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SYNOPSIS

Title of Study: A Double-Blind, Randomized, Parallel Group, Multi-Centre Study to Evaluate the Efficacy and Safety of Mirabegron Compared to Solifenacin in Subjects with Overactive Bladder (OAB) Treated with Antimuscarinics and Dissatisfied due to Lack of Efficacy

Investigator/Coordinating Investigator:

The Coordinating Investigators were Prof. Dr. [redacted], [redacted], Austria and Dr. [redacted] Spain.

Study Centers:

This was a multi-center study performed in 232 centers in 33 countries across Eastern Europe, Western Europe, Canada and Middle East.

Publication (reference):

Not applicable.

Study Period:

Date of first enrollment (Study initiation date): 12 June 2012

Date of last evaluation (Study completion date): 24 April 2013

Phase of Development: Phase 3b

Objectives:

The primary objective of the study was to assess the efficacy of mirabegron 50 mg versus solifenacin 5 mg in the treatment of patients with OAB who were dissatisfied with their treatment due to lack of efficacy.

The secondary objective of the study was to assess the safety and tolerability of mirabegron 50 mg versus solifenacin 5 mg in the treatment of patients with OAB who were dissatisfied with their treatment due to lack of efficacy.

Methodology:

This was a randomized, multi-center, multi-national Phase 3b parallel-group study with a single-blind placebo run-in period of 2 weeks, followed by a randomized, double-blind treatment period of 12 weeks, to evaluate the efficacy and safety of mirabegron compared to a commonly used antimuscarinic treatment, solifenacin, in a population of patients who were dissatisfied with their previous antimuscarinic due to lack of efficacy, provided that their previous antimuscarinic was not solifenacin. Patients who were dissatisfied with their previous antimuscarinic treatment solely or primarily due to tolerability issues were not eligible for this study.

Upon passing screening, patients were enrolled into a 2-week, single-blind, placebo run-in period. Patients completed a daily diary (including 3 consecutive days prior to the randomization visit for micturition and incontinence) to establish baseline data.

Patients who satisfied all selection criteria at the end of the placebo run-in period (Visit 2) were randomized 1:1 to receive mirabegron 50 mg or solifenacin 5 mg once daily for 12 weeks.

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Patients visited the study site at screening (within 2 weeks of the start of the single-blind placebo run-in period; Visit 1), at the end of the run-in period (Visit 2; Week 0), and after 4 (Visit 3), 8 (Visit 4) and 12 weeks (Visit 5, end-of-treatment visit) in the double-blind treatment period.

Number of Patients (Planned, Enrolled and Analyzed):

Approximately 1992 patients were to be screened to achieve 1692 randomized (846 in each group) and 1436 evaluable patients.

A total of 2586 patients were screened, including 25 patients who were re-screened after treatment of urinary tract infection. Of the 2586 patients, 2487 patients took ≥ 1 dose of single-blind run-in study drug and of these, 1887 patients were randomized (943 to mirabegron 50 mg and 944 to solifenacin 5 mg).

- The Full Analysis Set (FAS) consisted of 1833 randomized patients who took ≥ 1 dose of double-blind study drug and who recorded ≥ 1 micturition measurement in the baseline diary and ≥ 1 micturition measurement in a post-baseline diary.
- The Full Analysis Set-Incontinence (FAS-I) consisted of 818 FAS patients with ≥ 1 incontinence episode at baseline.
- The Per Protocol Set (PPS) included 1719 FAS patients who had completed the study with no major protocol violations which could impact the primary efficacy endpoint of micturitions.
- The Per Protocol Set-Incontinence (PPS-I) consisted of 755 PPS patients with ≥ 1 incontinence episode at baseline.
- The Safety Analysis Set (SAF) consisted of 1870 randomized patients who received ≥ 1 dose of double-blind study drug.

Diagnosis and Main Criteria for Inclusion:

Eligible patients were men and women, 18 years of age and older, who had symptoms of OAB for ≥ 3 months prior to study entry, who were being treated with antimuscarinics at study entry or had received treatment with ≥ 1 antimuscarinic in the past, and who were dissatisfied with their last antimuscarinic treatment due to lack of efficacy (non-responders), as determined by the patient using a Treatment Satisfaction-Likert Scale, provided that their previous last antimuscarinic was not solifenacin. Patients who were dissatisfied with their previous antimuscarinic treatment solely or primarily due to tolerability issues were not eligible for this study. Eligible patients had been treated with their last antimuscarinic for ≥ 4 weeks and had taken it within 6 months prior to the screening visit. At randomization, patients were eligible if they had experienced ≥ 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary, and a micturition frequency of on average ≥ 8 times per 24-hour period during the 3-day micturition diary period. Patients who had urgency urinary incontinence or mixed urinary incontinence with urgency incontinence being the predominant complaint as determined by the clinician were also considered for this study. Patients with stress urinary incontinence or mixed urinary incontinence with stress incontinence being the predominant complaint were not allowed to participate in the study.

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

Mirabegron 50 mg Oral Controlled Absorption System (OCAS) modified release tablets.
Batch number: [redacted].

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

- Placebo run-in period of 2 weeks.
- Randomized treatment period of 12 weeks.

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

Solifenacin marketed 5 mg tablets. Batch number: [redacted]
Placebo tablets matching mirabegron OCAS tablets. Batch number: [redacted].
Placebo tablets matching solifenacin tablets. Batch number: [redacted].

Criteria for Evaluation:

The primary efficacy variable was the change from baseline to the final visit in the mean number of micturitions per 24 hours, based on a 3-day micturition diary.

The key secondary variable was the proportion of patients reporting ≥ 1 treatment-emergent adverse event (TEAE) of dry mouth, constipation and/or blurred vision during the double-blind treatment period.

Additional secondary efficacy variables, derived from the 3-day micturition diary, were:

- Change from baseline in mean number of micturitions per 24 hours after 4, 8 and 12 weeks of treatment
- Number of incontinence episodes after 4, 8 and 12 weeks of treatment and at the final visit
- Change from baseline in mean number of incontinence episodes per 24 hours after 4, 8 and 12 weeks of treatment
- Number of urgency incontinence episodes after 4, 8 and 12 weeks of treatment and at the final visit
- Change from baseline in mean number of urgency incontinence episodes per 24 hours after 4, 8 and 12 weeks of treatment
- Change from baseline in mean number of urgency episodes (grade 3 or 4) per 24 hours after 4, 8 and 12 weeks of treatment and at the final visit
- Change from baseline in mean level of urgency after 4, 8 and 12 weeks of treatment and at the final visit
- Number of pads used after 4, 8 and 12 weeks of treatment and at the final visit
- Change from baseline in mean number of pads used per 24 hours after 4, 8 and 12 weeks of treatment
- Number of nocturia episodes after 4, 8 and 12 weeks of treatment and at the final visit
- Change from baseline in mean number of nocturia episodes per 24 hours after 4, 8 and 12 weeks of treatment

The following responder analyses were performed at Weeks 4, 8, 12 and the final visit:

- Responder for normalization of micturitions, defined as a FAS/PPS patient who had ≥ 8 micturitions at baseline and had < 8 micturitions per 24 hours post-baseline, where change from baseline was < 0.
- Responder for zero incontinence episodes, defined as a FAS-I/PPS-I patient who was incontinent at baseline and had 0 incontinence episodes reported post-baseline.
- Responder for 50% reduction in incontinence episodes, defined as a FAS-I/PPS-I patient who was incontinent at baseline and had ≥ 50% decrease from baseline in mean number of incontinence episodes per 24 hours

Additional secondary efficacy variables (not derived from the 3-day micturition diary) which were assessed at Weeks 4, 8, 12, and at the final visit were:

- Change from baseline in scores as assessed by the European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire
- Change from baseline in symptom bother and Health-Related Quality of Life (HRQoL) scores as assessed by the OAB-questionnaire (OAB-q)
- Change from baseline in Patient Perception of Bladder Condition (PPBC)

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Additional secondary efficacy variables (not derived from the 3-day micturition diary) which were assessed at Week 12 and at the final visit were:

- Change from baseline in the patient's assessment of Treatment Satisfaction-Visual Analogue Scale (TS-VAS)
- Change from baseline in the patient's assessment of Treatment Satisfaction Questionnaire-Likert Scale

The following responder analyses were performed at Week 12 and at the final visit for FAS and PPS:

- Responders in symptom bother or HRQoL scales as assessed by the OAB-q: ≥ 10 points improvement in OAB-q from baseline (based on the transformed scores)
- Improvement of Treatment Satisfaction Questionnaire-Likert Scale: ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5 and 6-item improvement from baseline
- Improvement of PPBC: ≥ 1 point improvement from baseline
- Major improvement of PPBC: ≥ 2 points improvement from baseline

Safety was assessed from the proportion of patients with ≥ 1 TEAE of dry mouth, constipation or blurred vision during the double-blind treatment period (key secondary variable), the incidence and severity of (serious) adverse events (AEs), change from baseline in clinical laboratory evaluations (biochemistry, hematology and urinalysis), vital signs, and electrocardiogram parameters. Physical examination and a bladder scan at screening to assess post-void residual (PVR) volume were also performed.

Statistical Methods:

Efficacy

Seven population sets were used for analyses in this study.

The Run-in Period Analysis Set (RPAS) consisted of all patients who took≥ 1 dose of single-blind run-in study drug (placebo) and was used to summarize the disposition of patients who entered the run-in period.

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

The Full Analysis Set (FAS) consisted of all randomized patients who took≥ 1 dose of double-blind study drug and who recorded ≥ 1 micturition measurement in the baseline diary and≥ 1 micturition measurement in a post-baseline diary. 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. The FAS was regarded as the main analysis set for all secondary efficacy endpoints. For the primary endpoint testing of non-inferiority, it was regarded as secondary to PPS. 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 Full Analysis Set-Incontinence (FAS-I) consisted of all FAS patients with ≥ 1 incontinence episode at baseline. The FAS-I 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-I who had ≥ 1 urgency (grade 3 or 4) incontinence episode in the baseline diary. The FAS-I was regarded as the main analysis set for all secondary efficacy endpoints based on incontinence episodes.

The Per Protocol Set (PPS) included all FAS patients who had completed the study with no major protocol violations which could impact the primary efficacy endpoint of micturitions. The PPS was used for demographic and baseline OAB characteristics and efficacy analyses. The PPS was regarded as the main

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analysis set for the primary endpoint testing non-inferiority. For all other efficacy endpoints, the PPS was regarded as secondary to the FAS.

The Per Protocol Set-Incontinence (PPS-I) consisted of all PPS patients with ≥ 1 incontinence episode at baseline. The PPS-I was used for demographic and baseline OAB characteristics and efficacy analyses on incontinence episodes and was regarded as secondary to FAS-I.

The Safety Analysis Set (SAF) consisted of all randomized patients who received ≥ 1 dose of double-blind study medication and was used for summaries of the demographic and baseline OAB characteristics and all safety analyses.

The primary efficacy analysis of non-inferiority was performed on the PPS. An analysis of covariance (ANCOVA) model was used for change from baseline to the final visit in the number of micturitions per 24 hours including treatment group and randomization stratification factors (sex, age group [<65years, ≥ 65 years], number of prior antimuscarinics [1, ≥ 2], and geographic region [Canada, Eastern Europe, Middle East, and Western Europe]) as fixed factors and baseline number of micturitions per 24 hours as a covariate. Within the framework on this ANCOVA model, point estimates and 95% CIs for the mean change from baseline within each treatment group as well as for the difference in mean change from baseline between solifenacin and mirabegron treatment groups were calculated. If the resulting lower limit of the 2-sided 95% CI for difference in mean change from baseline between solifenacin and mirabegron was > -0.20, then non-inferiority was concluded. This analysis was repeated for the FAS to examine the robustness of the conclusion.

Analysis of the key secondary variable (proportion of patients reporting ≥ 1TEAE of dry mouth, constipation and/or blurred vision during the double-blind treatment period) was performed on the SAF. Descriptive statistics were presented by treatment group and proportions were analyzed using a logistic regression model with treatment group and randomization stratification factors (sex, age group, number of prior antimuscarinics, and geographic region) as factors. The number and percentage of patients who reported ≥ 1 of these TEAEs by treatment group and the difference in the percentage of solifenacin and mirabegron were summarized using point estimates and 2-sided 95% CIs based on normal approximation. The p-value and 95% CI for the odds ratio for the proportion of patients with ≥ 1of these TEAEs for solifenacin vs mirabegron were presented.

Secondary efficacy variables were analyzed descriptively and the superiority of mirabegron over solifenacin for these variables was investigated. Variables for which a continuous change from baseline could be calculated were analyzed using the same ANCOVA model which was used to assess the primary endpoint for both the FAS and PPS. Responder analyses used the same logistic regression model used for the analysis of the key secondary variable.

Secondary efficacy variables based on count data (i.e. incontinence episodes, urgency incontinence episodes, number of pads, and nocturia episodes) were analyzed in 2 ways for the FAS/FAS-I and PPS/PPS-I, respectively. The primary analysis method for these variables was a mixed effects Poisson regression model, where the number of episodes reported during the 3-day micturition diary was treated as a count variable. This model included treatment group, randomization stratification factors (sex, age, number of prior antimuscarinics, and geographic region) and baseline number of episodes. An offset term for the log of the number of valid diary days within the 3-day period was included. The rate ratio (RR) for mirabegron over solifenacin as well as the corresponding 2-sided 95% CIs of the RR and p-value were derived. As a sensitivity analysis, the change from baseline to final visit in the mean number of episodes per 24 hours was analyzed. For variables which did not appear to be normally distributed (i.e. incontinence episodes, urgency incontinence episodes), a stratified rank ANCOVA model was used, where the response variable was the standardized ranks on change from baseline to final visit with baseline standardized ranks, sex, age and number of prior antimuscarinics as covariates and geographic region as a stratum. LS mean estimates and two-sided 95% CIs for mean changes from baseline within each treatment group, as well as the mean change from baseline in the difference between treatment

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groups was derived from the corresponding ANCOVA model with treatment group and randomization stratification factors as fixed factors and baseline number of episodes per 24 hours as a covariate. For variables which appeared to be normally distributed (i.e. number of pads and nocturia episodes), change from baseline to final visit was analyzed using the same ANCOVA model which was used to assess the primary endpoint.

All statistical comparisons were made using 2-sided tests at the 0.05 significance level. 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.

Safety

All safety variables were analyzed for the SAF. Adverse events were summarized separately for the run-in period and for the double-blind treatment period. The number and percentage of patients with TEAEs, classified by System Organ Class (SOC) and Preferred Term (PT) were summarized for each treatment group and overall. Similar summaries were provided for drug-related TEAEs, serious TEAEs, TEAEs that led to study discontinuation, AEs of interest and most common TEAEs (reported in ≥ 2% of patients in a treatment group). For AEs of interest also 95% CI next to the absolute and relative frequencies of patients was provided.

Laboratory test results, vital signs (systolic and diastolic blood pressure, and pulse rate) and electrocardiogram (ECG) interpretation were summarized descriptively, including changes from baseline, by treatment group. Changes from baseline to final visit for vital signs were analyzed using the same ANCOVA model which was used to assess the primary endpoint.

Summary of Results/Conclusions:

Population:

A total of 1887 patients were randomized of whom 1870 patients took ≥ 1 dose of double-blind study drug (SAF) and 1833 patients took ≥ 1 dose of double-blind study drug and recorded ≥ 1 micturition measurement in the baseline diary and ≥ 1 micturition measurement in a post-baseline diary (FAS) [Figure 1].

Six-hundred patients discontinued before randomization (Figure 1). The majority of these patients discontinued because they did not fulfill the inclusion or exclusion criteria (n = 532; 88.7%). Other reasons included withdrawal (by the patient) (n = 47; 7.8%), AEs (n = 13; 2.2%), 'other' (n = 7; 1.2%), and patient lost to follow-up (n = 1; 0.2%). A total of 131 patients discontinued after randomization, including 17 patients who were erroneously randomized and who did not receive any double-blind study drug. The SAF thus consisted of 1870 patients, of whom 114 (6.1%) discontinued during the double-blind study period. The main reasons for discontinuation were withdrawal (by the patient) (n = 45; 2.4%), AEs (n = 30; 1.6%) and protocol violation (n = 24; 1.3%). There were no relevant differences between the treatment groups.

Demographics and OAB-related history for the SAF were well-matched between treatment groups [Table 1]. The majority of the patients were female (76%). The overall mean age was 57.0 years (range: 18-88 years); approximately one-third of patients were ≥ 65 years (33.6%) and 8.4% of patients were ≥ 75 years. Most patients were of Caucasian origin (99.1%); the majority were from Eastern (61.0%) or Western Europe (30.9%). The overall mean BMI was 27.6 kg/m^2 (range: 16-54 kg/m^2); about one-third of patients had a BMI of < 25 kg/m^2 (33.9%) and 28.6% of patients had a BMI of ≥ 30 kg/m^2. Similar results were found for the FAS and PPS.

Overall, patients in the SAF reported a mean number of 11.5 micturitions, 2.1 incontinence, 2.0 urgency incontinence and 2.3 nocturia episodes per 24 hours. The micturitions were mainly of moderate (average ≥ 10 to ≤ 15 micturitions per 24 hours; 60.6%) or mild (average ≥ 8 to < 10 micturitions per 24 hours; 30.2%) intensity. Incontinence was primarily rated as mild (baseline average ≥ 0 to ≤ 2 incontinence episodes per 24 hours; 68.2%). The mean number of urgency episodes (grade 3 or grade 4) per 24 hours was 7.8, and the mean level of

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urgency was rated as 2.6 (i.e., moderate to severe urgency). Patients used a mean number of 3.2 pads per 24 hours. Results were similar for both treatment groups. Similar results were observed for the FAS and the PPS.

For the SAF, the mean PVR volume in the mirabegron 50 mg group (19.5 mL [range: 0-188 mL]) was similar to the solifenacin 5 mg group (18.6 mL [range: 0-182 mL]).

The mean treatment duration in the SAF was 81.3 days and the median duration in the SAF was 84 days (range: 1-113 days). There were no differences between treatment groups. Almost all patients (> 95%) were treated for 56 days or longer and more than 70% of patients were treated for 84 days or longer [Table 2].

Efficacy Results:

Primary Efficacy Variable

Primary Analysis

The primary analysis of non-inferiority was performed on the PPS, using an ANCOVA model including treatment group and randomization stratification factors (gender, age group, number of prior antimuscarinics and geographic region) as fixed factors and baseline number of micturitions per 24 hours as a covariate. If the resulting lower limit of the 2-sided 95% CI for the difference in mean change from baseline between solifenacin 5 mg and mirabegron 50 mg was > -0.20, then non-inferiority would be concluded.

A summary of the change from baseline to the final visit in the mean number of micturitions per 24 hours for the PPS is presented in Table 3. Both treatment groups demonstrated a clinically meaningful improvement, i.e., an adjusted mean decrease of 2.95 micturitions per 24 hours from baseline to the final visit in the mirabegron 50 mg group, and an adjusted mean decrease of 3.13 micturitions per 24 hours from baseline to the final visit in the solifenacin 5 mg group. The adjusted mean (SE) difference in the change from baseline to the final visit between solifenacin 5 mg and mirabegron 50 mg was -0.18 (0.124). The corresponding 95% CI was -0.42, 0.06. As the lower limit of the 95% CI was not > -0.20, non-inferiority was not demonstrated. However, the difference between the groups was also not large enough to conclude that mirabegron 50 mg was inferior to solifenacin 5 mg.

Secondary Analyses

The primary analysis for the PPS was repeated for the FAS [Table 4]. The adjusted mean (SE) difference in the change from baseline to the final visit for the mean number of micturitions per 24 hours between solifenacin 5 mg and mirabegron 50 mg was -0.20 (0.124). The corresponding 95% CI was -0.44, 0.05. As the lower limit of the 95% CI was not > -0.20, non-inferiority was not demonstrated. Similar results were found at Week 4 and Week 8 for FAS and PPS.

Key Secondary Variable

There was a statistically significant difference (P = 0.03) between the treatment groups in favor of mirabegron with respect to the percentage of patients with dry mouth, constipation or blurred vision (SAF). The incidence of these events was 7.4% in the solifenacin 5 mg group and 5.0% in the mirabegron 50 mg group, i.e., a 2.4% difference. The effect was mainly driven by a higher percentage of patients with dry mouth [Table 5]. The odds ratio (95% CI) was 1.53 (1.04, 2.25), i.e., the chance of having an of dry mouth, constipation, and/or blurred vision was approximately 1.5 times higher for a patient receiving solifenacin 5 mg than for a patient receiving mirabegron 50 mg.

Secondary Efficacy Variables – Micturition Diary

Both treatment groups demonstrated clinically meaningful improvements from baseline to the final visit in the mean number of incontinence episodes and urgency incontinence episodes reported during the 3-day micturition

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diary period in the FAS-I population, and for the mean number of nocturia episodes and number of pads used during the 3-day diary period for the FAS population [Table 6]. There were also no statistically significant differences between the 2 treatments at the other time points.

Results of the non-parametric stratified rank ANCOVA showed non-significant differences between the treatment groups for the baseline-adjusted mean reduction in the number of incontinence episodes and urgency incontinence episodes per 24 hours at the final visit in the FAS-I. Similar conclusions were found for ANCOVA results for urgency episodes (grade 3 or 4), number of pads used and nocturia episodes per 24 hours at the final visit in the FAS [Table 7]. In the FAS, the baseline-adjusted mean reduction in the mean level of urgency at the final visit was similar between the treatment groups. For urgency episodes (grade 3 or 4) a statistically significant result in favor of solifenacin 5 mg ($P = 0.027$) was observed only at Week 8, the results at Week 4 and Week 12 were not statistically significant. For the other variables no statistically significant treatment differences were observed at any time point. Similar results were observed for the PPS-I or PPS, as applicable.

Responder Analyses -Incontinence Episodes

In the FAS-I, the percentage of responders achieving a clinically meaningful improvement with at least a 50% decrease in the mean number of incontinence episodes at the final visit was high and similar between treatment groups, with respectively 85.1% and 88.1% of the mirabegron 50 mg and solifenacin 5 mg patients achieving a treatment response. The odds ratio (95% CI) for solifenacin 5 mg versus mirabegron 50 mg was 1.25 (0.82, 1.90) and not statistically significant (P = 0.29). The results for the PPS-I were similar.

In the FAS-I, the percentage of patients achieving a clinically meaningful response with zero incontinence episodes at the final visit was high and similar in both treatment groups with respectively 67.3% and 68.5% of the mirabegron 50 mg and solifenacin 5 mg patients achieving a treatment response. The odds ratio (95% CI) for solifenacin 5 mg versus mirabegron 50 mg was 1.02 (0.73, 1.42) and not statistically significant (P = 0.90). The results for the PPS-I were similar.

Secondary Efficacy Variables – HRQoL

Both mirabegron 50 mg and solifenacin 5 mg treatment groups showed clinically meaningful improvements in HRQoL assessments from baseline to the final visit. Statistically significant but non-clinically significant differences in favor of solifenacin were observed for OAB-q symptom bother and concern subscale scores, the TS-VAS, the TS-Likert and the PPBC. No statistically significant difference was seen between the treatment groups for OAB-q subscales coping, social interaction and sleep, and for the HRQoL total score.

Between 29% and 39% of patients improved on the EQ-5D-5L questionnaire dimensions mobility, usual activities, pain/discomfort and anxiety/depression. The improvement in self-care was lower (15%), but most of the patients reported no problem with self-care at baseline, so the room for improvement was smaller. The percentage of patients with improvement was comparable between the treatment groups for anxiety/depression, but numerically slightly higher for patients in the solifenacin 5 mg group for the other 4 dimensions.

Safety Results:

Overall, 59 (6.3%) patients in the mirabegron 50 mg group and 69 (7.4%) patients in the solifenacin 5 mg group reported ≥ 1 AEs during the placebo run-in period. The most commonly reported AEs during the placebo run-in period were dry mouth (0.9% of patients overall), headache (0.8%), and nasopharyngitis (0.6%).

The overall incidence of AEs during the double-blind treatment period was 29.7% (556 patients), with no clinically relevant difference between the mirabegron 50 mg group (274 patients; 29.3%) and solifenacin 5 mg group (282 patients; 30.2%) [Table 8]. AEs reported in ≥ 2% of patients in each treatment group were dry mouth [3.1% of patients in the mirabegron 50 mg group and 5.8% of patients in the solifenacin 5 mg group],

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constipation [2.2% and 2.5%, respectively], and nervous system disorders (headache [3.0% and 2.4%, respectively]) [Table 9].

AEs that were considered related to treatment by the investigator were reported for 239 (12.8%) patients overall. The incidence of treatment-related AEs in the mirabegron 50 mg group (104 patients; 11.1%) was lower compared to the solifenacin 5 mg group (135 patients; 14.5%) [Table 8]. The most commonly reported treatment-related AEs (reported in ≥ 2.0% of patients in any treatment group) were dry mouth (3.1% of patients in the mirabegron 50 mg group and 5.6% of patients in the solifenacin 5 mg group) and constipation (1.7% and 2.2%, respectively).

Most AEs were of mild or moderate intensity. There were 49 AEs of severe intensity (30 in the mirabegron 50 mg group and 19 in the solifenacin 5 mg group), and 20 of these events (12 in the mirabegron 50 mg group and 8 in the solifenacin 5 mg group) were considered related to treatment by the investigator. Treatment-related AEs of severe intensity that were reported in more than 1 patient overall were headache and dry mouth (3 patients each).

There were no deaths during the study.

Fourteen (1.5%) patients in the mirabegron 50 mg group and 13 (1.4%) patients in the solifenacin 5 mg group reported a total of 36 AEs that were considered serious. Thirteen of these events (4 patients [9 events] in the mirabegron 50 mg group and 4 patients [4 events] in the solifenacin 5 mg group) were considered related to treatment by the investigator. SAEs reported by more than 1 patient overall were pneumonia (3 patients) and abdominal pain upper and vertigo (2 patients each). Abdominal pain upper was the only treatment-related SAE that was reported in more than 1 patient overall (1 patient in each treatment group).

Thirteen (1.4%) patients in the mirabegron 50 mg group and 17 (1.8%) patients in the solifenacin 5 mg group discontinued from the study due to AEs. For 9 (1.0%) and 14 (1.5%) patients, respectively, the AEs leading to discontinuation were considered related to treatment by the investigator. AEs leading to discontinuation reported by more than 1 patient overall were headache (4 patients), hypertension (3 patients) and abdominal pain upper, constipation, nausea and rash (2 patients each).

The SAF population was predominantly female (76.0%). The incidence of AEs was higher in female patients (442 of 1421 patients; 31.1%) than in male patients (114 of 449 patients; 25.4%). This was mainly driven by more female patients reporting infections and infestations AEs, most commonly influenza and urinary tract infection. There were no clinically relevant differences between the mirabegron 50 mg and solifenacin 5 mg groups.

Approximately two thirds of the SAF population was < 65 years (66.4%). The incidence of AEs was comparable in both age groups: 374 of 1241 patients (30.1%) < 65 years and 182 of 629 patients (28.9%) aged ≥ 65 years reported at least 1 AE. There were also no clinically relevant differences between the mirabegron 50 mg and solifenacin 5 mg groups.

The incidence of each of the AEs of special interest was low (< 4.0%), with no clinically relevant differences between treatment groups [Table 10].

There were no clear or consistent differences between treatment groups in changes from baseline to the end of the study in vital signs, laboratory parameters or ECG.

CONCLUSIONS:

Patients were eligible for this study if the primary or sole reason for dissatisfaction with previous antimuscarinic treatment was due to lack of efficacy. Therefore, patients who were able to tolerate their previous antimuscarinic treatment were included, which may explain the apparent underreporting of tolerability issues

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Name of Finished Product: Betmiga®		
Name of Active Ingredient: Mirabegron		

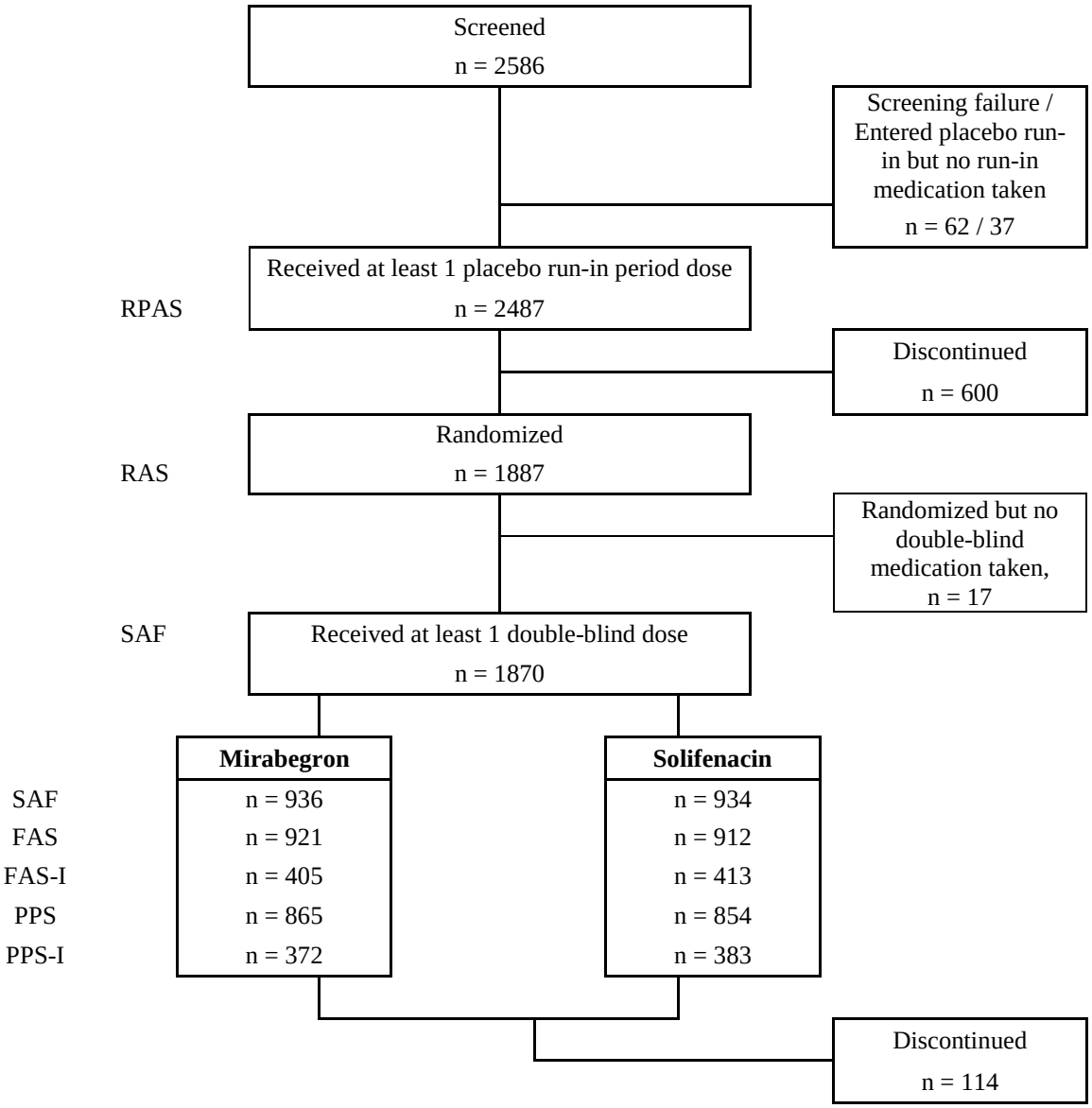
for solifenacin in this study. Furthermore, the treatment response assumptions for this study were based on a post hoc analysis from a pivotal mirabegron phase III study which showed a higher treatment response for mirabegron than tolterodine for patients dissatisfied with prior antimuscarinic treatment. Given that solifenacin performed better than assumed, it is likely that solifenacin may have better efficacy than tolterodine. The primary objective of this study for demonstrating non-inferiority of mirabegron 50 mg versus solifenacin 5 mg for reduction in micturition frequency in patients who were dissatisfied with previous antimuscarinic treatment due to lack of efficacy was not met. Both OAB medications demonstrated improvement from baseline to the end of treatment for key OAB symptoms, utilizing objective and subjective outcome measures, with little clinically relevant differences between treatment groups. Clinically meaningful improvements in HRQoL and treatment satisfaction were seen with both mirabegron 50 mg and solifenacin 5 mg, with statistically but non-clinically significant differences in favor of solifenacin 5 mg for HRQoL outcome measures, including OAB-q symptom bother and concern subscale score, TS-VAS, treatment satisfaction questionnaire-Likert scale, and PPBC. It is important to note that a substantial proportion of wet OAB patients in both treatment groups reported no incontinence episodes by the end of treatment, and the differences between treatment groups were small and not statistically significantly different.

The percentage of AEs of dry mouth, constipation and/or blurred vision was higher with solifenacin 5 mg than with mirabegron 50 mg. Patients were eligible for this study if they were dissatisfied with their previous antimuscarinic solely or primarily due to lack of efficacy. This may explain why patients generally were able to tolerate commonly experienced antimuscarinic side effects e.g., dry mouth while receiving solifenacin 5 mg and why there was a lower percentage reporting of adverse events in this study compared to previous OAB trials. Nevertheless, the good safety and tolerability profiles for mirabegron 50 mg and solifenacin 5 mg were confirmed in this study.

Date of Report:

25 March 2014

Figure 1 Patient Disposition



FAS: Full Analysis Set; FAS-I: FAS-Incontinence Set; PPS: Per Protocol Set; PPS-I: PPS-Incontinence set: RAS: Randomized Analysis Set: RPAS: Run-In Period Analysis Set; SAF: Safety Analysis Set.

Source: Tables 12.1.1.1 and 12.1.1.2

Table 1 Baseline Demographics and Overactive Bladder-Related History (SAF)

	Mirabegron 50 mg (N = 936)	**Solifenacin 5 mg (N = 934)**	**Total (N = 1870)**
Gender, n (%)			
Female	712 (76.1%)	709 (75.9%)	1421 (76.0%)
Male	224 (23.9%)	225 (24.1%)	449 (24.0%)
Age (years)			
Mean (SD)	56.7 (14.25)	57.4 (13.60)	57.0 (13.93)
Median (Min, Max)	59.0 (18, 88)	60.0 (18, 87)	59.0 (18, 88)
Age ≥ 65 years, n (%)	315 (33.7%)	314 (33.6%)	629 (33.6%)
Age ≥ 75 years, n (%)	83 (8.9%)	75 (8.0%)	158 (8.4%)
Geographic region, n (%)			
Canada	30 (3.2%)	33 (3.5%)	63 (3.4%)
Eastern Europe	568 (60.7%)	573 (61.3%)	1141 (61.0%)
Middle East	45 (4.8%)	43 (4.6%)	88 (4.7%)
Western Europe	293 (31.3%)	285 (30.5%)	578 (30.9%)
BMI (kg/m^2)			
Mean (SD)	27.7 (5.39)	27.5 (5.11)	27.6 (5.25)
Median (Min, Max)	27.0 (16, 54)	26.9 (16, 51)	27.0 (16, 54)
BMI < 25, n (%)	322 (34.4%)	311 (33.3%)	633 (33.9%)
BMI ≥ 25 and < 30, n (%)	342 (36.6%)	359 (38.5%)	701 (37.5%)
BMI ≥ 30, n (%)	271 (29.0%)	263 (28.2%)	534 (28.6%)
Type of OAB, n (%)†			
Urgency incontinence‡	383 (40.9)	387 (41.4)	770 (41.2)
Mixed stress / urgency incontinence§	131 (14.0)	162 (17.3)	293 (15.7)
Frequency / urgency w/o incontinence	422 (45.1)	385 (41.2)	807 (43.2)
OAB duration (months)			
Mean (SD)	63.4 (79.82)	58.9 (68.84)	61.1 (74.55)
Median (Min, Max)	37.1 (3, 701)	37.8 (3, 459)	37.5 (3, 701)
OAB type, n (%)¶			
Dry	523 (56.1%)	508 (54.5%)	1031 (55.3%)
Wet	410 (43.9%)	424 (45.5%)	834 (44.7%)
Number of prior antimuscarinics, n (%)			
1	529 (56.5%)	539 (57.7%)	1068 (57.1%)
2	269 (28.7%)	253 (27.1%)	522 (27.9%)
> 2	138 (14.7%)	142 (15.2%)	280 (15.0%)
Reasons for discontinuation of ≥ 1 prior antimuscarinic, n (%)††			
Insufficient effect	936 (100.0%)	934 (100.0%)	1870 (100.0%)
Poor tolerability	187 (20.0%)	177 (19.0%)	364 (19.5%)
Other reasons	158 (16.9%)	156 (16.7%)	314 (16.8%)

OAB: overactive bladder; SAF: Safety Analysis Set; w/o: without.

† Type of OAB, as assessed by the investigator.

‡ Urgency incontinence only.

§ Mixed stress/urgency incontinence with urge as predominant factor.

¶ OAB type derived as: Dry = 0 incontinence episodes at baseline; Wet: ≥ 1 incontinence episode at baseline.

†† More than 1 discontinuation reason could have been reported for a medication.

Source: Tables 12.1.2.1.1 and 12.1.2.3.1

Table 2 Double-blind Study Drug Exposure (SAF)

		Mirabegron 50 mg (N = 936)	Solifenacin 5 mg (N = 934)	Total (N = 1870)
Duration category (days)	N	936	934	1870
	< 7	3 (0.3%)	5 (0.5%)	8 (0.4%)
	≥ 7 and < 14	1 (0.1%)	7 (0.7%)	8 (0.4%)
	≥ 14 and < 28	13 (1.4%)	13 (1.4%)	26 (1.4%)
	≥ 28 and < 56	29 (3.1%)	21 (2.2%)	50 (2.7%)
	≥ 56 and < 84	221 (23.6%)	234 (25.1%)	455 (24.3%)
	≥ 84	669 (71.5%)	654 (70.0%)	1323 (70.7%)
Cumulative duration category (days)	N	936	934	1870
	≥ 7	933 (99.7%)	929 (99.5%)	1862 (99.6%)
	≥ 14	932 (99.6%)	922 (98.7%)	1854 (99.1%)
	≥ 28	919 (98.2%)	909 (97.3%)	1828 (97.8%)
	≥ 56	890 (95.1%)	888 (95.1%)	1778 (95.1%)
	≥ 84	669 (71.5%)	654 (70.0%)	1323 (70.7%)
Duration (days)	N	936	934	1870
	Mean (SD)	81.4 (12.75)	81.1 (13.86)	81.3 (13.31)
	Median	84.0	84.0	84.0
	Min, Max	1, 98	1, 113	1, 113

SAF: Safety Analysis Set

Source: Table 12.2.1

Table 3 Change from Baseline to the Final Visit in Mean Number of Micturitions per 24 Hours (PPS)

	Statistics	Mirabegron 50mg N = 865	Solifenacin 5 mg N = 854
Baseline	N	865	853
	Mean (SE)	11.65 (0.109)	11.44 (0.096)
	Min, Max	8.0, 40.0	8.0, 35.0
Final Visit	Mean (SE)	8.67 (0.112)	8.36 (0.102)
	Min, Max	2.0, 38.3	2.0, 29.5
Change from Baseline to the Final Visit	Mean (SE)	-2.99 (0.106)	-3.08 (0.099)
	Min, Max	-18.3, 7.3	-15.7, 12.8
Adjusted change from Baseline to the Final Visit	Mean (SE)	-2.95 (0.087)	-3.13 (0.088)
	95% CI	(-3.12, -2.78)	(-3.30, -2.95)
Difference versus Mirabegron	Mean (SE)	-0.18 (0.124)	
	95% CI	(-0.42, 0.06)	
	NI Met?	No	

NI: non-inferiority; PPS: Per Protocol Set

Adjusted change from baseline values were generated from the ANCOVA model with treatment group, gender, age group (< 65, ≥ 65), number of prior antimuscarinics (1, ≥ 2) and geographic region as fixed factors and baseline number of micturitions per 24 hours as a covariate. Differences of adjusted means were calculated by subtracting the adjusted mean of mirabegron 50 mg from the adjusted mean of solifenacin 5 mg.

Non-inferiority was concluded if the lower limit of the 95% CI for difference of adjusted change from baseline between solifenacin and mirabegron was > -0.20.

Baseline values were calculated by taking the average of the last 3 consecutive valid micturition diary days prior to dosing. Post-baseline values were calculated by taking the average of all valid micturition diary days falling into pre-specified visit windows. Patients with < 2 valid diary days for a visit had visit value set equal to missing.

Source: Table 12.3.1.1.1.2

Table 4 Change from Baseline to the Final Visit in Mean Number of Micturitions per 24 Hours (FAS)

	Statistics	Mirabegron 50 mg N = 921	Solifenacin 5 mg N = 912
Baseline	N	920	910
	Mean (SE)	11.56 (0.108)	11.37 (0.095)
	Min, Max	2.0, 40.0	1.7, 35.0
Final Visit	Mean (SE)	8.54 (0.110)	8.22 (0.100)
	Min, Max	1.0, 38.3	1.0, 29.5
Change from Baseline to the Final Visit	Mean (SE)	-3.02 (0.104)	-3.15 (0.102)
	Min, Max	-20.6, 7.3	-18.2, 12.8
Adjusted change from Baseline to the Final Visit	Mean (SE)	-2.98 (0.087)	-3.18 (0.088)
	95% CI	(-3.16, -2.81)	(-3.35, -3.01)
Difference versus Mirabegron	Mean (SE)	-0.20 (0.124)	
	95% CI	(-0.44, 0.05)	
	NI met	No	

FAS: Full Analysis Set; NI: non-inferiority.

Details of the ANCOVA model that was used are provided in the footnotes below Table 3.

Source: Table 12.3.1.1.1.1

Table 5 Summary of Preferred Terms Related to Key Secondary Efficacy Variable (SAF)

Number of Patients with ≥ 1 TEAE of Dry Mouth, Constipation, and/or Blurred Vision	Mirabegron 50 mg (N = 936) N (%); 95% CI	Solifenacin 5 mg (N = 934) N (%); 95% CI	Total (N = 1870) N (%); 95% CI
Overall	47 (5.0%); (3.6, 6.4)	69 (7.4%); (5.7, 9.1)	116 (6.2%); (5.1, 7.3)
Dry mouth	29 (3.1%); (2.0, 4.2)	54 (5.8%); (4.3, 7.3)	83 (4.4%); (3.5, 5.4)
Dry throat	1 (0.1%); (0.0, 0.3)	1 (0.1%); (0.0, 0.3)	2 (0.1%); (0.0, 0.3)
Blurred vision	6 (0.6%); (0.1, 1.2)	4 (0.4%); (0.0, 0.8)	10 (0.5%); (0.2, 0.9)
Constipation	21 (2.2%); (1.3, 3.2)	23 (2.5%); (1.5, 3.5)	44 (2.4%); (1.7, 3.0)

LLT: lower level term; PT: preferred term; SAF: Safety Analysis Set; TEAE: treatment emergent adverse event.

The PTs and LLTs for each of interest were either based on a standardized MedDRA Query (SMQ; if available) or a pre-defined customized SMQ.

Source: Tables 12.6.1.16, 12.6.1.32, 12.6.1.33, 12.6.1.34

Table 6 Number of Incontinence, Urgency Incontinence and Nocturia Episodes and Number of Pads Used During the 3-Day Micturition Diary Period at Baseline and at the Final Visit (FAS-I / FAS)

	FAS-I	Mirabegron 50 mg (N=405)	Solifenacin 5 mg (N=413)	Rate Ratio (95% CI) vs Mirabegron RR (95% CI)	P-value
	Incontinence episodes (FAS-I)				
Baseline	N	404	413		
	Mean (SE)	6.23 (0.343)	5.99 (0.283)		
	Min, Max	1.0, 66.0	1.0, 42.0		
Final Visit	Mean (SE)	2.13 (0.533)	1.29 (0.157)	0.92 (0.68, 1.24)	0.57
	Min, Max	0.0, 196.0	0.0, 26.0		
	Urgency incontinence episodes (FAS-I)				
Baseline	N	395	402		
	Mean (SE)	5.79 (0.301)	5.77 (0.268)		
	Min, Max	1.0, 36.0	1.0, 36.0		
Final Visit	Mean (SE)	1.51 (0.211)	1.23 (0.150)	0.97 (0.71, 1.33)	0.85
	Min, Max	0.0, 41.0	0.0, 26.0		
	FAS	**Mirabegron 50 mg (N=921)**	**Solifenacin 5 mg (N=912)**	**Rate Ratio (95% CI) vs Mirabegron RR (95% CI)**	**P-value**
	Number of Pads (FAS)				
Baseline	N	576	565		
	Mean (SE)	9.34 (0.431)	9.70 (0.446)		
	Min, Max	1.0, 72.0	1.0, 56.0		
Final Visit	Mean (SE)	3.32 (0.300)	3.19 (0.248)	1.08 (0.90, 1.31)	0.40
	Min, Max	0.0, 74.0	0.0, 47.0		
	Number of Nocturia Episodes (FAS)				
Baseline	N	879	875		
	Mean (SE)	6.76 (0.143)	6.85 (0.139)		
	Min, Max	1.0, 38.0	1.0, 24.0		
Final Visit	Mean (SE)	4.05 (0.120)	4.13 (0.114)	1.03 (0.96, 1.10)	0.44
	Min, Max	0.0, 36.0	0.0, 23.0		

FAS-I: Full Analysis Set-Incontinence; RR: rate ratio

Rate ratio from the mixed effects Poisson regression model with treatment group, sex, age group (< 65, ≥ 65), number of prior antimuscarinics (1, ≥ 2), geographic region and baseline as covariates, using an offset of the log of the number of valid diary days at each visit.

P-value is for treatment comparisons from the Poisson regression analysis with the model described above; if $P < 0.05$, this indicates superiority in favor of the treatment group with the largest improvement at specified visit.

Baseline values were calculated by taking the sum of the last 3 consecutive valid micturition diary days prior to dosing. Post-baseline values were calculated by taking the sum of all valid micturition diary days falling into pre-specified visit windows. Patients with < 2 valid diary days for a visit had visit value set equal to missing.

Source: Table 12.3.2.1.1, Table 12.3.3.1.1, Table 12.3.6.1.1, Table 12.3.7.1.1

Table 7 Adjusted Change From Baseline to the Final Visit in Secondary Efficacy Variables – Micturition Diary (FAS-I / FAS)

FAS-I	Mirabegron 50 mg (N=405)	Solifenacin 5 mg (N=413)	Difference vs Mirabegron	P-value
Incontinence episodes per 24 hours (FAS-I)				
N at baseline	404	413		
Mean (SE)	-1.40 (0.112)	-1.60 (0.111)	-0.20 (0.157)	0.49
95% CI	(-1.62,-1.18)	(-1.82,-1.38)	(-0.51,0.11)	
Urgency incontinence episodes per 24 hours (FAS-I)				
N at baseline	395	402		
Mean (SE)	-1.47 (0.050)	-1.53 (0.050)	-0.07 (0.071)	0.98
95% CI	(-1.57,-1.37)	(-1.63,-1.44)	(-0.20,0.07)	
FAS	**Mirabegron 50 mg (N=921)**	**Solifenacin 5 mg (N=912)**	**Difference vs Mirabegron**	**P-value**
Urgency Episodes Grade 3 or 4 per 24 hours (FAS)				
N at baseline	919	909		
Mean (SE)	-4.61 (0.115)	-4.84 (0.115)	-0.23 (0.163)	0.16
95% CI	-4.83, -4.38	-5.06, -4.61	(-0.55, 0.09)	
Mean level of Urgency (FAS)				
N at baseline	920	910		
Mean (SE)	-0.58 (0.022)	-0.57 (0.022)	0.01 (0.031)	0.74
95% CI	(-0.63, -0.54)	(-0.62, -0.53)	(-0.05, 0.07)	
Pads Used per 24 hours (FAS)				
N at baseline	576	565		
Mean (SE)	-2.10 (0.077)	-2.15 (0.078)	-0.05 (0.110)	0.66
95% CI	(-2.25,-1.95)	(-2.30,-2.00)	(-0.26,0.17)	
Nocturia Episodes per 24 hours (FAS)				
N at baseline	879	875		
Mean (SE)	-0.95 (0.033)	-0.94 (0.033)	0.01 (0.046)	0.88
95% CI	(-1.02,-0.89)	(-1.01,-0.88)	(-0.08, 0.10)	

FAS: Full Analysis Set; FAS-I: FAS-Incontinence.

Adjusted change from baseline values were generated from the ANCOVA model with treatment group, gender, age group ($< 65, \geq 65$), number of prior antimuscarinics ($1, \geq 2$) and geographic region as fixed factors and baseline number of micturitions per 24 hours as a covariate. Differences of adjusted means were calculated by subtracting the adjusted mean of mirabegron 50 mg from the adjusted mean of solifenacin 5 mg.

P-value for incontinence and urgency incontinence episodes is for treatment comparisons from the stratified rank ANCOVA analysis; for all other variables in the table, p-values were from ANCOVA model; $P < 0.05$ indicates superiority in favor of the treatment group with the largest improvement at specified visit

Source: Table 12.3.2.3.1, Table 12.3.3.2.1, Table 12.3.4.1.1, Table 12.3.5.1.1, Table 12.3.6.2.1, Table 12.3.7.2.1

Table 8 Summary Table of Adverse Events (SAF)

		Mirabegron 50 mg (N = 936)	Solifenacin 5 mg (N = 934)	Total (N = 1870)
N (%) with any TEAE		274 (29.3%)	282 (30.2%)	556 (29.7%)
Total TEAEs		458	484	942
N (%) with treatment-related§ TEAEs		104 (11.1%)	135 (14.5%)	239 (12.8%)
Total treatment-related§ TEAEs		175	198	373
N (%) deaths†		0	0	0
N (%) with serious TEAEs		14 (1.5%)	13 (1.4%)	27 (1.4%)
Total serious TEAEs		22	14	36
N (%) with treatment-related§ serious TEAEs		4 (0.4%)	4 (0.4%)	8 (0.4%)
Total treatment-related§ serious TEAEs		9	4	13
N (%) discontinued due to TEAE‡		13 (1.4%)	17 (1.8%)	30 (1.6%)
Total TEAEs leading to discontinuation		20	20	40
N (%) discontinued due to treatment-related[#] TEAE‡		9 (1.0%)	14 (1.5%)	23 (1.2%)
Total treatment-related§ TEAEs leading to discontinuation		15	16	31
N (%) with TEAE by severity	Mild	166 (17.7%)	172 (18.4%)	338 (18.1%)
	Moderate	87 (9.3%)	93 (10.0%)	180 (9.6%)
	Severe	21 (2.2%)	17 (1.8%)	38 (2.0%)

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

† Only adverse events with outcome 'fatal' are counted.

‡ Only adverse events that were the primary reason for discontinuation are taken into account.

§ Adverse events that are possibly or probably treatment-related, or for which the relationship is missing.

Source: Table 12.6.1.1 and Table 12.6.1.4

Table 9 Adverse Events in ≥ 2.0% of Patients in Either Treatment Group (SAF)

System Organ Class Preferred Term	Mirabegron 50 mg (N = 936) N (%)	Solifenacin 5 mg (N = 934) N (%)	Total (N = 1870) N (%)
Overall	274 (29.3%)	282 (30.2%)	556 (29.7%)
Gastrointestinal disorders	78 (8.3%)	113 (12.1%)	191 (10.2%)
Dry mouth	29 (3.1%)	54 (5.8%)	83 (4.4%)
Constipation	21 (2.2%)	23 (2.5%)	44 (2.4%)
Nervous system disorders	46 (4.9%)	34 (3.6%)	80 (4.3%)
Headache	28 (3.0%)	22 (2.4%)	50 (2.7%)

SAF: Safety Analysis Set.

Source: Table 12.6.1.11

Table 10 Adverse Events of Special Interest (SAF)

Adverse Event of Special Interest†	Mirabegron 50 mg (N = 936) N (%)	95% CI	Solifenacin 5 mg (N = 934) N (%)	95% CI	Total (N = 1870) N (%)	95% CI
Hypertension	10 (1.1%)	(0.4, 1.7)	14 (1.5%)	(0.7, 2.3)	24 (1.3%)	(0.8, 1.8)
QT prolongation	2 (0.2%)	(0.0, 0.5)	0		2 (0.1%)	(0.0, 0.3)
Cardiac arrhythmia	13 (1.4%)	(0.6, 2.1)	10 (1.1%)	(0.4, 1.7)	23 (1.2%)	(0.7, 1.7)
Cardiac failure	5 (0.5%)	(0.1, 1.0)	1 (0.1%)	(0.0, 0.3)	6 (0.3%)	(0.1, 0.6)
Tachycardia‡	1 (0.1%)	(0.0, 0.3)	2 (0.2%)	(0.0, 0.5)	3 (0.2%)	(0.0, 0.3)
Tachycardia§	16 (1.7%)	(NC)	17 (1.8%)	(NC)	33 (1.8%)	(NC)
Atrial fibrillation¶	1 (0.1%)	(NC)	1 (0.1%)	(NC)	2 (0.1%)	(NC)
Adverse events suggestive of UTI	22 (2.4%)	(1.4, 3.3)	24 (2.6%)	(1.6, 3.6)	46 (2.5%)	(1.8, 3.2)
Urinary retention	1 (0.1%)	(0.0, 0.3)	1 (0.1%)	(0.0, 0.3)	2 (0.1%)	(0.0, 0.3)
Acute urinary retention	0		0		0	
Seizure	0		0		0	
Syncope, falls, postural hypotension	9 (1.0%)	(0.3, 1.6)	9 (1.0%)	(0.3, 1.6)	18 (1.0%)	(0.5, 1.4)
Hypersensitivity	32 (3.4%)	(2.3, 4.6)	35 (3.7%)	(2.5, 5.0)	67 (3.6%)	(2.7, 4.4)
Neoplasm	5 (0.5%)	(0.1, 1.0)	4 (0.4%)	(0.0, 0.8)	9 (0.5%)	(0.2, 0.8)
Glaucoma	7 (0.7%)	(0.2, 1.3)	7 (0.7%)	(0.2, 1.3)	14 (0.7%)	(0.4, 1.1)
Hepatotoxicity	4 (0.4%)	(0.0, 0.8)	2 (0.2%)	(0.0, 0.5)	6 (0.3%)	(0.1, 0.6)

CI; confidence interval; LLT: lower level term; NC: not calculated; PT: preferred term; SAF: Safety Analysis Set; UTI: urinary tract infection.

† The PTs and LTTs for each of interest were either based on a Standardized MedDRA Query (SMQ; if available) or a pre-defined customized SMQ.

‡ Tachycardia reported as only.

§ Tachycardia based on AEs and pulse rate ≥ 100bpm; NC: not calculated.

¶ Treatment-emergent cases considered of medical importance.

Source: Tables 12.6.1.17, 12.6.1.18, 12.6.1.19, 12.6.1.20, 12.6.1.21.1, 12.6.1.21.2, 12.6.1.22, 12.6.1.23, 12.6.1.24, 12.6.1.25, 12.6.1.26, 12.6.1.27, 12.6.1.28, 12.6.1.29, 12.6.1.30, 12.6.1.31