 (4.9)	10 (6.5)	18 (5.8)	34 (4.5)	67 (5.1)
No	76 (93.8)	70 (90.9)	75 (96.2)	75 (94.9)	146 (93.6)	74 (94.9)	142 (95.3)	142 (95.3)	136 (94.4)	147 (96.1)	79 (97.5)	77 (95.1)	145 (93.5)	295 (94.2)	723 (95.5)	1239 (94.9)
Primary reason for discontinuation†																
Adverse event	0	1 (1.3)	2 (2.6)	0	1 (0.6)	2 (2.6)	2 (1.3)	1 (0.7)	4 (2.8)	1 (0.7)	1 (1.2)	3 (3.7)	3 (1.9)	3 (1.0)	12 (1.6)	18 (1.4)
Lack of efficacy	0	0	0	0	0	0	1 (0.7)	1 (0.7)	1 (0.7)	0	0	0	0	0	3 (0.4)	3 (0.2)
Lost to follow-up	0	1 (1.3)	0	0	0	0	1 (0.7)	0	0	1 (0.7)	0	0	1 (0.6)	0	2 (0.3)	3 (0.2)
Protocol violation‡	1 (1.2)	2 (2.6)	0	0	6 (3.8)	0	0	1 (0.7)	2 (1.4)	2 (1.3)	0	0	2 (1.3)	6 (1.9)	5 (0.7)	14 (1.1)
Withdrawal by patient	4 (4.9)	3 (3.9)	1 (1.3)	3 (3.8)	3 (1.9)	2 (2.6)	3 (2.0)	4 (2.7)	1 (0.7)	2 (1.3)	0	1 (1.2)	4 (2.6)	8 (2.6)	11 (1.5)	27 (2.1)
Other	0	0	0	1 (1.3)	0	0	0	0	0	0	1 (1.2)	0	0	1 (0.3)	1 (0.1)	2 (0.2)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF)

C: combination (solifenacin + mirabegron); M: mirabegron; S: solifenacin; SAF: Safety Analysis Set

† The reason recorded in the end of treatment form was used.

‡ Recorded if the patient did not meet eligibility criteria or if the patient did not comply with protocol procedures

Source: Table 12.1.1.3.4

Table 3 Demographic Characteristics (SAF and FAS)

Population Parameter Category/Statistic	Placebo	M 25 mg	M 50 mg	S 2.5 mg	S 5 mg	S 10 mg	S 2.5 mg + M 25 mg	S 2.5 mg + M 50 mg	S 5 mg + M 25 mg	S 5 mg + M 50 mg	S 10 mg + M 25 mg	S 10 mg + M 50 mg	M Total	S Total	C Total	Grand Total
SAF	**(n=81)**	**(n=77)**	**(n=78)**	**(n=79)**	**(n=156)**	**(n=78)**	**(n=149)**	**(n=149)**	**(n=144)**	**(n=153)**	**(n=81)**	**(n=81)**	**(n=155)**	**(n=313)**	**(n=757)**	**(n=1306)**
Gender, n (%)																
Female	54 (66.7)	52 (67.5)	52 (66.7)	51 (64.6)	103 (66.0)	53 (67.9)	100 (67.1)	100 (67.1)	95 (66.0)	101 (66.0)	52 (64.2)	54 (66.7)	104 (67.1)	207 (66.1)	502 (66.3)	867 (66.4)
Male	27 (33.3)	25 (32.5)	26 (33.3)	28 (35.4)	53 (34.0)	25 (32.1)	49 (32.9)	49 (32.9)	49 (34.0)	52 (34.0)	29 (35.8)	27 (33.3)	51 (32.9)	106 (33.9)	255 (33.7)	439 (33.6)
Age (years)																
Mean	54.6	55.2	53.4	56.1	54.2	55.0	55.8	53.7	55.0	54.1	56.5	55.5	54.3	54.9	54.9	54.8
Median	57.0	58.0	56.5	57.0	59.0	56.0	58.0	55.0	58.0	57.0	57.0	59.0	57.0	57.0	57.0	57.0
≥ 65 years, n (%)	22 (27.2)	21 (27.3)	20 (25.6)	21 (26.6)	43 (27.6)	21 (26.9)	39 (26.2)	43 (28.9)	39 (27.1)	41 (26.8)	24 (29.6)	23 (28.4)	41 (26.5)	85 (27.2)	209 (27.6)	357 (27.3)
≥ 75 years, n (%)	3 (3.7)	7 (9.1)	2 (2.6)	2 (2.5)	6 (3.8)	1 (1.3)	9 (6.0)	11 (7.4)	9 (6.3)	5 (3.3)	1 (1.2)	2 (2.5)	9 (5.8)	9 (2.9)	37 (4.9)	58 (4.4)
FAS	**(n=80)**	**(n=76)**	**(n=77)**	**(n=77)**	**(n=150)**	**(n=76)**	**(n=146)**	**(n=147)**	**(n=141)**	**(n=150)**	**(n=78)**	**(n=80)**	**(n=153)**	**(n=303)**	**(n=742)**	**(n=1278)**
Gender, n (%)																
Female	53 (66.3)	50 (65.8)	51 (66.2)	51 (66.2)	100 (66.7)	52 (68.4)	100 (68.5)	98 (66.7)	92 (65.2)	100 (66.7)	51 (65.4)	53 (66.3)	101 (66.0)	203 (67.0)	494 (66.6)	851 (66.6)
Male	27 (33.8)	26 (34.2)	26 (33.8)	26 (33.8)	50 (33.3)	24 (31.6)	46 (31.5)	49 (33.3)	49 (34.8)	50 (33.3)	27 (34.6)	27 (33.8)	52 (34.0)	100 (33.0)	248 (33.4)	427 (33.4)
Age (years)																
Mean	54.7	55.0	53.6	56.3	54.1	55.0	56.0	53.8	55.2	54.0	56.6	55.3	54.3	54.9	55.0	54.9
Median	57.0	58.0	57.0	57.0	59.0	56.0	58.0	55.0	58.0	57.5	57.0	59.0	57.0	57.0	57.5	57.0
≥ 65 years, n (%)	22 (27.5)	20 (26.3)	20 (26.0)	21 (27.3)	41 (27.3)	20 (26.3)	39 (26.7)	43 (29.3)	39 (27.7)	41 (27.3)	24 (30.8)	22 (27.5)	40 (26.1)	82 (27.1)	208 (28.0)	352 (27.5)
≥ 75 years, n (%)	3 (3.8)	7 (9.2)	2 (2.6)	2 (2.6)	6 (4.0)	1 (1.3)	9 (6.2)	11 (7.5)	9 (6.4)	5 (3.3)	1 (1.3)	2 (2.5)	9 (5.9)	9 (3.0)	37 (5.0)	58 (4.5)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF) and all patients in the SAF who had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS)

C: combination (solifenacin + mirabegron); FAS: Full Analysis Set; M: mirabegron; S: solifenacin

Source: Tables 12.1.2.1.1 and 12.1.2.1.2

Table 4 OAB-Related Baseline Characteristics (FAS)

Parameter Category/Statistic	Placebo (n=80)	M 25 mg (n=76)	M 50 mg (n=77)	S 2.5 mg (n=77)	S 5 mg (n=150)	S 10 mg (n=76)	S 2.5 mg + M 25 mg (n=146)	S 2.5 mg + M 50 mg (n=147)	S 5 mg + M 25 mg (n=141)	S 5 mg + M 50 mg (n=150)	S 10 mg + M 25 mg (n=78)	S 10 mg + M 50 mg (n=80)	M Total (n=153)	S Total (n=303)	C Total (n=742)	Grand Total (n=1278)
Type of OAB, n (%)																
n	78	75	76	76	149	76	145	146	141	150	78	79	151	301	739	1269
Urgency incontinence†	14 (17.9)	27 (36.0)	18 (23.7)	17 (22.4)	38 (25.5)	19 (25.0)	40 (27.6)	33 (22.6)	35 (24.8)	35 (23.3)	22 (28.2)	20 (25.3)	45 (29.8)	74 (24.6)	185 (25.0)	318 (25.1)
Mixed stress/urgency incontinence‡	9 (11.5)	8 (10.7)	10 (13.2)	10 (13.2)	25 (16.8)	11 (14.5)	21 (14.5)	19 (13.0)	18 (12.8)	18 (12.0)	13 (16.7)	10 (12.7)	18 (11.9)	46 (15.3)	99 (13.4)	172 (13.6)
Frequency/urgency without incontinence	55 (70.5)	40 (53.3)	48 (63.2)	49 (64.5)	86 (57.7)	46 (60.5)	84 (57.9)	94 (64.4)	88 (62.4)	97 (64.7)	43 (55.1)	49 (62.0)	88 (58.3)	181 (60.1)	455 (61.6)	779 (61.4)
Duration of OAB symptoms (months)																
Mean	48.5	60.6	57.3	55.1	62.9	53.5	56.7	57.0	55.8	57.8	65.8	58.0	59.0	58.5	57.9	57.6
Median	40.5	44.0	28.0	34.0	37.0	37.0	34.5	32.0	41.0	31.5	40.5	23.5	39.0	36.0	33.5	36.0
Previous medication for OAB, n (%)																
Yes	40 (50.0)	42 (55.3)	38 (49.4)	29 (37.7)	70 (46.7)	29 (38.2)	73 (50.0)	65 (44.2)	64 (45.4)	71 (47.3)	42 (53.8)	40 (50.0)	80 (52.3)	128 (42.2)	355 (47.8)	603 (47.2)

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug (Safety Analysis Set) and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS)

C: combination (solifenacin + mirabegron); FAS: Full Analysis Set; M: mirabegron; OAB: overactive bladder; S: solifenacin

†Urgency incontinence only

‡ Mixed stress/urgency incontinence with urgency as predominant factor

Source: Table 12.1.2.2.2

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Primary Efficacy Variable: Change from Baseline to EOT in Mean Volume Voided per Micturition

At baseline, the mean volume voided per micturition ranged from 140.1 mL in the 10 + 25 combination to 159.0 mL in the solifenacin 2.5 mg treatment group [Table 5]. For solifenacin monotherapy, significant differences in mean volume voided vs placebo were found without an apparent dose-response relationship. For mirabegron monotherapy, a dose-response relationship was observed for mean volume voided. Increasing doses of solifenacin in the combination groups resulted in increased treatment effects. Overall, across all combination groups, a clear dose-response was observed with an increasing treatment effect on mean volume voided with increasing doses of solifenacin and mirabegron in combination [Table 5].

In all active treatment groups, except mirabegron 25 mg, the mean increase in mean volume voided was statistically significantly greater than in the placebo group.

For all combinations with 5 or 10 mg solifenacin, the mean change from baseline in mean volume voided was statistically significantly greater than with solifenacin 5 mg monotherapy. The largest adjusted mean difference (SE) compared to solifenacin 5 mg was 26.3 (7.32) mL, observed with the 10 + 50 combination. The combinations with 2.5 mg solifenacin showed similar treatment effects as solifenacin 5 mg monotherapy.

Table 5 Change from Baseline to EOT in Mean Volume Voided per Micturition (FAS)

Parameter Mirabegron	**Statistic**	**Solifenacin Succinate**			
		0 mg	**2.5 mg**	**5 mg**	**10 mg**
Baseline and EOT					
0 mg	n	80	77	150	76
	Baseline Mean (SE)	157.1 (5.90)	159.0 (5.92)	145.5 (4.89)	148.8 (6.10)
	EOT Mean (SE)	171.5 (6.19)	195.9 (8.37)	180.8 (6.43)	184.9 (7.95)
25 mg	n	76	146	141	78
	Baseline Mean (SE)	153.4 (6.46)	158.1 (5.10)	153.5 (4.56)	140.1 (5.80)
	EOT Mean (SE)	178.1 (7.73)	198.1 (7.08)	207.2 (6.73)	196.9 (9.15)
50 mg	n	77	147	150	80
	Baseline Mean (SE)	154.9 (5.69)	149.7 (4.14)	153.5 (4.24)	156.0 (6.96)
	EOT Mean (SE)	189.6 (8.98)	191.5 (6.06)	207.6 (6.78)	218.5 (11.29)
Adjusted change from baseline (mL)					
0 mg	Mean (SE)	14.0 (5.91)	36.4 (6.02)	36.0 (4.32)	36.2 (6.06)
	95% CI	(2.4, 25.6)	(24.6, 48.2)	(27.5, 44.4)	(24.3, 48.1)
25 mg	Mean (SE)	24.9 (6.06)	39.4 (4.37)	53.6 (4.45)	57.6 (5.99)
	95% CI	(13.1, 36.8)	(30.8, 48.0)	(44.8, 62.3)	(45.9, 69.4)
50 mg	Mean (SE)	34.5 (6.02)	41.9 (4.36)	54.2 (4.31)	62.3 (5.90)
	95% CI	(22.7, 46.3)	(33.3, 50.4)	(45.7, 62.6)	(50.7, 73.8)

Table continued on next page

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	Solifenacin Succinate 2.5 mg	Solifenacin Succinate 5 mg	Solifenacin Succinate 10 mg
Adjusted difference† vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				0.3 (7.44)
	95% CI	---	---	---	(-14.3, 14.9)
	P value‡				0.97
25 mg	Mean (SE)		3.4 (6.15)	17.6 (6.20)	21.7 (7.37)
	95% CI	---	(-8.6, 15.5)	(5.4, 29.8)	(7.2, 36.1)
	P value‡		0.58	0.005*	0.003*
50 mg	Mean (SE)		5.9 (6.13)	18.2 (6.10)	26.3 (7.32)
	95% CI	---	(-6.1, 18.0)	(6.2, 30.2)	(11.9, 40.7)
	P value‡		0.33	0.003*	< 0.001*
Adjusted difference† vs placebo					
0 mg	Mean (SE)		22.4 (8.43)	22.0 (7.32)	22.2 (8.46)
	95% CI	---	(5.9, 39.0)	(7.6, 36.3)	(5.6, 38.8)
	P value‡		0.008*	0.003*	0.009*
25 mg	Mean (SE)	11.0 (8.46)	25.4 (7.35)	39.6 (7.39)	43.6 (8.42)
	95% CI	(-5.6, 27.6)	(11.0, 39.8)	(25.1, 54.1)	(27.1, 60.1)
	P value‡	0.20	< 0.001*	< 0.001*	< 0.001*
50 mg	Mean (SE)	20.5 (8.43)	27.9 (7.34)	40.2 (7.31)	48.3 (8.35)
	95% CI	(4.0, 37.1)	(13.5, 42.3)	(25.8, 54.5)	(31.9, 64.7)
	P value‡	0.015*	< 0.001*	< 0.001*	< 0.001*

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS)

---: not applicable; ANCOVA: analysis of covariance; EOT: end of treatment; FAS: Full Analysis Set

† Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin succinate 5 mg or placebo from the adjusted mean of the combination treatment group.

‡ P values were from pairwise comparison of the combination treatment groups vs solifenacin succinate 5 mg or placebo within the ANCOVA model.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.1.1

Key Secondary Efficacy Variable: Change from Baseline to End of Treatment in Mean Number of Micturitions per 24 h

At baseline, the mean number of micturitions per 24 h ranged from 10.41 in the placebo group to 11.40 in the solifenacin 5 mg group. Thus, despite randomization, the baseline severity of the placebo group was lower than in the other treatment groups. The adjusted mean change from baseline for placebo was -2.43 micturitions per 24 h.

For the monotherapy treatments, there were no statistically significant differences vs placebo. Adjusted differences vs placebo were lower than reported in previous phase 2 and 3 studies with mirabegron and solifenacin. For all the treatment combinations, a trend towards a decrease in the mean number of micturitions per 24 h from baseline to end of treatment was observed with increasing solifenacin and mirabegron dose. The

treatment combinations 5 + 50, 10 + 25 and 10 + 50 showed statistically significant decreases vs placebo and vs solifenacin 5 mg. The greatest decrease in adjusted mean change was observed with the 10 + 50 combination (-0.98) [Table 6].

Table 6 Change from Baseline to EOT in Mean Number of Micturitions per 24 h (FAS)

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Baseline and EOT					
0 mg	n	80	77	150	76
	Baseline Mean (SE)	10.41 (0.223)	11.08 (0.348)	11.40 (0.260)	11.31 (0.335)
	EOT Mean (SE)	8.14 (0.262)	8.65 (0.493)	8.80 (0.257)	8.03 (0.317)
25 mg	n	76	146	141	78
	Baseline Mean (SE)	11.32 (0.294)	11.24 (0.301)	10.94 (0.195)	11.07 (0.246)
	EOT Mean (SE)	8.80 (0.323)	8.63 (0.457)	8.42 (0.215)	7.67 (0.327)
50 mg	n	77	147	150	80
	Baseline Mean (SE)	10.79 (0.258)	11.00 (0.187)	11.31 (0.253)	11.18 (0.270)
	EOT Mean (SE)	8.30 (0.333)	8.10 (0.213)	7.93 (0.262)	7.64 (0.256)
Adjusted change from baseline					
0 mg	Mean (SE)	-2.43 (0.291)	-2.44 (0.296)	-2.54 (0.212)	-3.22 (0.298)
	95% CI	(-3.00, -1.86)	(-3.02, -1.86)	(-2.96, -2.12)	(-3.81, -2.64)
25 mg	Mean (SE)	-2.48 (0.298)	-2.58 (0.215)	-2.56 (0.219)	-3.42 (0.294)
	95% CI	(-3.07, -1.89)	(-3.00, -2.15)	(-2.99, -2.13)	(-3.99, -2.84)
50 mg	Mean (SE)	-2.56 (0.296)	-2.93 (0.215)	-3.34 (0.212)	-3.52 (0.291)
	95% CI	(-3.14, -1.98)	(-3.35, -2.51)	(-3.76, -2.93)	(-4.09, -2.95)
Adjusted difference† vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				-0.68 (0.366)
	95% CI	---	---	---	(-1.40, 0.03)
	P value‡				0.062
25 mg	Mean (SE)		-0.04 (0.302)	-0.02 (0.305)	-0.88 (0.363)
	95% CI	---	(-0.63, 0.56)	(-0.62, 0.58)	(-1.59, -0.16)
	P value‡		0.91	0.96	0.016*
50 mg	Mean (SE)		-0.39 (0.302)	-0.80 (0.300)	-0.98 (0.360)
	95% CI	---	(-0.98, 0.20)	(-1.39, -0.22)	(-1.68, -0.27)
	P value‡		0.20	0.007*	0.007*

Table continued on next page

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Adjusted difference† vs placebo					
0 mg	Mean (SE)		-0.01 (0.416)	-0.11 (0.361)	-0.79 (0.417)
	95% CI	---	(-0.82, 0.81)	(-0.82, 0.60)	(-1.61, 0.03)
	P value‡		0.99	0.77	0.058
25 mg	Mean (SE)	-0.05 (0.417)	-0.14 (0.362)	-0.12 (0.364)	-0.98 (0.414)
	95% CI	(-0.87, 0.77)	(-0.85, 0.57)	(-0.84, 0.59)	(-1.80, -0.17)
	P value‡	0.91	0.69	0.73	0.018*
50 mg	Mean (SE)	-0.13 (0.415)	-0.50 (0.362)	-0.91 (0.361)	-1.08 (0.412)
	95% CI	(-0.94, 0.69)	(-1.21, 0.21)	(-1.62, -0.20)	(-1.89, -0.28)
	P value‡	0.76	0.17	0.012*	0.009*

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS)

ANCOVA: analysis of covariance; EOT: end of treatment; FAS: Full Analysis Set

† Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin succinate 5 mg or placebo from the adjusted mean of the combination treatment group.

‡ P values were from pairwise comparison of the combination treatment groups vs solifenacin succinate 5 mg or placebo within the ANCOVA model.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.3.1.1

Key Secondary Efficacy Variable: Change from Baseline to End of Treatment in Mean Number of Incontinence Episodes per 24 h

There were only 281 (22% of the FAS population) patients with incontinence at baseline (therefore eligible for the FAS-Incontinence), having a low median of 1.0 in mean number of incontinence episodes per 24 h.

All treatment groups, including placebo, experienced a reduction in the number of incontinence episodes during the 3-day micturition diary period. It is probably that due to the low number of incontinent patients in this study, their low baseline values and the substantial differences across baseline values, there is too much random variation in the data to discern a clear dose-response pattern. In the prespecified Poisson regression model, the 5 + 50 mg group did not show a statistically significant reduction in the rate of incontinence episodes vs placebo. The prespecified nonparametric stratified rank ANCOVA model is a less efficient method for the analysis of count data and demonstrated a statistically significant reduction of mean number of incontinence episodes only for the 5 + 25 mg group vs solifenacin 5 mg. The posthoc mixed effect Poisson regression model demonstrated a statistically significant reduction in the rate of incontinence episodes vs both solifenacin 5 mg and placebo for the 5 + 25 and 5 + 50 combination groups [Table 7].

Table 7 Mixed Effect Poisson Regression Model of Number of Incontinence Episodes During the 3-day Micturition Diary Period (FAS-Incontinence)

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	Solifenacin Succinate 2.5 mg	Solifenacin Succinate 5 mg	Solifenacin Succinate 10 mg
Baseline and EOT					
0 mg	n	17	15	35	15
	Baseline Mean (SE)	3.1 (0.65)	4.9 (0.89)	4.0 (0.63)	4.2 (0.99)
	EOT Mean (SE)	0.7 (0.49)	0.8 (0.47)	1.3 (0.43)	0.9 (0.41)
25 mg	n	13	35	32	24
	Baseline Mean (SE)	5.6 (1.31)	3.8 (0.56)	3.7 (0.59)	4.4 (0.62)
	EOT Mean (SE)	2.5 (0.81)	1.6 (0.38)	0.3 (0.18)	1.3 (1.00)
50 mg	n	18	33	24	20
	Baseline Mean (SE)	3.8 (0.71)	3.4 (0.41)	3.5 (0.73)	3.8 (0.58)
	EOT Mean (SE)	1.1 (0.49)	1.2 (0.33)	0.5 (0.32)	0.8 (0.34)
Change from baseline					
0 mg	Mean (SE)	-2.4 (0.71)	-4.1 (0.91)	-2.7 (0.52)	-3.3 (0.97)
25 mg	Mean (SE)	-3.2 (1.28)	-2.2 (0.50)	-3.4 (0.48)	-3.0 (0.89)
50 mg	Mean (SE)	-2.7 (0.55)	-2.2 (0.35)	-3.0 (0.55)	-3.0 (0.51)
Rate ratio† vs solifenacin succinate 5 mg					
0 mg	Rate ratio				1.12
	95% CI	---	---	---	(0.34, 3.66)
	P value‡				0.86
25 mg	Rate ratio		1.45	0.12	0.42
	95% CI	---	(0.60, 3.53)	(0.03, 0.43)	(0.14, 1.28)
	P value‡		0.41	0.001*	0.13
50 mg	Rate ratio		0.86	0.14	0.66
	95% CI	---	(0.35, 2.12)	(0.04, 0.53)	(0.21, 2.05)
	P value‡		0.74	0.003*	0.47
Rate ratio† vs placebo					
0 mg	Rate ratio		0.65	1.51	1.69
	95% CI	---	(0.16, 2.64)	(0.47, 4.89)	(0.42, 6.74)
	P value‡		0.55	0.49	0.46
25 mg	Rate ratio	1.46	2.20	0.18	0.64
	95% CI	(0.37, 5.71)	(0.71, 6.84)	(0.04, 0.78)	(0.17, 2.38)
	P value‡	0.58	0.17	0.022*	0.51
50 mg	Rate ratio	1.19	1.30	0.22	1.00
	95% CI	(0.33, 4.38)	(0.41, 4.12)	(0.05, 0.94)	(0.27, 3.78)
	P value‡	0.79	0.66	0.041*	1.0

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS) and who had at least 1 baseline incontinence episode (FAS-Incontinence)

Descriptive summaries refer to the total number of incontinence episodes during the micturition diary period prior to each visit.

Footnotes continued on next page

---: not applicable; EOT: end of treatment; FAS: Full Analysis Set

† P values were from the mixed effect Poisson regression model that included treatment groups, sex, age group, geographic region as factors and baseline as a covariate. Statistical significance was determined at the 0.05 level.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.3.2.8

Additional Secondary Efficacy Variables

Change from Baseline in Mean Volume Voided Over Time

A dose-dependent increase over time was observed in the mean volume voided for the mirabegron monotherapy groups; this dose-dependency was not evident with the solifenacin monotherapy. However, across all dose groups, after an initial increase, the values plateaued between 4 and 8 weeks of active treatment. In addition, the insignificant P value in the repeated measures model provided evidence that there was no time-by-treatment interaction. The pattern observed was consistent between the repeated measures ANOVA model and the ANCOVA model at each time point.

A statistically significant difference in the increase from baseline compared with placebo was noted in most active treatment groups beginning at week 2. The 5 + 50 combination and 10 + 50 combination groups showed a statistically significant difference vs solifenacin 5 mg monotherapy beginning at week 2; the 5 + 25 combination and 10 + 25 combination groups showed a statistically significant difference vs solifenacin 5 mg monotherapy beginning at week 4.

Change from Baseline in Mean Number of Micturitions per 24 h Over Time

Mirabegron monotherapy did not show a dose-dependent decrease over time in the mean number of micturitions per 24 h. For solifenacin monotherapy, higher dose levels of solifenacin monotherapy showed greater decreases in the mean number of micturitions per 24 h beginning at 8 weeks of treatment. Similarly, the treatment combinations showed a trend towards a decrease in the mean number of micturitions per 24 h with increasing solifenacin and mirabegron dose beginning at 8 weeks. The change from baseline in the all treatment groups was generally maximal by week 8. Across all the treatment groups, after the initial decrease, the values plateaued; the insignificant P value in the repeated measures model also provided evidence that there was no time-by-treatment interaction. The pattern observed was consistent between the repeated measures ANOVA model and the ANCOVA model at each time point.

A statistically significant difference for reduction in micturition frequency per 24 h was observed beginning at week 4 for the 5 + 50 combination, 10 + 25 combination and 10 + 50 combination groups vs solifenacin 5 mg and vs placebo.

Additional Secondary Efficacy Variables for Incontinence

No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or with the combination therapies over time in the mean number of incontinence episodes per 24 h or the number of urgency incontinence episodes over time. Few statistically significant differences for active treatment vs placebo or for combination treatment vs solifenacin 5 mg were noted.

Change from Baseline in Mean Number of Episodes with Urgency Grade 3 or 4 per 24 h (PPIUS)

At baseline, the mean number of urgency episodes (grades 3 or 4) per 24 h was comparable across the active

treatment groups and slightly lower in the placebo group. All treatment groups, including placebo, showed a decrease in mean number of episodes with urgency grade 3 or 4 per 24 h (based on the mean PPIUS). None of the active treatment arms showed statistically significant differences vs placebo. Beginning at week 2 through the end of treatment, all combination groups except the 2.5 + 25 and 10 + 50 combination groups showed a statistically significant difference in the reduction from baseline in mean number of urgency episodes (grade 3 or 4) vs solifenacin 5 mg. Due to the absence of significance of solifenacin monotherapy vs placebo and the fact that the change from baseline in the solifenacin group was less than in the placebo group, the result of comparisons between the combination groups and solifenacin monotherapy should be interpreted with caution [Table 8].

Table 8 Change from Baseline to EOT in Mean Number of Episodes with Urgency Grade 3 or 4 per 24 h (FAS)

Parameter Mirabegron	**Statistic**	**Solifenacin Succinate**			
		0 mg	**2.5 mg**	**5 mg**	**10 mg**
Baseline and EOT					
0 mg	n	80	77	150	76
	Baseline Mean (SE)	5.26 (0.346)	6.29 (0.442)	6.41 (0.344)	6.40 (0.522)
	EOT Mean (SE)	2.33 (0.339)	2.72 (0.379)	3.68 (0.332)	2.41 (0.409)
25 mg	n	76	146	141	78
	Baseline Mean (SE)	6.26 (0.381)	6.07 (0.310)	6.21 (0.330)	6.91 (0.490)
	EOT Mean (SE)	3.11 (0.375)	3.03 (0.296)	2.44 (0.246)	2.92 (0.506)
50 mg	n	77	147	150	80
	Baseline Mean (SE)	6.58 (0.457)	6.78 (0.283)	6.54 (0.346)	6.86 (0.482)
	EOT Mean (SE)	3.03 (0.411)	2.60 (0.259)	2.38 (0.266)	2.69 (0.354)
Adjusted change from baseline					
0 mg	Mean (SE)	-3.53 (0.328)	-3.62 (0.334)	-2.73 (0.239)	-3.98 (0.336)
	95% CI	(-4.17, -2.88)	(-4.27, -2.96)	(-3.20, -2.26)	(-4.64, -3.33)
25 mg	Mean (SE)	-3.23 (0.336)	-3.21 (0.242)	-3.86 (0.247)	-3.71 (0.332)
	95% CI	(-3.89, -2.57)	-3.68, -2.73	(-4.34, -3.38)	(-4.36, -3.06)
50 mg	Mean (SE)	-3.44 (0.334)	-3.97 (0.242)	-4.10 (0.239)	-3.91 (0.327)
	95% CI	(-4.09, -2.78)	(-4.44, -3.49)	(-4.57, -3.63)	(-4.56, -3.27)
Adjusted difference† vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				-1.26 (0.412)
	95% CI	---	---	---	(-2.06, -0.45)
	P value‡				0.002*
25 mg	Mean (SE)		-0.48 (0.340)	-1.13 (0.343)	-0.98 (0.409)
	95% CI	---	(-1.15, 0.19)	(-1.80, -0.46)	(-1.78, -0.18)
	P value‡		0.16	0.001*	0.017*
50 mg	Mean (SE)		-1.24 (0.340)	-1.37 (0.338)	-1.18 (0.405)
	95% CI	---	(-1.91, -0.57)	(-2.03, -0.70)	(-1.98, -0.39)
	P value‡		< 0.001*	< 0.001*	0.004*

Table continued on next page

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Adjusted difference† vs placebo					
0 mg	Mean (SE)	---	-0.09 (0.468)	0.80 (0.406)	-0.46 (0.469)
	95% CI		(-1.01, 0.83)	(-0.00, 1.59)	(-1.38, 0.46)
	P value‡		0.84	0.050	0.33
25 mg	Mean (SE)	0.29 (0.469)	0.32 (0.407)	-0.33 (0.410)	-0.18 (0.467)
	95% CI	(-0.63, 1.22)	(-0.48, 1.12)	(-1.14, 0.47)	(-1.10, 0.73)
	P value‡	0.53	0.44	0.42	0.70
50 mg	Mean (SE)	0.09 (0.468)	-0.44 (0.408)	-0.57 (0.406)	-0.39 (0.464)
	95% CI	(-0.83, 1.01)	(-1.24, 0.36)	(-1.37, 0.23)	(-1.30, 0.52)
	P value‡	0.85	0.28	0.16	0.40

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline (FAS)

Adjusted change from baseline values were generated from the ANCOVA model with 2 main factors mirabegron dose (0, 25 and 50 mg) and solifenacin succinate dose (0, 2.5, 5 and 10 mg) and their corresponding dose combination interaction term to reflect the factorial design. The model further included the main factors gender, age group, geographic region and baseline measurement as covariate.

---: not applicable; ANCOVA: analysis of covariance; EOT: end of treatment; FAS: Full Analysis Set

† Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin succinate 5 mg or placebo from the adjusted mean of the combination treatment group.

‡ P values were from pairwise comparison of the combination treatment groups vs solifenacin succinate 5 mg or placebo within the ANCOVA model.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.5.9

Change from Baseline in Mean Number of Pads Used per 24 h Over Time

Only patients who used at least 1 pad at baseline were included in the analysis of the mean number of pads used per 24 h; this was the case for between 32% and 59% of the patients in the different treatment groups in the FAS. The mean number of pads used per 24 hours was comparable across all treatment groups at baseline and ranged from a mean of 2.06 pads in the 2.5 + 50 combination group to 2.65 pads in the 10 + 50 combination group. In all treatment groups, including placebo, there was a reduction in the mean number of pads used per 24 h from baseline to end of treatment. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or with the combination therapies over time. The active treatment groups showed a trend towards a decrease in the mean number of pads used per 24 h compared with placebo beginning at week 4. Statistically significant reductions in the mean number of pads used per 24 h were noted in most combination groups compared with placebo at the end of treatment. No statistically significant differences were noted with the combination groups vs solifenacin 5 mg monotherapy.

Change from Baseline in Number of Nocturia Episodes Over Time

At baseline, there was some imbalance among the treatment groups in the mean number of nocturia episodes per 24 h (e.g., 2.15 for the 2.5 + 50 combination group vs 2.80 for the 10 + 25 combination group). In all treatment groups, there was a reduction in the mean number of nocturia episodes per 24 h from baseline to the end of treatment. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or

with the combination therapies over time. The active treatment groups showed a trend towards a decrease in the mean number nocturia episodes per 24 h compared with placebo beginning at week 8, but few statistically significant reductions were noted over time compared with placebo or with solifenacin 5 mg monotherapy using the ANCOVA model.

A Poisson regression analysis was also performed for this variable. Using this model, P values calculated for the rate ratios showed statistically significant differences vs placebo for the 5 + 50 combination and 10 + 25 combination groups at the end of treatment. All treatment groups except the 2.5 + 50 combination and 5 + 25 combination groups showed statistically significant differences vs solifenacin 5 mg in the number of nocturia episodes during the 3-day micturition diary period. However, this result needs to be interpreted with caution, as few statistically significant differences vs placebo were observed.

Responder Analyses

Zero Incontinence Episodes

The definition of a responder was a patient in the FAS-Incontinence with zero incontinence episodes postbaseline. Mirabegron monotherapy showed a numerical trend with increases in the percentage of patients meeting the responder criterion that correlated with increased doses of mirabegron beginning at week 2. No dose-dependent effect was observed with solifenacin monotherapy. A numerical trend was noted in the treatment combinations beginning at week 8, with the higher dose combination groups showing a higher percentage of responders compared with the lower dose combination groups.

In this study, the percentage of responders at the end of treatment in the placebo group was high (82.4%); consequently, no statistically significant differences were noted vs this group. At the end of treatment, both the 5 + 25 combination and 5 + 50 combination groups showed a statistically significant difference vs solifenacin 5 mg.

Reduction in Incontinence Episodes

The criterion for a responder for reduction in incontinence episodes required that a patient in the FAS-Incontinence had a ≥ 50% decrease from baseline in the mean number of incontinence episodes per 24 h. Mirabegron monotherapy showed a numerical trend with increases in the percentage of patients meeting the responder criterion that correlated with increased doses of mirabegron beginning at week 2. No dose-dependent effect was observed with solifenacin monotherapy. A numerical trend was noted in the treatment combinations beginning at week 8, with the higher dose combination groups showing a higher percentage of responders compared with the lower dose combination groups.

In this study, the percentage of responders at the end of treatment in the placebo group was high (94.1%); consequently, no statistically significant differences were noted vs this group. At the end of treatment, > 95% of patients in the 5 + 25 combination, 10 + 25 combination and 5 + 50 combination groups met the criterion for responders. All 3 groups showed a statistically significant difference vs solifenacin 5 mg.

Micturition Frequency Normalization

A responder for normalization of micturition frequency was defined as a patient who had at least 8 micturitions per 24 h at baseline, at most 8 micturitions per 24 h postbaseline and a negative change from baseline. Mirabegron monotherapy showed a numerical trend with increases in the percentage of patients meeting the responder criterion that correlated with increased doses of mirabegron beginning at week 2. No dose-dependent

effect was observed with solifenacin monotherapy. A numerical trend was noted in the treatment combinations beginning at week 8, with the higher dose combination groups showing a higher percentage of responders compared with the lower dose combination groups.

At the end of treatment, the 10 + 25 combination and 5 + 50 combination groups showed a statistically significant difference vs placebo. Both the 10 + 25 combination and 5 + 50 combination groups also showed a statistically significant difference vs solifenacin 5 mg at the end of treatment.

Additional Secondary Variables Not Derived from the Micturition Diary

Change from Baseline in PPBC

The PPBC uses a 6-point Likert scale on which a score of 1 indicates "no problems at all" and a score of 6 indicates "many severe problems." Decreases in the score indicate improvement on the PPBC. Mean baseline values in PPBC were similar across all treatment groups. All treatment groups, including placebo, showed improvement in PPBC scores. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy; a weak dose-response relationship was observed for all combination groups except for the 10 + 50 combination group.

At the end of treatment, mirabegron 50 mg, solifenacin 2.5 mg, solifenacin 10 mg and all the combination treatment groups except 2.5 + 25 combination showed a greater improvement in the adjusted mean change from baseline compared with placebo. The adjusted mean difference vs placebo was statistically significant for the 5 + 25 combination, 5 + 50 combination and 10 + 25 combination groups.

In addition, all the combination treatment groups except the 2.5 + 25 combination group showed a greater improvement in the adjusted mean change from baseline compared with solifenacin 5 mg. The adjusted mean difference vs solifenacin 5 mg was statistically significant for the 2.5 + 50 combination, 5 + 25 combination, 5 + 50 combination and 10 + 25 combination groups.

Improvement in PPBC

The criterion for a responder for improvement in PPBC required that a patient had an improvement of ≥ 1 point from baseline. Mirabegron and solifenacin monotherapy each showed a numerical dose-response trend with increases in the percentage of patients meeting the responder criterion that correlated with increased doses of the monotherapy treatment at week 12 and the end of treatment. In the treatment combinations, the higher dose combination groups generally also showed a higher percentage of responders compared with the lower dose combination groups.

At the end of treatment, only the solifenacin 10 mg and 5 + 50 combination groups showed a statistically significant difference vs placebo in the percentage of responders with an improvement of ≥ 1 point in the PPBC. These 2 groups also showed a statistically significant difference vs solifenacin 5 mg.

Major Improvement in PPBC

The criterion for a responder for major improvement in PPBC required that a patient had an improvement of ≥ 2 points from baseline. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy; a weak dose-response relationship was observed for all combination groups except for the 10 + 50 combination group. At the end of treatment, only the 5 + 50 combination group showed a statistically

significant difference vs placebo; the 5 + 25 combination and 5 + 50 combination groups showed a statistically significant difference vs solifenacin 5 mg.

Deterioration in PPBC

The criterion for deterioration in PPBC required that a patient had a decrease of ≥ 1 point from baseline. A low percentage of patients met this criterion. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy; a weak dose-response relationship was observed for all combination groups except for the 10 + 50 combination group. No statistically significant differences were noted vs placebo or solifenacin 5 mg.

Health-related QoL Efficacy Assessment: Change from Baseline in OAB-q Symptom Bother Score

A decrease in the Symptom Bother score indicates improvement. At baseline, mean Symptom Bother scores were similar across all treatment groups. All treatment groups, including placebo, showed improvement in the Symptom Bother score, with numerically greater improvements recorded at the later weeks of treatment. At the end of treatment, the adjusted mean difference vs placebo was statistically significant for all the combination treatment groups except for the 2.5 + 25 combination group. None of the monotherapy groups showed statistically significant differences vs placebo. The adjusted mean difference vs solifenacin 5 mg was statistically significant for the 2.5 + 50 combination, 5 + 25 combination, 5 + 50 combination and 10 + 25 combination groups [Table 9].

Health-related QoL Efficacy Assessment: Change from Baseline in OAB-q Total Score

A higher score on the Health-related QoL total score indicates improvement. At baseline, mean Health-related QoL scores were similar across all treatment groups. All treatment groups, including placebo, showed improvement in the Health-related QoL scores, with numerically greater improvements recorded at the later weeks of treatment. At the end of treatment, all active treatment groups except mirabegron 25 mg and solifenacin 5 mg showed numerically greater improvement in the adjusted mean change from baseline in the Health-related QoL scores compared with placebo; the difference vs placebo was statistically significant for the 5 + 50 combination and 10 + 25 combination groups. At the end of treatment, all the combination treatment groups except the 2.5 + 25 combination group showed statistically significant differences in the adjusted mean change from baseline in the Health-related QoL scores compared with solifenacin 5 mg monotherapy [Table 9].

Table 9 Change from Baseline to EOT in OAB-q Scores (FAS)

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Symptom Bother					
Baseline and EOT					
0 mg	n	79	77	150	75
	Baseline Mean (SE)	52.6 (2.14)	58.7 (2.30)	55.3 (1.66)	54.2 (2.23)
	EOT Mean (SE)	29.4 (2.17)	27.3 (2.33)	29.1 (1.67)	25.5 (2.00)
25 mg	n	75	144	139	78
	Baseline Mean (SE)	56.3 (2.12)	55.5 (1.65)	56.1 (1.74)	57.1 (1.87)
	EOT Mean (SE)	29.1 (2.23)	27.8 (1.63)	24.2 (1.50)	23.0 (2.04)
50 mg	n	76	145	146	78
	Baseline Mean (SE)	55.1 (2.06)	57.7 (1.58)	56.2 (1.47)	58.3 (1.90)
	EOT Mean (SE)	28.3 (2.01)	25.0 (1.49)	22.7 (1.48)	25.4 (2.00)
Adjusted change from baseline†					
0 mg	Mean (SE)	-25.5 (1.96)	-29.8 (1.99)	-26.8 (1.42)	-29.9 (2.01)
	95% CI	(-29.4, -21.7)	(-33.7, -25.9)	(-29.5, -24.0)	(-33.8, -25.9)
25 mg	Mean (SE)	-27.1 (2.01)	-28.0 (1.45)	-32.0 (1.48)	-33.6 (1.97)
	95% CI	(-31.1, -23.2)	(-30.9, -25.2)	(-34.9, -29.1)	(-37.4, -29.7)
50 mg	Mean (SE)	-27.5 (2.00)	-31.7 (1.45)	-33.5 (1.44)	-31.4 (1.97)
	95% CI	(-31.4, -23.6)	(-34.5, -28.8)	(-36.3, -30.7)	(-35.3, -27.5)
Adjusted difference‡ vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				-3.1 (2.47)
	95% CI	---	---	---	(-8.0, 1.7)
	P value§				0.21
25 mg	Mean (SE)		-1.3(2.03)	-5.2 (2.05)	-6.8 (2.43)
	95% CI	---	(-5.2, 2.7)	(-9.3, -1.2)	(-11.6, -2.0)
	P value§		0.54	0.011*	0.005*
50 mg	Mean (SE)		-4.9 (2.03)	-6.7 (2.03)	-4.7 (2.44)
	95% CI	---	(-8.9, -0.9)	(-10.7, -2.8)	(-9.4, 0.1)
	P value§		0.016*	< 0.001*	0.056
Adjusted difference‡ vs placebo					
0 mg	Mean (SE)		-4.3 (2.80)	-1.2 (2.42)	-4.4 (2.81)
	95% CI	---	(-9.8, 1.2)	(-6.0, 3.5)	(-9.9, 1.2)
	P value§		0.13	0.61	0.12
25 mg	Mean (SE)	-1.6 (2.81)	-2.5 (2.44)	-6.5 (2.46)	-8.0 (2.78)
	95% CI	(-7.1, 3.9)	(-7.3, 2.3)	(-11.3, -1.7)	(-13.5, -2.6)
	P value§	0.56	0.31	0.008*	0.004*
50 mg	Mean (SE)	-2.0 (2.80)	-6.1 (2.44)	-8.0 (2.44)	-5.9 (2.79)
	95% CI	(-7.5, 3.5)	(-10.9, -1.3)	(-12.8, -3.2)	(-11.4, -0.4)
	P value§	0.48	0.012*	0.001*	0.035*

Table continued on next page

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Health-related Quality of Life (Total)					
Baseline and EOT					
0 mg	n	79	77	150	75
	Baseline Mean (SE)	60.2 (2.28)	56.4 (2.30)	55.5 (1.75)	53.5 (2.53)
	EOT Mean (SE)	79.5 (2.01)	80.5 (2.24)	77.1 (1.70)	78.2 (2.24)
25 mg	n	75	144	139	78
	Baseline Mean (SE)	56.4 (2.40)	55.5 (1.78)	57.1 (1.79)	53.8 (2.34)
	EOT Mean (SE)	76.1 (2.13)	78.4 (1.65)	82.5 (1.49)	82.2 (2.19)
50 mg	n	76	145	146	78
	Baseline Mean (SE)	60.0 (2.33)	52.8 (1.61)	55.7 (1.69)	50.4 (2.38)
	EOT Mean (SE)	80.6 (2.13)	80.3 (1.41)	84.0 (1.31)	80.3 (1.98)
Adjusted change from baseline†					
0 mg	Mean (SE)	22.0 (1.83)	24.6 (1.85)	21.6 (1.33)	23.5 (1.88)
	95% CI	(18.4, 25.6)	(21.0, 28.2)	(19.0, 24.2)	(19.8, 27.2)
25 mg	Mean (SE)	20.2 (1.88)	22.7 (1.35)	26.4 (1.38)	27.4 (1.84)
	95% CI	(16.5, 23.9)	(20.1, 25.4)	(23.7, 29.1)	(23.8, 31.1)
50 mg	Mean (SE)	23.1 (1.87)	26.0 (1.35)	28.4 (1.34)	27.0 (1.84)
	95% CI	(19.4, 26.8)	(23.4, 28.7)	(25.8, 31.0)	(23.4, 30.6)
Adjusted difference‡ vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				1.9 (2.30)
	95% CI	---	---	---	(-2.6, 6.4)
	P value§				0.41
25 mg	Mean (SE)		1.1 (1.90)	4.8 (1.91)	5.8 (2.27)
	95% CI	---	(-2.6, 4.8)	(1.0, 8.5)	(1.4, 10.3)
	P value§		0.57	0.013*	0.011*
50 mg	Mean (SE)		4.4 (1.89)	6.8 (1.89)	5.4 (2.27)
	95% CI	---	(0.7, 8.1)	(3.1, 10.5)	(0.9, 9.8)
	P value§		0.021*	< 0.001*	0.018*
Adjusted difference‡ vs placebo					
0 mg	Mean (SE)		2.6 (2.60)	-0.3 (2.26)	1.5 (2.62)
	95% CI	---	(-2.5, 7.7)	(-4.8, 4.1)	(-3.6, 6.7)
	P value§		0.31	0.88	0.56
25 mg	Mean (SE)	-1.8 (2.62)	0.7 (2.28)	4.4 (2.29)	5.5 (2.60)
	95% CI	(-6.9, 3.4)	(-3.7, 5.2)	(-0.1, 8.9)	(0.4, 10.6)
	P value§	0.50	0.74	0.055	0.036*
50 mg	Mean (SE)	1.1 (2.61)	4.0 (2.28)	6.4 (2.27)	5.0 (2.60)
	95% CI	(-4.0, 6.2)	(-0.4, 8.5)	(2.0, 10.9)	(-0.1, 10.1)
	P value§	0.67	0.078	0.005*	0.053

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline and at least 1 postbaseline visit (FAS)

Footnotes continued on next page

The symptom bother score ranged from 0 to 100 (i.e., 100=worst severity). A negative change in the symptom bother score indicated an improvement. For the health-related quality of life scores, higher scores indicated a better quality of life; a positive change indicated an improvement.

---: not applicable; ANCOVA: analysis of covariance; EOT: end of treatment; FAS: Full Analysis Set; OAB-q: Overactive Bladder Questionnaire

† Adjusted change from baseline values were generated from the ANCOVA model with 2 main factors mirabegron dose (0, 25 and 50 mg) and solifenacin succinate dose (0, 2.5, 5 and 10 mg) and their corresponding dose combination interaction term to reflect the factorial design. The model included the main factors of sex, age group, geographic region and baseline measurement as covariates.

‡ Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin succinate 5 mg or placebo from the adjusted mean of the combination treatment group.

§ P values were from pairwise comparison of the combination treatment groups vs solifenacin succinate 5 mg or placebo within the ANCOVA model.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.6.2.1 and 12.3.6.2.2

Improvement in OAB-q

The criterion for a responder for improvement in OAB-q required that a patient had an improvement of ≥ 10 points from baseline. No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or with the combination therapy. For the Symptom Bother score, ≥ 78.9% patients in each active treatment group met the criterion at the end of treatment. All treatment groups showed greater percentages of responders compared with the placebo group; the 5 + 25 combination and 5 + 50 combination groups showed statistically significant differences vs placebo for an improvement of ≥ 10 points in the Symptom Bother score. All the combination groups also showed greater percentages of responders compared with solifenacin 5 mg monotherapy; however, no statistically significant differences were observed.

No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or with the combination therapy for the improvement in the Health-related QoL score (OAB-q score without the Symptom Bother component). At the end of treatment, ≥ 71.1% patients in each active treatment group except mirabegron 25 mg met the criterion. All treatment groups except mirabegron 25 mg showed greater percentages of responders compared with the placebo group; the 5 + 50 combination group showed statistically significant differences vs placebo for an improvement of ≥ 10 points in the Health-related QoL score. All the combination groups also showed greater percentages of responders compared with solifenacin 5 mg monotherapy; the 5 + 50 combination group showed a statistically significant difference.

EQ-5D Questionnaire

The EQ-5D consists of 2 components: the EQ-5D descriptive system and the EQ-5D VAS. The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 response levels. The EQ-5D VAS elicits a self-rating by the respondent of his/her health status. At the end of treatment, there were no clear differences between treatment groups in the percentages of patients shifting between response levels in the EQ-5D descriptive system and no consistent trends were noted in the mean change from baseline in the EQ-5D VAS.

WPAI:SHP Questionnaire

On the WPAI:SHP, a decrease from baseline indicates improvement. Four parameters were assessed: work time missed, impairment while working, overall work impairment and activity impairment. The improvement

from baseline to end of treatment was generally greater in the active treatment groups compared with placebo for all parameters except work time missed. For the parameters of work time missed, impairment while working and overall work impairment, the combination treatment groups did not show a consistent trend of improvement compared with solifenacin 5 mg monotherapy. For the parameter of activity impairment, all combination treatment groups except the 2.5 + 25 combination group showed a greater improvement from baseline compared with solifenacin 5 mg monotherapy.

Change from Baseline in Patient Treatment Satisfaction on TS-VAS

On the TS-VAS, an increase from baseline indicates improvement. There was some imbalance in the scores at baseline (e.g., placebo 5.22 and 2.5 + 50 combination 3.63). No dose-response relationship was apparent with solifenacin monotherapy; a dose-response relationship was observed for mirabegron monotherapy and for all combination groups except for the 5 + 50 combination group [Table 10]. In all treatment groups, including placebo, an increase in treatment satisfaction, based on the TS-VAS, was observed. All the treatment combination groups, except for the 2.5 + 25 combination group, showed statistically significant differences vs placebo in adjusted mean change from baseline. The 5 + 25 combination, 10 + 25 combination and 10 + 50 combination groups showed statistically significant differences vs solifenacin 5 mg.

Table 10 Change from Baseline to EOT in Patient TS-VAS (FAS)

Parameter Mirabegron	**Statistic**	**Solifenacin Succinate**			
		0 mg	**2.5 mg**	**5 mg**	**10 mg**
Baseline and EOT					
0 mg	n	78	75	147	73
	Baseline Mean (SE)	5.22 (0.415)	4.60 (0.459)	3.89 (0.295)	4.54 (0.445)
	EOT Mean (SE)	6.91 (0.326)	7.45 (0.327)	7.02 (0.240)	7.32 (0.294)
25 mg	n	73	141	136	76
	Baseline Mean (SE)	3.86 (0.438)	4.35 (0.310)	4.53 (0.334)	4.25 (0.437)
	EOT Mean (SE)	6.84 (0.348)	7.29 (0.239)	7.81 (0.210)	7.81 (0.292)
50 mg	n	76	143	144	78
	Baseline Mean (SE)	4.59 (0.454)	3.63 (0.308)	4.61 (0.317)	4.13 (0.413)
	EOT Mean (SE)	7.53 (0.313)	7.43 (0.224)	7.60 (0.221)	8.00 (0.258)
Adjusted change from baseline					
0 mg	Mean (SE)	2.44 (0.298)	3.10 (0.303)	2.78 (0.217)	2.96 (0.307)
	95% CI	(1.86, 3.03)	(2.51, 3.70)	(2.35, 3.20)	(2.36, 3.56)
25 mg	Mean (SE)	2.61 (0.307)	2.96 (0.221)	3.47 (0.225)	3.51 (0.301)
	95% CI	(2.01, 3.21)	(2.53, 3.40)	(3.03, 3.91)	(2.92, 4.10)
50 mg	Mean (SE)	3.17 (0.301)	3.24 (0.220)	3.24 (0.219)	3.72 (0.297)
	95% CI	(2.58, 3.77)	(2.81, 3.67)	(2.81, 3.67)	(3.14, 4.30)

Table continued on next page

Parameter Mirabegron	Statistic	Solifenacin Succinate 0 mg	2.5 mg	5 mg	10 mg
Adjusted difference† vs solifenacin succinate 5 mg					
0 mg	Mean (SE)				0.18 (0.376)
	95% CI	---	---	---	(-0.56, 0.92)
	P value‡				0.63
25 mg	Mean (SE)		0.18 (0.310)	0.69 (0.313)	0.73 (0.371)
	95% CI	---	(-0.43, 0.79)	(0.08, 1.30)	(0.00, 1.46)
	P value‡		0.56	0.027*	0.049*
50 mg	Mean (SE)		0.46 (0.308)	0.46 (0.308)	0.94 (0.368)
	95% CI	---	(-0.15, 1.06)	(-0.14, 1.07)	(0.22, 1.66)
	P value‡		0.14	0.13	0.011*
Adjusted difference† vs placebo					
0 mg	Mean (SE)		0.66 (0.425)	0.34 (0.369)	0.52 (0.428)
	95% CI	---	(-0.18, 1.49)	(-0.39, 1.06)	(-0.32, 1.36)
	P value‡		0.12	0.36	0.23
25 mg	Mean (SE)	0.17 (0.428)	0.52 (0.371)	1.03 (0.373)	1.07 (0.423)
	95% CI	(-0.67, 1.01)	(-0.21, 1.25)	(0.30, 1.76)	(0.24, 1.90)
	P value‡	0.70	0.16	0.006*	0.012*
50 mg	Mean (SE)	0.73 (0.423)	0.79 (0.371)	0.80 (0.369)	1.28 (0.421)
	95% CI	(-0.10, 1.56)	(0.07, 1.52)	(0.07, 1.52)	(0.45, 2.10)
	P value‡	0.084	0.032*	0.031*	0.002*

All patients randomized to a double-blind treatment who took at least 1 dose of double-blind study drug and had primary efficacy data (mean volume voided) derived from the diary at baseline (FAS)

Treatment satisfaction was assessed by patients on a 10 cm VAS scale; a score of 10 indicated complete satisfaction.

Adjusted change from baseline values were generated from the ANCOVA model with 2 main factors mirabegron dose (0, 25 and 50 mg) and solifenacin succinate dose (0, 2.5, 5 and 10 mg) and their corresponding dose combination interaction term to reflect the factorial design. The model further included the main factors gender, age group, geographic region and baseline measurement as covariate.

---: not applicable; ANCOVA: analysis of covariance; EOT: end of treatment; FAS: Full Analysis Set; TS-VAS: Treatment Satisfaction–Visual Analog Scale

† Differences of the adjusted means were calculated by subtracting the adjusted mean of solifenacin succinate 5 mg or placebo from the adjusted mean of the combination treatment group.

‡ P values were from pairwise comparison of the combination treatment groups vs solifenacin succinate 5 mg or placebo within the ANCOVA model.

* Statistically significantly superior compared to solifenacin 5 mg or placebo, as appropriate

Source: Tables 12.3.6.6

Subgroup Evaluations

Mean Volume Voided per Micturition: Previous OAB Medication

In the FAS, 47.2% of the patients previously received OAB medication and 52.8% were treatment-naïve. For patients in the FAS who had previously received OAB medication, the 95% CI for the adjusted mean difference in mean volume voided per micturition vs placebo did not include 0 for the mirabegron 50 mg group, the solifenacin 5 mg group and for all combination groups. For these patients, the analysis of the adjusted mean

difference in mean volume voided in the combination treatment groups vs solifenacin 5 mg was similar to that observed with the full FAS population. A difference vs solifenacin 5 mg was shown for the 5 + 25 combination, 10 + 25 combination, 5 + 50 combination and 10 + 50 combination groups.

For the treatment-naïve patients in the FAS, the 95% CI for the adjusted mean difference in mean volume voided per micturition vs placebo did not include 0 for all the combination groups but not for either the mirabegron or the solifenacin monotherapy groups. For these patients, a difference vs solifenacin 5 mg in mean volume voided per micturition was noted for the 5 + 50 combination and the 10 + 50 combination groups.

In both subgroups (patients with previous or without previous OAB medication), all treatment combinations showed improvement vs placebo. The placebo effect was larger in the treatment-naïve patients vs the patients previously treated with OAB medication. The differences for combination therapies and all mirabegron monotherapy vs placebo (point estimates of effect size) tended to be higher in patients previously treated with OAB medication vs treatment-naïve patients. It should be noted that although the point estimate of effect size tends to be higher in patients previously treated with OAB medication, this should be interpreted with caution due to largely overlapping 95% CIs.

Mean Volume Voided per Micturition: Incontinence at Baseline

In the FAS, 22% of the patients had at least 1 baseline incontinence episode. For patients in the FAS-Incontinence, the 95% CI for the adjusted mean difference in mean volume voided per micturition vs placebo did not include 0 for all the combination groups as well as for both the mirabegron and the solifenacin monotherapy groups compared to patients without incontinence. For patients in the FAS-Incontinence, a difference in mean volume voided per micturition vs solifenacin 5 mg was noted for the 5 + 25 combination and the 10 + 25 combination groups.

For the patients in the FAS with no incontinence episode at baseline, the 95% CI for the adjusted mean difference in mean volume voided per micturition vs placebo did not include 0 for the solifenacin 5 mg group and for all combination groups. For patients in the FAS with no incontinence episodes at baseline, the analysis of the adjusted mean difference in mean volume voided per micturition in the combination treatment groups vs solifenacin 5 mg was similar to that observed with the full FAS population, except for the 10 + 25 combination group. A difference in mean volume voided per micturition vs solifenacin 5 mg was shown for the 5 + 25 combination, 5 + 50 combination and 10 + 50 combination groups. It should be noted that although the point estimate of effect size tends to be higher in patients with at least 1 incontinence episode at baseline, this should be interpreted with caution due to largely overlapping 95% CIs.

Compared to placebo, in patients who reported at least 1 incontinence episode at baseline, a greater change from baseline in mean volume voided per micturition was observed than in patients with no incontinence episodes at baseline across all treatment groups. Compared to solifenacin 5 mg, there were comparable effects on mean volume voided per micturition between the 2 subgroups (patients with at least 1 incontinence episode or no incontinence episodes at baseline).

Subgroup Analyses of the Key Secondary Variables

The secondary efficacy variable of change from baseline to end of treatment in mean number of micturitions per 24 h was analyzed using the FAS for the following subgroups: sex, age group (< 65, ≥ 65), geographic region, type of OAB, previous OAB medication, discontinuation of previous OAB medication due to insufficient effect, discontinuation of previous OAB medication due to poor tolerability, effectiveness of previous OAB

medication, previous treatment with solifenacin, number of previous OAB treatments, incontinence at baseline and OAB severity at baseline. No clear trends relating to the subgroups were evident in these analyses.

Pharmacokinetics:

Solifenacin Pharmacokinetics:

Summary statistics of the pharmacokinetic parameters are presented for once-daily solifenacin 2.5 mg [Table 11], once-daily solifenacin 5 mg [Table 12] and once-daily solifenacin 10 mg [Table 13].

In the absence of mirabegron, the mean C_{trough} of solifenacin was 8.128 ng/mL at a dose of 2.5 mg. The plasma concentration increased to a mean C_{max} of 11.61 ng/mL, which was reached at a mean t_{max} of 4.206 h. Increasing the solifenacin dose to 5 mg resulted in a dose proportional increase of C_{trough} and C_{max}; at solifenacin 5 mg, the mean C_{trough} was 17.25 ng/mL and the mean C_{max} was 25.02 ng/mL. With solifenacin 5 mg, C_{max} was reached at a mean t_{max} of 4.446 h. A further doubling of the solifenacin dose to 10 mg resulted in an approximately 2.5-fold increase in C_{trough} (45.07 ng/mL) and C_{max} (57.82 ng/mL). Compared to the other 2 doses (2.5 and 5 mg), C_{max} was reached somewhat later; the mean t_{max} was 5.922 h. The increase in AUC_{last} followed the same pattern in terms of dose proportionality; mean values were 79.89, 161.2, and 396.0 ng·h/mL at doses of 2.5, 5 and 10 mg, respectively. The peak-trough ratio (PTR) was approximately 1.4 at all 3 doses. The interpatient variability in the exposure parameters varied from 25.3% for AUC_{last} at a dose of 10 mg to 41.62% for C_{trough} at a dose of 2.5 mg.

Coadministration of mirabegron did not result in a consistent change in the solifenacin pharmacokinetic parameters. AUC_{last}, C_{max} and C_{trough} increased approximately dose proportionally. At a dose of 2.5 mg solifenacin, exposure parameters were about 10% higher in the presence of mirabegron: 85.74 to 91.16 ng·h/mL for AUC_{last}, 12.04 to 12.20 ng/mL for C_{max}, and 8.921 to 9.769 ng/mL for C_{trough}. There was no consistent change with the increase in mirabegron dose. At a dose of solifenacin 5 mg, the C_{trough} was higher in combination with mirabegron, but C_{max} was lower in the presence of mirabegron 25 mg and higher in the presence of mirabegron 50 mg.

Mean AUC_{last}, C_{max}, and C_{trough} values were 175.3 to 218.0 ng·h/mL, 24.76 to 27.26 ng/mL and 18.78 to 19.30 ng/mL, respectively. With a dose of 10 mg solifenacin, lower values for the exposure parameters were obtained; mean AUC_{last}, C_{max}, and C_{trough} values were 343.7 to 380.1 ng·h/mL, 49.14 to 53.83 ng/mL, and 36.47 to 37.96 ng/mL, respectively. No consistent changes in t_{max} were observed; the mean values were approximately 4 h. Mean PTR values varied around the value obtained for solifenacin alone, approximately 1.4. Interpatient variability in exposure parameters was comparable to the values obtained with solifenacin monotherapy. For several parameters, changes in the mean values were observed in combination with mirabegron; however, there remained a considerable overlap in the individual values obtained with the combination therapy and the values observed with solifenacin monotherapy.

Overall, no consistent effect of mirabegron on the pharmacokinetics of solifenacin was observed.

Table 11 Descriptive Statistics of Solifenacin Pharmacokinetic Parameters at a Once-Daily Dose of 2.5 mg

Parameter Statistic	**S 2.5 mg**	**S 2.5 mg + M 25 mg**	**S 2.5 mg + M 50 mg**
AUC_{last} (ng·h/mL)			
n	10	13	18
Mean	79.89	85.74	91.16
(SD, CV)	(28.335, 35.5%)	(31.377, 36.6%)	(38.767, 42.5%)
Min – Max	41.9 – 129	39.4 – 141	26.0 – 196
Median	71.35	89.04	88.29
C_{max} (ng/mL)			
n	10	13	18
Mean	11.61	12.20	12.04
(SD, CV)	(4.307, 37.1%)	(4.151, 34.0%)	(4.417, 36.7%)
Min – Max	6.24 – 18.5	6.28 – 19.6	4.33 – 19.0
Median	10.24	12.98	11.91
C_{trough} (ng/mL)			
n	10	12	17
Mean	8.128	9.769	8.921
(SD, CV)	(3.3830, 41.6%)	(4.4376, 45.4%)	(3.7689, 42.2%)
Min – Max	4.06 – 14.5	3.80 – 19.4	2.55 – 16.3
Median	7.220	10.720	8.190
Peak-trough ratio			
n	10	12	17
Mean	1.464	1.340	1.423
(SD, CV)	(0.2012, 13.7%)	(0.1806, 13.5%)	(0.2491, 17.5%)
Min – Max	1.00 – 1.72	1.01 – 1.65	1.00 – 1.79
Median	1.489	1.320	1.379
t_{max} (h)			
n	10	13	18
Mean	4.206	4.035	4.174
(SD, CV)	(2.4427)	(1.5452)	(1.8632)
Min – Max	0.00 – 8.00	1.00 – 7.03	0.00 – 8.00
Median	3.990	4.000	4.000

All patients in the PKAS (patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded) for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained (Full Profile PKAS)

AUC_{last}: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration; C: combination (solifenacin + mirabegron); C_{max}: maximum observed concentration in plasma; C_{trough}: concentration at the end of the dosing interval; CV: coefficient of variation; M: mirabegron; Max: maximum; Min: minimum; PKAS: Pharmacokinetic Analysis Set; S: solifenacin; t_{max}: time to attain C_{max}

Source: Table 12.4.3

Table 12 Descriptive Statistics of Solifenacin Pharmacokinetic Parameters at a Once-Daily Dose of 5 mg

Parameter Statistic	S 5 mg	S 5 mg + M 25 mg	S 5 mg + M 50 mg
AUC_{last} (ng·h/mL)			
n	12	12	12
Mean	161.2	175.3	218.0
(SD, CV)	(44.28, 27.5%)	(80.86, 46.1%)	(185.49, 85.1%)
Min – Max	102 – 269	68.8 – 328	12.5 – 725
Median	155.0	171.6	171.6
C_{max} (ng/mL)			
n	12	12	12
Mean	25.02	24.76	27.26
(SD, CV)	(6.759, 27.0%)	(10.885, 44.0%)	(11.311, 41.5%)
Min – Max	14.6 – 38.3	11.5 – 46.3	12.4 – 51.7
Median	24.47	24.36	24.79
C_{trough} (ng/mL)			
n	12	12	12
Mean	17.25	19.30	18.78
(SD, CV)	(5.804, 33.6%)	(9.975, 51.7%)	(8.994, 47.9%)
Min – Max	8.87 – 26.6	6.86 – 35.3	5.94 – 37.0
Median	17.76	20.26	17.82
Peak-trough ratio			
n	12	12	12
Mean	1.496	1.363	1.529
(SD, CV)	(0.2236, 14.9%)	(0.2305, 16.9%)	(0.2927, 19.1%)
Min – Max	1.18 – 1.92	1.02 – 1.75	1.17 – 2.09
Median	1.480	1.327	1.436
t_{max} (h)			
n	12	12	12
Mean	4.446	4.866	4.096
(SD, CV)	(1.8456)	(1.7491)	(1.6987)
Min – Max	1.00 – 7.00	2.00 – 8.00	0.83 – 6.37
Median	4.000	5.010	4.000

All patients in the PKAS (patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded) for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained (Full Profile PKAS)

AUC_{last}: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration; C: combination (solifenacin + mirabegron); C_{max}: maximum observed concentration in plasma; C_{trough}: concentration at the end of the dosing interval; CV: coefficient of variation; M: mirabegron; Max: maximum; Min: minimum; PKAS: Pharmacokinetic Analysis Set; S: solifenacin; t_{max}: time to attain C_{max}

Source: Table 12.4.3

Table 13 Descriptive Statistics of Solifenacin Pharmacokinetic Parameters at a Once-Daily Dose of 10 mg

Parameter Statistic	S 10 mg	S 10 mg + M 25 mg	S 10 mg + M 50 mg
AUC_{last} (ng·h/mL)			
n	9	10	12
Mean	396.0	343.7	380.1
(SD, CV)	(100.13, 25.3%)	(117.44, 34.2%)	(170.62, 44.9%)
Min – Max	211 – 503	170 – 578	108 – 620
Median	418.1	354.5	346.7
C_{max} (ng/mL)			
n	9	10	12
Mean	57.82	49.14	53.83
(SD, CV)	(16.921, 29.3%)	(16.846, 34.9%)	(22.811, 42.4%)
Min – Max	30.1 – 79.3	25.3 – 84.7	15.8 – 84.4
Median	59.99	50.82	49.86
C_{trough} (ng/mL)			
n	9	10	11
Mean	45.07	36.47	37.96
(SD, CV)	(15.593, 34.6%)	(12.304, 33.7%)	(20.398, 53.7%)
Min – Max	23.3 – 69.8	15.2 – 61.8	6.51 – 72.5
Median	41.20	36.44	32.25
Peak-trough ratio			
n	9	10	11
Mean	1.303	1.382	1.491
(SD, CV)	(0.1491, 11.4%)	(0.1793, 13.0%)	(0.3566, 23.9%)
Min – Max	1.11 – 1.52	1.20 – 1.69	1.10 – 2.42
Median	1.249	1.330	1.414
t_{max} (h)			
n	9	10	12
Mean	5.922	4.427	3.860
(SD, CV)	(1.3912)	(1.6884)	(1.3974)
Min – Max	3.00 – 7.17	2.02 – 7.15	2.00 – 7.00
Median	8.050	4.525	4.000

All patients in the PKAS (patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded) for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained (Full Profile PKAS)

AUC_{last}: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration; C: combination (solifenacin + mirabegron); C_{max}: maximum observed concentration in plasma; C_{trough}: concentration at the end of the dosing interval; CV: coefficient of variation; M: mirabegron; Max: maximum; Min: minimum; PKAS: Pharmacokinetic Analysis Set; S: solifenacin; t_{max}: time to attain C_{max}

Source: Table 12.4.3

Mirabegron Pharmacokinetics

Summary statistics of the pharmacokinetic parameters are presented for once-daily mirabegron 25 mg [Table 14] and once-daily mirabegron 50 mg [Table 15].

In the absence of solifenacin, the mean C_{trough} of mirabegron was 2.313 ng/mL at a dose of 25 mg. The plasma concentration increased to a mean C_{max} of 5.993 ng/mL, which was reached at a mean t_{max} of 2.621 h. An increase in the mirabegron dose to 50 mg resulted in a more than dose proportional increase in C_{trough} and C_{max}; the mean C_{trough} reached a value of 6.628 ng/mL, while the mean C_{max} increased to 16.54 ng/mL. C_{max} was

observed at a mean t_{max} of 3.279 h. AUC_{last} increased more than 2-fold when the mirabegron dose was increased from 25 to 50 mg (32.55 to 73.72 ng·h/mL, respectively). The PTR amounted to approximately 3 at both doses. The interpatient variability in the exposure parameters was generally high and varied from 34.3% for AUC_{last} at a mirabegron dose of 25 mg to 101.2% for C_{trough} at a mirabegron dose of 50 mg.

Coadministration of solifenacin did not result in a consistent change in the mirabegron pharmacokinetic parameters. At a dose of mirabegron 25 mg, C_{trough}, C_{max} and AUC_{last} were higher in the presence of solifenacin, but there was no consistent change with increasing solifenacin doses. In the absence of solifenacin, the mean C_{trough} was 2.313 ng/mL, the mean C_{max} was 5.993 ng/mL and the mean AUC_{last} was 32.55 ng·h/mL. In combination with solifenacin, an increase in the mean values was generally observed, especially for C_{max} and AUC_{last}, but with an almost complete overlap in the ranges of the individual values. With solifenacin, the mean C_{trough} values ranged from 2.404 to 2.983 ng/mL, the mean C_{max} values ranged from 6.804 to 7.331 ng/mL and the mean AUC_{last} values ranged from 36.12 to 38.95 ng·h/mL. At a dose of mirabegron 50 mg, the mean C_{trough} was lower in combination with 2.5 mg and 5 mg solifenacin, but higher with 10 mg solifenacin compared to mirabegron 50 mg alone. However, there was an almost complete overlap in individual values between the combination treatments and mirabegron alone. Compared with 50 mg mirabegron monotherapy, the mean C_{max} was lower in combination with 5 mg solifenacin, but higher in combination with 2.5 mg and 10 mg solifenacin. However, there was a large overlap in individual values for the combination treatments when compared with mirabegron monotherapy. The mean AUC_{last} was consistently higher with mirabegron 50 mg combinations compared with mirabegron 25 mg combinations; the mean AUC_{last} values ranged from 82.86 to 118.0 ng·h/mL for mirabegron 50 mg in combination with solifenacin compared to 73.72 ng·h/mL for mirabegron 50 mg alone, but with a large overlap in individual values. Solifenacin resulted in an increase in the t_{max} of mirabegron by approximately 0.5 to 2 h, except for the 5 + 50 combination group where a slight decrease in t_{max} was observed. For the individual t_{max} values, a large overlap was observed for the combination treatments compared to mirabegron monotherapy. Mean PTR values varied around the values obtained for mirabegron alone (approximately 3 for mirabegron monotherapy and 2.330 to 3.660 for combination treatment). Interpatient variability in exposure parameters was high for all treatments, independent of whether mirabegron was dosed alone or in combination with solifenacin.

At doses of 25 mg and 50 mg mirabegron, 2.5 mg to 10 mg solifenacin generally resulted in an increase in mean C_{max} and AUC_{last} values, and to a lesser extent mean C_{trough}, but no obvious relationship with the dose of solifenacin was observed. The overlap in the range of individual values of the combination treatment with the values obtained with mirabegron monotherapy was substantial.

Table 14 Descriptive Statistics of Mirabegron Pharmacokinetic Parameters at a Once-Daily Dose of 25 mg

Parameter Statistic	M 25 mg	S 2.5 mg + M 25 mg	S 5 mg + M 25 mg	S 10 mg + M 25 mg
AUC_{last} (ng·h/mL)				
n	8	13	12	10
Mean	32.55	36.12	38.95	36.89
(SD, CV)	(11.165, 34.3%)	(20.555, 56.9%)	(27.152, 69.7%)	(15.632, 42.4%)
Min – Max	21.1 – 51.0	11.6 – 94.4	10.4 – 104	18.5 – 66.0
Median	31.29	35.99	31.22	32.39
C_{max} (ng/mL)				
n	8	13	12	10
Mean	5.993	7.331	7.153	6.804
(SD, CV)	(3.6716, 61.3%)	(5.2657, 71.8%)	(6.4728, 90.5%)	(3.2417, 47.6%)
Min – Max	2.85 – 14.0	1.76 – 18.8	1.92 – 25.0	3.89 – 11.9
Median	4.850	6.170	5.610	5.575
C_{trough} (ng/mL)				
n	8	12	12	10
Mean	2.313	2.404	2.983	2.416
(SD, CV)	(1.0876, 47.0%)	0.9646, 40.1%()	(1.4258, 47.8%)	(0.9164, 37.9%)
Min – Max	1.11 – 4.80	1.20 – 4.83	0.98 – 4.82	0.79 – 4.07
Median	2.210	2.375	3.365	2.355
Peak-trough ratio				
n	8	12	12	10
Mean	3.351	3.046	3.172	2.335
(SD, CV)	(3.7841, 112.9%)	(1.4302, 47.0%)	(3.6126, 113.9%)	(1.3720, 58.8%)
Min – Max	1.29 – 12.6	1.55 – 5.90	1.33 – 14.4	1.00 – 5.20
Median	2.141	2.792	2.065	1.896
t_{max} (h)				
n	8	13	12	10
Mean	2.621	3.187	3.518	4.528
(SD, CV)	(1.3533)	(1.2387)	(1.8348)	(1.8892)
Min – Max	0.920 – 5.05	0.850 – 5.02	0.000 – 7.00	1.00 – 8.18
Median	2.040	3.070	3.540	4.515

All patients in the PKAS (patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded) for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained (Full Profile PKAS)

AUC_{last}: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration; C: combination (solifenacin + mirabegron); C_{max}: maximum observed concentration in plasma; C_{trough}: concentration at the end of the dosing interval; CV: coefficient of variation; M: mirabegron; Max: maximum; Min: minimum; PKAS: Pharmacokinetic Analysis Set; S: solifenacin; t_{max}: time to attain C_{max}

Source: Table 12.4.4

Table 15 Descriptive Statistics of Mirabegron Pharmacokinetic Parameters at a Once-Daily Dose of 50 mg

Parameter Statistic	M 50 mg	S 2.5 mg + M 50 mg	S 5 mg + M 50 mg	S 10 mg + M 50 mg
AUC_{last} (ng·h/mL)				
n	11	18	12	12
Mean	73.72	99.73	82.86	118.0
(SD, CV)	(40.948, 55.5%)	(65.130, 65.3%)	(62.020, 74.9%)	(82.54, 69.9%)
Min – Max	31.1 – 148	19.7 – 304	8.20 – 257	14.4 – 279
Median	54.99	79.29	72.69	95.96
C_{max} (ng/mL)				
n	11	18	12	12
Mean	16.54	18.30	13.13	24.84
(SD, CV)	(11.290, 68.2%)	(16.294, 89.0%)	(4.476, 34.1%)	(21.977, 88.5%)
Min – Max	4.77 – 35.2	2.87 – 60.9	5.80 – 19.6	2.16 – 73.3
Median	11.18	13.67	12.57	16.29
C_{trough} (ng/mL)				
n	11	17	12	12
Mean	6.628	6.165	6.010	7.240
(SD, CV)	(6.7052, 101.2%)	(2.6595, 43.1%)	(2.0621, 34.3%)	(4.3075, 59.5%)
Min – Max	1.78 – 25.5	1.72 – 13.0	2.24 – 8.80	0.92 – 16.3
Median	4.290	3.254	1.296	5.825
Peak-trough ratio				
n	11	17	12	12
Mean	3.006	3.053	2.330	3.660
(SD, CV)	(1.6816, 55.9%)	(2.4288, 79.6%)	(0.7828, 33.6%)	(3.7022, 101.1%)
Min – Max	1.00 – 7.55	1.00 – 10.1	1.30 – 3.70	1.48 – 14.6
Median	2.570	2.102	2.262	2.134
t_{max} (h)				
n	11	18	12	12
Mean	3.279	4.338	2.921	4.027
(SD, CV)	(1.5545)	(1.6147)	(2.2343)	(1.4779)
Min – Max	0.000 – 5.00	0.000 – 7.00	0.830 – 7.00	2.00 – 7.00
Median	3.020	4.010	2.500	4.010

All patients in the PKAS (patients who received active treatment, for whom at least 1 quantifiable plasma concentration of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained and for whom the dosing and sampling history were recorded) for whom a full pharmacokinetic profile of at least 1 of the active treatments (solifenacin succinate or mirabegron) was obtained (Full Profile PKAS)

AUC_{last}: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration; C: combination (solifenacin + mirabegron); C_{max}: maximum observed concentration in plasma; C_{trough}: concentration at the end of the dosing interval; CV: coefficient of variation; M: mirabegron; Max: maximum; Min: minimum; PKAS: Pharmacokinetic Analysis Set; S: solifenacin; t_{max}: time to attain C_{max}

Source: Table 12.4.4

Safety Results:

Overall, treatment-emergent adverse events (TEAEs) were reported by 623 (47.7%) patients [Table 16]. The highest percentages of patients with TEAEs were reported in the solifenacin 10 mg (60.3%) and 10 + 50 combination groups (59.3%); the lowest percentages of patients with TEAEs were reported in placebo (39.5%) and solifenacin 2.5 mg groups (40.5%). The majority of TEAEs were mild in severity (77.4%), whereas 29 TEAEs were judged by the investigator as severe in intensity. The highest proportion of patients

with severe TEAEs was reported in the mirabegron 50 mg group (3/78; 3.8%). The highest proportion of patients with severe study drug-related TEAEs was reported in the 10 + 25 combination group (2/81; 2.5%).

Overall, the 2 most commonly reported TEAEs were dry mouth, reported by 159 (12.2%) patients, and hypertension reported by 118 (9.0%) patients [Table 17]. All events of dry mouth were considered by the investigator to be related to study drug. Overall, 69 of 1306 (5.3%) patients reported study drug-related TEAE of hypertension. There were no clear differences or trends in the proportion of patients with drug-related TEAEs of hypertension across the treatment groups. The proportion of patients who experienced drug-related TEAEs of hypertension ranged from 2/81 (2.5%) in the 10 + 25 combination group to 8/81 (9.9%) in the10 + 50 combination group.

The percentage of patients who experienced drug-related TEAEs (as assessed by the investigator) ranged from 15.2% in the solifenacin 2.5 mg group to 44.4% in the 10 + 50 combination group. Of the 362/1306 (27.7%) patients who experienced a drug-related TEAE, 266 (20.4%) patients experienced at least 1 drug-related TEAE with a maximum severity of mild, 85 (6.5%) patients experienced at least 1 drug-related TEAE with maximum severity of moderate and 11 (0.8%) patients experienced at least 1 drug-related TEAE with a maximum severity of severe. Overall, the 3 most commonly reported study drug-related TEAEs were dry mouth (12.2%), hypertension (5.3%) and constipation (3.1%). Overall, 6 of 1306 (0.5%) patients experienced severe study drug-related events of dry mouth. None of the study drug-related events of hypertension or constipation were considered to be severe in intensity. Details about the number of patients experiencing TEAEs and most common TEAEs, occurring in at least 2% of patients in any treatment arm are summarized ([Table 16] and [Table 17]).

No patients died during the double-blind treatment period. One patient (Patient No. [redacted]) died in the placebo run-in period due to myocardial ischemia.

Overall, 15 patients experienced a total of 18 serious TEAEs. The percentage of patients who experienced serious TEAEs ranged from 0 in the placebo, mirabegron 25 mg and solifenacin 5 mg groups to 2.6% in the mirabegron 50 mg group [Table 18].

Table 16 Number of Patients with TEAEs (SAF)

Category	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Patients with TEAEs, n (%)	32 (39.5)	38 (49.4)	41 (52.6)	32 (40.5)	70 (44.9)	47 (60.3)	69 (46.3)	61 (40.9)	71 (49.3)	67 (43.8)	47 (58.0)	48 (59.3)	79 (51.0)	149 (47.6)	363 (48.0)	623 (47.7)
Patients with drug-related TEAEs†, n (%)	14 (17.3)	20 (26.0)	15 (19.2)	12 (15.2)	49 (31.4)	28 (35.9)	46 (30.9)	37 (24.8)	44 (30.6)	32 (20.9)	29 (35.8)	36 (44.4)	35 (22.6)	89 (28.4)	224 (29.6)	362 (27.7)
Patients with TEAEs leading to death, n (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patients with serious TEAEs, n (%)	0	0	2 (2.6)	1 (1.3)	0	1 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	2 (1.3)	1 (1.2)	1 (1.2)	2 (1.3)	2 (0.6)	11 (1.5)	15 (1.1)
Patients with drug-related serious TEAEs, n (%)	0	0	0	0	0	1 (1.3)	1 (0.7)	0	0	0	0	0	0	1 (0.3)	1 (0.1)	2 (0.2)
Patients with TEAEs leading to discontinuation‡, n (%)	0	1 (1.3)	2 (2.6)	0	1 (0.6)	2 (2.6)	2 (1.3)	1 (0.7)	4 (2.8)	1 (0.7)	1 (1.2)	3 (3.7)	3 (1.9)	3 (1.0)	12 (1.6)	18 (1.4)
Patients with drug-related TEAEs leading to discontinuation, n (%)	0	1 (1.3)	1 (1.3)	0	1 (0.6)	2 (2.6)	1 (0.7)	1 (0.7)	3 (2.1)	0	0	2 (2.5)	2 (1.3)	3 (1.0)	7 (0.9)	12 (0.9)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF)

Adverse events that were summarized were reported after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug.

C: combination (solifenacin + mirabegron); M: mirabegron; S: solifenacin; SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event

† Possible or probable, as assessed by the investigator, or records where relationship was missing

‡ Permanent discontinuation of study drug

Source: Table 12.6.1.1

Table 17 Most Common (≥ 2% in any Treatment Arm) TEAEs (SAF)

MedDRA v12.1 Preferred Term, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Overall	32 (39.5)	38 (49.4)	41 (52.6)	32 (40.5)	70 (44.9)	47 (60.3)	69 (46.3)	61 (40.9)	71 (49.3)	67 (43.8)	47 (58.0)	48 (59.3)	79 (51.0)	149 (47.6)	363 (48.0)	623 (47.7)
Dry mouth	3 (3.7)	2 (2.6)	4 (5.1)	6 (7.6)	18 (11.5)	23 (29.5)	19 (12.8)	13 (8.7)	21 (14.6)	20 (13.1)	16 (19.8)	14 (17.3)	6 (3.9)	47 (15.0)	103 (13.6)	159 (12.2)
Hypertension	7 (8.6)	9 (11.7)	11 (14.1)	8 (10.1)	18 (11.5)	5 (6.4)	11 (7.4)	11 (7.4)	11 (7.6)	9 (5.9)	7 (8.6)	11 (13.6)	20 (12.9)	31 (9.9)	60 (7.9)	118 (9.0)
Nasopharyngitis	2 (2.5)	5 (6.5)	5 (6.4)	5 (6.3)	6 (3.8)	2 (2.6)	4 (2.7)	6 (4.0)	7 (4.9)	6 (3.9)	6 (7.4)	6 (7.4)	10 (6.5)	13 (4.2)	35 (4.6)	60 (4.6)
Constipation	0	0	3 (3.8)	1 (1.3)	3 (1.9)	4 (5.1)	7 (4.7)	6 (4.0)	4 (2.8)	2 (1.3)	6 (7.4)	8 (9.9)	3 (1.9)	8 (2.6)	33 (4.4)	44 (3.4)
Tachycardia	1 (1.2)	3 (3.9)	2 (2.6)	2 (2.5)	6 (3.8)	2 (2.6)	3 (2.0)	7 (4.7)	5 (3.5)	3 (2.0)	4 (4.9)	3 (3.7)	5 (3.2)	10 (3.2)	25 (3.3)	41 (3.1)
Headache	2 (2.5)	3 (3.9)	1 (1.3)	2 (2.5)	4 (2.6)	2 (2.6)	4 (2.7)	3 (2.0)	3 (2.1)	2 (1.3)	3 (3.7)	2 (2.5)	4 (2.6)	8 (2.6)	17 (2.2)	31 (2.4)
Escherichia UTI	2 (2.5)	1 (1.3)	2 (2.6)	1 (1.3)	6 (3.8)	5 (6.4)	3 (2.0)	2 (1.3)	3 (2.1)	4 (2.6)	3 (3.7)	1 (1.2)	3 (1.9)	12 (3.8)	16 (2.1)	33 (2.5)
Influenza	1 (1.2)	1 (1.3)	2 (2.6)	2 (2.5)	3 (1.9)	0	1 (0.7)	3 (2.0)	2 (1.4)	3 (2.0)	0	3 (3.7)	3 (1.9)	5 (1.6)	12 (1.6)	21 (1.6)
Dyspepsia	0	1 (1.3)	0	1 (1.3)	4 (2.6)	3 (3.8)	2 (1.3)	3 (2.0)	1 (0.7)	1 (0.7)	3 (3.7)	1 (1.2)	1 (0.6)	8 (2.6)	11 (1.5)	20 (1.5)
UTI	3 (3.7)	1 (1.3)	2 (2.6)	1 (1.3)	4 (2.6)	5 (6.4)	1 (0.7)	2 (1.3)	2 (1.4)	3 (2.0)	0	3 (3.7)	3 (1.9)	10 (3.2)	11 (1.5)	27(2.1)
Bronchitis	0	1 (1.3)	0	0	0	2 (2.6)	2 (1.3)	4 (2.7)	0	3 (2.0)	0	1 (1.2)	1 (0.6)	2 (0.6)	10 (1.3)	13 (1.0)
Dizziness	0	1 (1.3)	0	1 (1.3)	1 (0.6)	3 (3.8)	5 (3.4)	3 (2.0)	1 (0.7)	0	0	0	1 (0.6)	5 (1.6)	9 (1.2)	15 (1.1)
ECG QT prolonged	1 (1.2)	0	0	0	0	2 (2.6)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.7)	0	4 (4.9)	0	2 (0.6)	9 (1.2)	12 (0.9)
Blood creatinine increased	1 (1.2)	1 (1.3)	1 (1.3)	0	3 (1.9)	1 (1.3)	4 (2.7)	1 (0.7)	1 (0.7)	1 (0.7)	0	1 (1.2)	2 (1.3)	4 (1.3)	8 (1.1)	15(1.1)
Fatigue	1 (1.2)	1 (1.3)	0	0	6 (3.8)	0	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.3)	1 (1.2)	1 (1.2)	1 (0.6)	6 (1.9)	8 (1.1)	16 (1.2)
Dysuria	0	0	0	0	1 (0.6)	0	0	1 (0.7)	2 (1.4)	1 (0.7)	0	3 (3.7)	0	1 (0.3)	7 (0.9)	8 (0.6)
Nausea	0	2 (2.6)	2 (2.6)	0	1 (0.6)	2 (2.6)	2 (1.3)	2 (1.3)	0	1 (0.7)	1 (1.2)	1 (1.2)	4 (2.6)	3 (1.0)	7 (0.9)	14 (1.1)
Somnolence	1 (1.2)	0	1 (1.3)	0	0	0	2 (1.3)	1 (0.7)	1 (0.7)	0	2 (2.5)	1 (1.2)	1 (0.6)	0	7 (0.9)	9 (0.7)
AST increased	0	2 (2.6)	0	0	0	0	1 (0.7)	1 (0.7)	1 (0.7)	0	1 (1.2)	2 (2.5)	2 (1.3)	0	6 (0.8)	8 (0.6)
Upper respiratory tract infection	0	0	2 (2.6)	0	0	1 (1.3)	2 (1.3)	1 (0.7)	0	0	1 (1.2)	2 (2.5)	2 (1.3)	1 (0.3)	6 (0.8)	9 (0.7)
Vomiting	0	0	0	0	1 (0.6)	0	3 (2.0)	2 (1.3)	0	0	0	1 (1.2)	0	1 (0.3)	6 (0.8)	7 (0.5)
ALT increased	0	2 (2.6)	0	0	0	0	1 (0.7)	1 (0.7)	0	0	1 (1.2)	2 (2.5)	2 (1.3)	0	5 (0.7)	7 (0.5)
Residual urine volume increased	0	0	0	1 (1.3)	0	0	1 (0.7)	0	1 (0.7)	1 (0.7)	0	2 (2.5)	0	1 (0.3)	5 (0.7)	6 (0.5)

Table continued on next page

MedDRA v12.1 Preferred Term, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Back pain	0	0	2 (2.6)	1 (1.3)	1 (0.6)	1 (1.3)	1 (0.7)	0	1 (0.7)	2 (1.3)	0	0	2 (1.3)	3 (1.0)	4 (0.5)	9 (0.7)
Cough	1 (1.2)	0	1 (1.3)	0	1 (0.6)	2 (2.6)	0	3 (2.0)	0	1 (0.7)	0	0	1 (0.6)	3 (1.0)	4 (0.5)	9 (0.7)
Pharyngitis	0	0	0	1 (1.3)	1 (0.6)	1 (1.3)	0	3 (2.0)	1 (0.7)	0	0	0	0	3 (1.0)	4 (0.5)	7 (0.5)
UTI bacterial	0	0	1 (1.3)	0	0	0	1 (0.7)	0	1 (0.7)	0	2 (2.5)	0	1 (0.6)	0	4 (0.5)	5 (0.4)
Abdominal pain	0	1 (1.3)	1 (1.3)	0	0	2 (2.6)	1 (0.7)	1 (0.7)	1 (0.7)	0	0	0	2 (1.3)	2 (0.6)	3 (0.4)	7 (0.5)
Abdominal pain lower	0	1 (1.3)	0	0	0	1 (1.3)	0	0	1 (0.7)	0	2 (2.5)	0	1 (0.6)	1 (0.3)	3 (0.4)	5 (0.4)
Abdominal pain upper	1 (1.2)	0	2 (2.6)	0	0	0	0	0	0	0	2 (2.5)	0	2 (1.3)	0	2 (0.3)	5 (0.4)
Diarrhoea	1 (1.2)	1 (1.3)	2 (2.6)	1 (1.3)	2 (1.3)	1 (1.3)	0	0	0	1 (0.7)	0	1 (1.2)	3 (1.9)	4 (1.3)	2 (0.3)	10 (0.8)
Erectile dysfunction	1 (1.2)	0	0	0	0	0	0	0	0	0	0	2 (2.5)	0	0	2 (0.3)	3 (0.2)
Haematuria	0	1 (1.3)	0	0	1 (0.6)	2 (2.6)	0	1 (0.7)	1 (0.7)	0	0	0	1 (0.6)	3 (1.0)	2 (0.3)	6 (0.5)
Conjunctivitis	0	2 (2.6)	0	0	1 (0.6)	0	0	0	0	1 (0.7)	0	0	2 (1.3)	1 (0.3)	1 (0.1)	4 (0.3)
Sinusitis	0	0	2 (2.6)	0	0	0	1 (0.7)	0	0	0	0	0	2 (1.3)	0	1 (0.1)	3 (0.2)
Asthenia	0	2 (2.6)	0	0	0	0	0	0	0	0	0	0	2 (1.3)	0	0	2 (0.2)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF)

TEAEs summarized in this table were reported after the first dose of study drug and no more than 30 days after the last dose. Patients with 1 or more TEAEs within a level of the MedDRA term were counted only once in that level.

Sorting order: Descending in frequency in total combination column by preferred term

ALT: alanine aminotransferase; AST: aspartate aminotransferase; C: combination (solifenacin + mirabegron); ECG: electrocardiogram; M: mirabegron; S: solifenacin; SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event; UTI: urinary tract infection

Source: Table 12.6.1.5

Table 18 Serious TEAEs (SAF)

SOC (MedDRA v12.1) Preferred Term, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Overall	0	0	2 (2.6)	1 (1.3)	0	1 (1.3)	3 (2.0)	2 (1.3)	2 (1.4)	2 (1.3)	1 (1.2)	1 (1.2)	2 (1.3)	2 (0.6)	11 (1.5)	15 (1.1)
Gastrointestinal disorders																
Dysphagia	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.1)	1 (0.1)
Inguinal hernia	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.1)	1 (0.1)
Infections and infestations																
Gastroenteritis	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)
Pyelonephritis	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders																
Intervertebral disc protrusion	0	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.1)	1 (0.1)
Musculoskeletal pain	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)
Muscular weakness	0	0	0	1 (1.3)	0	0	0	0	0	0	0	0	0	1 (0.3)	0	1 (0.1)
Nervous system disorders																
Neuralgia	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	1 (0.1)	1 (0.1)
Paraesthesia	0	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.1)	1 (0.1)
Trigeminal nerve disorder	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	1 (0.1)	1 (0.1)
Ear and labyrinth disorders																
Vertigo	0	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.1)	1 (0.1)
General disorders and administration site conditions																
Fibrosis	0	0	0	0	0	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications																
Foreign body trauma	0	0	0	0	0	0	0	0	0	0	1 (1.2)	0	0	0	1 (0.1)	1 (0.1)
Renal and urinary disorders																
Urinary retention	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)
Surgical and medical procedures																
Abortion induced	0	0	0	0	0	0	0	0	0	0	0	1 (1.2)	0	0	1 (0.1)	1 (0.1)

Table continued on next page

SOC (MedDRA v12.1) Preferred Term, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)	M Total (n=155)	S Total (n=313)	C Total (n=757)	Grand Total (n=1306)
Pregnancy, puerperium and perinatal conditions																
Abortion spontaneous	0	0	1 (1.3)	0	0	0	0	0	0	0	0	0	1 (0.6)	0	0	1 (0.1)
Psychiatric disorders																
Confusional state	0	0	0	0	0	1 (1.3)	0	0	0	0	0	0	0	1 (0.3)	0	1 (0.1)
Reproductive system and breast disorders																
Pelvic pain	0	0	1 (1.3)	0	0	0	0	0	0	0	0	0	1 (0.6)	0	0	1 (0.1)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF)

TEAEs summarized in this table were reported after the first dose of study drug and no more than 30 days after the last dose. Patients with 1 or more TEAEs within a level of the MedDRA term were counted only once in that level.

Sorting order: Descending in frequency in total combination group column by SOC and within that descending order by preferred term.

C: combination (solifenacin + mirabegron); M: mirabegron; S: solifenacin; SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.6

Two serious TEAEs were considered by the investigator to be related to study drug. One patient in the 2.5 + 25 combination group experienced a serious TEAE of urinary retention and 1 patient in the solifenacin 10 mg group experienced a serious TEAE of confusional state. Both patients were discontinued from the study due to these events.

In 18 cases (1.4%), the TEAE led to premature withdrawal from the study [Table 16], 12 of which were considered by the investigator to be treatment-related. The highest rate of withdrawals due to a TEAE was reported in the 10 + 50 combination group (3.7%) and the lowest in the placebo and solifenacin 2.5 mg groups (0). Most TEAEs leading to discontinuation (by preferred term) were unique to a single patient. An ECG finding of prolonged QT resulted in discontinuation of 1 patient in the 5 + 25 combination group and 2 patients in the 10 + 50 combination group.

The frequency of antimuscarinic side effects (such as dry mouth) showed a dose-response relationship in the solifenacin monotherapy groups. With the possible exception of constipation, the frequency of these events was similar with the combination therapy compared to the respective solifenacin monotherapy. However, the low overall frequency of this event and small group sample sizes make it difficult to draw any definitive conclusion. A summary of TEAEs of interest is provided [Table 19].

Table 19 Summary of TEAEs of Special Interest (SAF)

Overall Category Preferred Term/Event, n (%)	Placebo (n=81)	M 25 mg (n=77)	M 50 mg (n=78)	S 2.5 mg (n=79)	S 5 mg (n=156)	S 10 mg (n=78)	S 2.5 mg + M 25 mg (n=149)	S 2.5 mg + M 50 mg (n=149)	S 5 mg + M 25 mg (n=144)	S 5 mg + M 50 mg (n=153)	S 10 mg + M 25 mg (n=81)	S 10 mg + M 50 mg (n=81)
Cardiovascular												
Hypertension	8 (9.9)	9 (11.7)	11 (14.1)	9 (11.4)	20 (12.8)	7 (9.0)	13 (8.7)	11 (7.4)	11 (7.6)	10 (6.5)	7 (8.6)	11 (13.6)
QT prolongation	1 (1.2)	0	0	0	0	2 (2.6)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.7)	0	4 (4.9)
Cardiac arrhythmia	3 (3.7)	4 (5.2)	3 (3.8)	2 (2.5)	7 (4.5)	5 (6.4)	4 (2.7)	12 (8.1)	8 (5.6)	4 (2.6)	6 (7.4)	7 (8.6)
Tachycardia (TEAEs)	5 (6.2)	4 (5.2)	4 (5.1)	3 (3.8)	8 (5.1)	2 (2.6)	6 (4.0)	12 (8.1)	7 (4.9)	4 (2.6)	5 (6.2)	3 (3.7)
Cardiac failure	0	0	0	0	1 (0.6)	0	0	0	0	1 (0.7)	1 (1.2)	0
UTI	7 (8.6)	3 (3.9)	6 (7.7)	2 (2.5)	11 (7.1)	9 (11.5)	8 (5.4)	7 (4.7)	13 (9.0)	8 (5.2)	7 (8.6)	6 (7.4)
Urinary retention	0	0	0	1 (1.3)	0	0	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)	0	2 (2.5)
Acute urinary retention	0	0	0	0	0	0	1 (0.7)	0	0	0	0	0
Seizure	0	0	0	0	0	0	0	0	0	0	0	0
Syncope/postural hypotension/falls	0	1 (1.3)	1 (1.3)	0	2 (1.3)	1 (1.3)	0	2 (1.3)	3 (2.1)	1 (0.7)	1 (1.2)	1 (1.2)
Hypersensitivity	2 (2.5)	5 (6.5)	3 (3.8)	1 (1.3)	9 (5.8)	4 (5.1)	8 (5.4)	7 (4.7)	1 (0.7)	3 (2.0)	1 (1.2)	0
Neoplasm	0	0	0	1 (1.3)	0	1 (1.3)	0	2 (1.3)	0	1 (0.7)	0	0
Glaucoma	0	0	0	0	0	0	0	0	0	0	0	0
Hepatotoxicity	1 (1.2)	3 (3.9)	0	1 (1.3)	0	1 (1.3)	3 (2.0)	4 (2.7)	2 (1.4)	1 (0.7)	1 (1.2)	2 (2.5)
Dry mouth	3 (3.7)	2 (2.6)	4 (5.1)	6 (7.6)	18 (11.5)	23 (29.5)	19 (12.8)	13 (8.7)	21 (14.6)	20 (13.1)	17 (21.0)	14 (17.3)
Blurred vision	0	0	1 (1.3)	0	0	1 (1.3)	1 (0.7)	0	2 (1.4)	2 (1.3)	2 (2.5)	1 (1.2)
Constipation	0	0	3 (3.8)	1 (1.3)	3 (1.9)	4 (5.1)	7 (4.7)	6 (4.0)	4 (2.8)	2 (1.3)	6 (7.4)	8 (9.9)
Dyspepsia	0	1 (1.3)	1 (1.3)	1 (1.3)	4 (2.6)	3 (3.8)	2 (1.3)	3 (2.0)	1 (0.7)	1 (0.7)	3 (3.7)	1 (1.2)

All patients randomized to a double-blind treatment who took at least 1 dose of study drug (SAF)

TEAEs summarized in this table were reported after the first dose of study drug and no more than 30 days after the last dose. Patients with 1 or more TEAEs within a level of the MedDRA term were counted only once in that level.

The preferred terms and lower level terms for each TEAE of interest were either based on a MedDRA SMQ (if available) or on a predefined 'customized' SMQ defined by the Sponsor.

Categories are shown in order of presentation in this section of the clinical study report.

SAF: Safety Analysis Set; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event; UTI: urinary tract infection

Source: Tables 12.6.1.14.2 to 12.6.1.32.2

There were no clinically significant treatment-emergent trends in laboratory safety findings and no pattern or dose-related trend was observed between combination and monotherapy groups.

None of the patients who met the criteria for potentially clinically significant (PCS) liver function values met the criteria for Hy's law and the number of patients with liver abnormalities meeting PCS values was comparable between the treatment groups.

No clear or dose-related differences between combination groups and mirabegron monotherapy were observed in mean change from baseline in SBP and DBP, as recorded in the patient diary or by the standard office device.

Small changes in pulse rate were observed with increasing doses of mirabegron in monotherapy and combination therapy, consistent with what was observed in earlier studies with mirabegron. Based on patient diary assessments, the maximum mean AM pulse rate change from baseline was 0.9 bpm for solifenacin monotherapy (solifenacin 5 mg), 1.5 bpm for mirabegron monotherapy (mirabegron 50 mg) and 2.2 bpm for combination therapy (5 + 50 combination). The maximum mean PM pulse rate change from baseline was 0.0 bpm for solifenacin monotherapy (solifenacin 2.5 mg), 0.2 bpm for mirabegron monotherapy (mirabegron 25 and 50 mg) and 1.6 bpm for combination therapy (2.5 + 50 combination). Based on the measurements using a standard office device, the maximum mean pulse rate change from baseline was 0.9 bpm for solifenacin monotherapy (solifenacin 10 mg), 1.0 bpm for mirabegron monotherapy (mirabegron 50 mg) and 1.5 bpm for combination therapy (5 + 25 combination).

Based on the 12 lead ECG results, the maximum mean heart rate change from baseline was 0.72 bpm for solifenacin monotherapy (solifenacin 5 mg), 2.83 bpm for mirabegron monotherapy (mirabegron 50 mg) and 2.47 bpm for combination therapy (10 + 50 combination). The 12 lead ECG heart rate results are comparable with the pulse rate assessments from the patient diary and office-based measurements.

Small dose-related increases from baseline in QTcF were observed during solifenacin monotherapy treatment; corresponding changes were not observed with mirabegron monotherapy. In the combination groups, the change from baseline in QTcF as well as the categorical outlier analyses showed similar effects compared to the corresponding solifenacin monotherapy groups. No patient had an average QTcF > 500 msec at one visit. QTcF absolute values > 480 msec averaged over 3 ECGs were observed for 1 patient (0.7%) in the 2.5 + 25 combination group and 1 patient (0.7%) in the 5 + 50 combination group. The percentage of patients with QTcF absolute values > 450 msec showed small dose-dependent increases with solifenacin monotherapy; the combination groups showed similar effects as the solifenacin monotherapy groups. The percentage of patients with increases in QTcF ≥ 30 msec was similar in the combination groups compared with the monotherapy treatment groups, except for the 2.5 + 25 combination group.

Of the 12 TEAEs of QTc prolongation that were reported, 6 events were determined by the Sponsor to be true postbaseline QTc interval abnormalities that constituted a prolongation compared to baseline values. Five of these 6 patients also had abnormal screening / baseline QTc intervals, 4 of the 6 patients had postbaseline increases that did not exceed 30 msec and in 2 of the 6 patients the postbaseline increase exceeded 30 msec but was below 60 msec. Overall, most reported TEAEs of QT prolongation were due to one of the following circumstances: 1) single ECGs with normal QTc and no true QT prolongation; 2) patients with clear baseline ECG and QT abnormalities without further deterioration during treatment with solifenacin, mirabegron or combination therapy; and 3) a pattern that suggests random variation with a few scattered outlier values that did not meet thresholds for PCS events.

The mean change from baseline to end of treatment in PVR volume was similar across all treatment arms although the possibility for a dose-response relationship in the combination groups cannot be fully excluded. Nine patients receiving the combination therapy had a PVR ≥ 150 mL at the end of treatment visit; this was reported as an AE for 2 patients. No patient receiving combination treatment had a PVR ≥ 300 mL at the end of treatment. Overall, 6 patients receiving the monotherapy (1 patient who received mirabegron and 5 patients who received solifenacin) had a PVR ≥ 150 mL at the end of treatment. One patient receiving solifenacin monotherapy (2.5 mg) had a PVR ≥ 300 mL at the end of treatment.

CONCLUSIONS:

Primary Efficacy Variable

Proof of concept of combination therapy was demonstrated by the results of the primary efficacy variable of mean volume voided per micturition.

- For all combinations with solifenacin 5 or 10 mg, the adjusted mean change from baseline was statistically significantly greater than with solifenacin 5 mg monotherapy.
- There was an apparent dose-dependent numerical increase in treatment effect with increasing doses of the individual monotherapy components in each combination.
- All active treatment groups, monotherapy or combination treatment, showed greater adjusted mean changes from baseline in the mean volume voided compared with the placebo group. The adjusted mean difference vs placebo was statistically significant for all treatment groups except for mirabegron 25 mg.
- While a dose-response relationship for monotherapy was observed with mirabegron, this was not apparent for solifenacin.

Secondary Efficacy Variables

The conclusions regarding the primary efficacy variable were supported by the results on the variable of micturition frequency per 24 h.

- In mean number of micturitions per 24 h, the adjusted mean change from baseline to end of treatment showed a numerically larger reduction in the 2.5 + 50, 5 + 50, 10 + 25 and 10 + 50 combinations compared with solifenacin 5 mg monotherapy. This was statistically significant for the 5 + 50, 10 + 25 and 10 + 50 combinations.
- Mirabegron 50 mg, solifenacin 5 mg, solifenacin 10 mg and all combination groups showed a numerically larger reduction in the adjusted mean change from baseline to end of treatment in the mean number of micturitions per 24 h compared with the placebo group. The adjusted mean difference vs placebo was statistically significant for the 5 + 50, 10 + 25 and 10 + 50 combinations.

For the key secondary variable of incontinence episode frequency, there are no clear trends across the combination therapy groups with very few groups showing improvements vs solifenacin 5 mg or placebo resulting in inconsistent and unsystematic changes overall.

- In the prespecified nonparametric stratified rank ANCOVA model, only the 5 + 25 combination group showed statistically significant reductions in incontinence episodes vs solifenacin 5 mg. There were no significant differences vs placebo.
- In the prespecified Poisson regression model, the 5 + 25 combination group showed statistically significant reductions in incontinence episodes vs both solifenacin 5 mg and placebo. In addition, the 5 + 50 combination group showed statistically significant reductions vs solifenacin 5 mg.

- The posthoc mixed effect Poisson regression model suggested a statistically significant reduction in the rate of incontinence episodes vs both solifenacin 5 mg and placebo for the 5 + 25 and 5 + 50 combinations.
- However, presumably due to the low number of incontinent patients in this study, their low baseline values, large spontaneous improvement and substantial differences across baseline values, there is too much random variation in the data to discern a clear dose-response pattern.

For the primary endpoint of mean volume voided per micturition and the key secondary endpoint of micturition frequency per 24 h, all the treatment combinations that reached statistical significance vs solifenacin 5 mg for the change from baseline at end of treatment already reached statistical significance by week 4. This indicates that a clinically relevant response to the combination therapy is well-developed by this time.

- Mean volume voided per micturition over time: a dose-dependent increase was observed in all combination groups compared with solifenacin 5 mg and compared with placebo beginning by week 4.
- Mean number of micturitions per 24 h over time: a statistically significant difference for reduction in the mean number of micturitions per 24 h was observed beginning at week 4 for the 5 + 50, 10 + 25 and 10 + 50 combination groups vs solifenacin 5 mg and vs placebo.

The results for combination therapy against urgency endpoints are broadly consistent with those observed for mean volume voided per micturition and mean number of micturitions per 24 h, supporting the advantage of combination therapy vs monotherapy.

- No dose-response relationship was apparent with mirabegron or solifenacin monotherapy or with the combination therapies over time in the mean number of incontinence episodes per 24 h or the number of urgency incontinence episodes over time. Few statistically significant differences for active treatment vs placebo or for combination treatment vs solifenacin 5 mg were noted.
- Beginning at week 2 through the end of treatment, all combination groups except the 2.5 + 25 and 10 + 50 combination groups showed a statistically significant difference in the reduction from baseline in mean number of urgency episodes (grade 3 or 4) compared with solifenacin 5 mg. Few statistically significant differences were noted vs placebo; therefore, the differences vs solifenacin 5 mg should be interpreted with caution.
- At baseline, the mean level of urgency was comparable across the treatment groups. Beginning at week 2 through the end of treatment, 2.5 + 50, 5 + 25, 5 + 50 and 10 + 25 combination groups showed a statistically significant reduction in the mean level of urgency compared with solifenacin 5 mg, with the exception of the 2.5 + 50 combination group at week 8. Few statistically significant differences were noted vs placebo; therefore, the differences vs solifenacin 5 mg should be interpreted with caution.

In all treatment groups, there was a reduction in the mean number of nocturia episodes per 24 h from baseline to the end of treatment. However, there were no discernible trends between treatment arms.

The results of patient reported outcomes on symptom bother, treatment satisfaction and health-related QoL were generally supportive of an efficacy advantage of combination therapy vs monotherapy and consistent with the conclusions made on the primary endpoint.

- For the PPBC assessment, OAB-q Symptom Bother score assessment, TS-VAS, Health-related QoL subscales and total score in the OAB-q all combination groups (with the exception of the 2.5 + 25 combination group for PPBC, Health-related QoL subscales and total score in the OAB-q) showed a greater improvement at the end of treatment in the adjusted mean change from baseline compared with placebo and compared with solifenacin monotherapy.

- In the EQ-5D there were no clear differences between treatment groups in the percentages of patients shifting between response levels.
- In the WPAI: SHP the improvement in change from baseline to end of treatment was generally greater in the active treatment groups compared with placebo. For the parameter of activity impairment, all combination groups except the 2.5 + 25 combination group showed a greater improvement compared with solifenacin 5 mg.

The conclusions regarding the primary efficacy variable were supported by the results of many of the secondary efficacy variables. However, it should be noted that this study was not powered to demonstrate statistical significance of secondary variables. The overall integrated conclusion from the efficacy data is that combination therapy with mirabegron and solifenacin has the potential to provide increased efficacy in the treatment of OAB more than that achievable with either monotherapy alone.

Pharmacokinetics Conclusions

- Mirabegron: Within the dose range of 25 to 50 mg mirabegron once-daily, a more than dose-proportional increase in C_{max}, C_{trough} and AUC_{last} was observed. The C_{max} was observed at a mean t_{max} of approximately 3 h, while the PTR amounted to approximately 3. No consistent effect of solifenacin on the pharmacokinetics of mirabegron was observed.
- Solifenacin: Within the dose range of 2.5 to 10 mg solifenacin, a close to dose-proportional increase in C_{max}, C_{trough} and AUC_{last} was observed. The C_{max} was observed at a mean t_{max} of approximately 5 h, while the PTR amounted to approximately 1.4. No consistent effect of mirabegron on the pharmacokinetics of solifenacin was observed.

Safety Conclusions

Based on the overall results of this study, combination therapy with mirabegron at doses of 25 and 50 mg and solifenacin at doses of 2.5, 5 and 10 mg was safe and well tolerated. There were no new safety signals of note resulting from combination treatment.

- In general and for the 2 most commonly reported study drug-related TEAEs of dry mouth and hypertension, the AE frequency data did not indicate an increase above monotherapy levels with the combination therapy.
- The frequency of serious TEAEs was low (between 0% and 2.6% in each treatment group) and withdrawal from the study due to TEAEs was infrequent (1.4 %). The highest rate was reported in the 10 + 50 combination group (3.7%) with no significant difference between treatment groups.
- The frequency of antimuscarinic side effects (such as dry mouth) showed a dose-response relationship in the solifenacin monotherapy groups, and was generally similar for combination therapy compared to the respective solifenacin monotherapy doses. While there was a slightly increased frequency of constipation with combination therapy, the low overall frequency of this event and small sample sizes make it difficult to draw any definitive conclusion at this time.
- The cardiovascular safety profile of combination therapy appears to be unchanged from the respective monotherapies.
    - No clear or dose-related differences between combination groups and mirabegron monotherapy were observed in mean change from baseline in SBP and DBP. Consistent with previous data, mirabegron monotherapy showed small dose-related increases from baseline in SBP.

  - There was no evidence of an increase in pulse rate in combination groups vs mirabegron monotherapy. Consistent with previous data, mirabegron monotherapy showed small dose-related increases from baseline in pulse rate.
  - In the combination groups, the change from baseline in QTcF as well as the categorical outlier analyses showed comparable effects to solifenacin monotherapy. Small dose-related increases from baseline in QTcF were observed with solifenacin monotherapy (consistent with previous findings), whereas mirabegron did not appear to affect QTcF.
- No trend in the frequency of notable shifts in PVR volume across treatment groups was observed, although a dose response for the mean PVR change from baseline could not be excluded. These data suggest that combination therapy is unlikely to pose a higher risk of urinary retention.
- There were no clinically significant treatment-emergent trends in laboratory safety findings and no pattern or dose-related trend was observed between combination and monotherapy groups.

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