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Name of Finished Product: Mirabegron		
Name of Active Ingredient: Mirabegron (YM178)		

SYNOPSIS

Title of Study:

A Randomized, Double-Blind, Parallel Group, Placebo and Active Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects with Symptoms of Overactive Bladder; Protocol 178-CL-046 (SCORPIO)

Responsible Medical Officer/Investigators:

[redacted] MD, [redacted]

Study Centers:

This multinational, multicenter study was conducted at 189 sites in 26 countries in Europe and Australia. A total of 200 sites were initiated; 189 sites enrolled patients.

Publication (reference):

None

Study Period:

Approximately 1 year

Date of first enrollment (Study initiation date):

28 April 2008

Date of last evaluation (Study completion date):

24 March 2009

Phase of Development:

Phase 3

Objectives:

The primary objective of the study was to assess the efficacy of mirabegron 50 mg once daily (qd) and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of overactive bladder (OAB).

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There were 2 secondary objectives:

- To assess the safety and tolerability of mirabegron 50 mg qd and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of OAB
- To compare the efficacy and safety of mirabegron with tolterodine SR 4 mg qd in the treatment of patients with symptoms of OAB.

Methodology:

This was a randomized, double-blind, parallel group, placebo- and active-controlled, multinational, multicenter study. After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). On completion of the run-in period, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1:1 ratio to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine SR 4 mg orally qd for 12 weeks. The 12-week treatment period consisted of visits at weeks 4, 8, and 12 and a 30 day follow up telephone contact or visit.

Number of Patients (planned, enrolled and analyzed):

Planned: 2160 patients enrolled, 1720 patients randomized

Actual: 2336 patients enrolled, 1987 patients randomized

- Randomized Set: 1987 patients
    - Placebo: 497 patients; mirabegron 50 mg: 497 patients; mirabegron 100 mg: 498 patients; tolterodine SR 4 mg: 495 patients
- Full Analysis Set (FAS): 1906 patients
    - Placebo: 480 patients; mirabegron 50 mg: 473 patients; mirabegron 100 mg: 478 patients; tolterodine SR 4 mg: 475 patients
- Full Analysis Set Incontinence (FAS-I): 1165 patients
    - Placebo: 291 patients; mirabegron 50 mg: 293 patients; mirabegron 100 mg: 281 patients; tolterodine SR 4 mg: 300 patients
- Safety Analysis Set (SAF): 1978 patients
    - Placebo: 494 patients; mirabegron 50 mg: 493 patients; mirabegron 100 mg: 496 patients; tolterodine SR 4 mg: 495 patients

Diagnosis and Main Criteria for Inclusion:

At screening, male and female patients at least 18 years of age, who provided written informed consent, were required to have had symptoms of OAB for ≥ 3 months. Patients

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were excluded if they had significant stress incontinence or mixed stress/urgency incontinence with stress as the predominant factor; an indwelling catheter; evidence of a symptomatic urinary tract infection (UTI), chronic inflammation, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; or severe hypertension (defined as a sitting average systolic blood pressure [SBP] ≥ 180 mm Hg and/or average diastolic blood pressure [DBP] ≥ 110 mm Hg). Additionally, patients were excluded if they practiced intermittent self-catheterization; received nondrug treatment including electro-stimulation therapy; or used medications intended to treat OAB, prohibited medications, or restricted medications without meeting conditions for use.

At baseline patients had to have experienced a micturition frequency on average ≥ 8 times per 24-hour period during the 3-day micturition diary period, experienced at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period and had to continue to meet all screening eligibility criteria. Patients were excluded if they had an average total daily urine volume > 3000 mL as recorded in the 3-day micturition diary period; they had serum creatinine of > 150 mcmol/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal (ULN) range or gamma glutamyl transferase (GGT) > 3 times the ULN, as assessed in screening samples and considered clinically significant by the investigator; or severe hypertension (defined as a sitting average systolic blood pressure [SBP] ≥ 180 mm Hg and/or average diastolic blood pressure [DBP] ≥ 110 mm Hg); or they had a clinically significant abnormal electrocardiogram (ECG).

Medications prohibited during the placebo run-in period and the double-blind treatment period included anticholinergics, antispasmodics and CYP2D6 substrates with narrow therapeutic indices.

Medications restricted (allowed, but with conditions) during the placebo run-in period and the double-blind treatment period included alpha blockers, 5-alpha reductase inhibitors, CYP3A4 inducers and loop diuretics. Restricted medications were permitted provided the patient had been taking the medication on a long-term basis (i.e., had not stopped, started or changed dose within 30 days prior to entering the study); no new drug of the same class had been added to the regimen within 30 days prior to entering the study; the patient remained on the medication at the same dose during the course of the placebo run-in period and the double-blind treatment period and the patient was monitored carefully for adverse events possibly resulting from drug interactions.

The only permitted nondrug treatment for OAB was ongoing bladder training or pelvic floor exercise programs that had started at least 30 days prior to start of the study.

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

Mirabegron (oral controlled absorption system [OCAS] formulation) tablets: 50 mg and 100 mg. One mirabegron tablet (and matching placebo for the other dose) was administered each morning (qd) by mouth with a glass of water with or without food to patients randomized to receive mirabegron 50 or 100 mg.

Lot numbers: [redacted] (50 mg tablet); [redacted] (100 mg tablet)

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

Single-blind, placebo run-in period: 2 weeks

Double-blind, placebo-controlled treatment period: 12 weeks with a follow-up telephone contact or visit 30 days after the week 12 visit.

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

Two placebo tablets to match mirabegron 50 mg and 100 mg were administered to patients randomized to placebo each morning (qd) by mouth with a glass of water with or without food.

Lot number: [redacted] (placebo to match mirabegron 50 mg tablet); [redacted] (placebo to match mirabegron 100 mg tablet)

Tolterodine SR 4 mg capsules (Detrusitol® SR 4 mg, Pfizer, Germany), used in this study as an active control, and placebo tablets to match tolterodine SR 4 mg capsules were administered qd by mouth with a glass of water with or without food to patients randomized to receive tolterodine SR 4 mg.

Batch number: [redacted] (tolterodine SR 4 mg capsules); [redacted] and [redacted] (placebo to match tolterodine SR 4 mg capsules).

Criteria for Evaluation:

The coprimary efficacy variables included:

- Change from baseline to Final Visit in the mean number of incontinence episodes per 24 hours based on a 3 day micturition diary
- Change from baseline to Final Visit in the mean number of micturitions per 24 hours based on a 3 day micturition diary

The key secondary efficacy variables included:

- Change from baseline to Final Visit in mean volume voided per micturition

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- Change from baseline to week 4 in mean number of incontinence episodes per 24 hours based on a 3 day micturition diary
- Change from baseline to week 4 in mean number of micturitions per 24 hours based on a 3 day micturition diary

Safety variables included:

- Treatment-emergent adverse events (TEAEs)
- Events adjudicated by the independent cardiovascular adjudication committee
- TEAEs of interest (i.e., hypertension, QTc prolongation, cardiac arrhythmias, urinary retention/acute urinary retention, hypersensitivity, syncope, seizure, hepatic events and renal and urinary events)
- Clinical laboratory evaluations (i.e., hematology and serum chemistry)
- Vital signs
- ECGs
- Postvoid residual volume (PVR)

Statistical Methods:

Since there are 2 coprimary efficacy variables and 3 key secondary efficacy variables, the multiplicity between the variables was controlled at type I error rate at the alpha = 0.05 level using a stepwise parallel gatekeeping procedure. At each of the 5 stages, the difference between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to the next stage. The stages and efficacy variables that were evaluated were as follows:

- Stage 1: incontinence episodes at the Final Visit
- Stage 2: micturitions at the Final Visit
- Stage 3: volume voided per micturition at the Final Visit
- Stage 4: incontinence episodes at week 4
- Stage 5: micturitions at week 4

Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the alpha = 0.05 level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the alpha = 0.025 level. Since the comparison between tolterodine and placebo was a secondary analysis, no adjustment for multiplicity was necessary.

Change from baseline to Final Visit (coprimary efficacy variable) and to week 4 (key secondary efficacy variable) in mean number of incontinence episodes per 24 hours was

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analyzed using a separate stratified rank analysis of covariance (ANCOVA) for each pairwise treatment group differences of interest. The response variable was standardized ranks on change from baseline to Final Visit value for the stratified rank ANCOVA with baseline standardized ranks and sex as covariates and geographical region as a stratum.

The stratified rank ANCOVA was utilized for hypothesis testing and calculating the pairwise P-values. The least squares mean estimates and 2-sided 95% CIs for mean changes from baseline within treatment group, as well as the mean change from baseline in the difference between each mirabegron treatment group and placebo and between tolterodine and placebo, were derived from the corresponding ANCOVA model with all treatment groups in the model.

Change from baseline to Final Visit (coprimary efficacy variable) and to week 4 (key secondary efficacy variable) in mean number of micturitions per 24 hours was analyzed using an ANCOVA including treatment, sex and geographical region as fixed factors and baseline as a covariate. This ANCOVA model also was used to analyze the change from baseline to Final Visit in mean volume voided per micturition.

Within the framework of this ANCOVA model, point estimates and 2-sided 95% CIs for the mean change from baseline within each treatment group, as well as for the difference in mean change from baseline between each mirabegron treatment group and placebo and between tolterodine and placebo, were calculated.

Summary of Results/Conclusions:

Population:

Demographic and baseline characteristics were consistent across treatment groups for patients in the SAF population. Overall, 72.2% of patients were female. The majority (62.9%) of patients were < 65 years of age and 91.3% were < 75 years of age. Overall, 99.1% of patients were white. Mean body mass index across all treatment groups was 27.8 kg/m^2.

Generally, demographic and baseline characteristics were similar across treatment groups in the FAS and FAS I. Overall, 72.0% and 83.4% of patients were female (FAS and FAS I). The higher proportion of female patients is the major difference in demographics and baseline characteristics observed between the FAS and the FAS I.

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Efficacy Results:

Efficacy of mirabegron and tolterodine was demonstrated in this study.

For the coprimary efficacy endpoints, mirabegron 50 mg and 100 mg groups demonstrated statistically significant greater reductions from baseline to Final Visit compared to placebo in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.41 and -0.29, mirabegron 50 mg and mirabegron 100 mg) and the mean number of micturitions per 24 hours (difference from placebo: -0.60 and -0.44, mirabegron 50 mg and mirabegron 100 mg). The reduction in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.10) and the mean number of micturitions per 24 hours (difference from placebo: -0.25) as compared to placebo for the tolterodine SR 4 mg group was not statistically significant.

For the key secondary efficacy endpoints:

- Both mirabegron 50 mg and 100 mg groups had statistically significant greater increases from baseline to Final Visit compared to placebo in the mean volume voided per micturition (difference from placebo: 11.9 mL and 13.2 mL, mirabegron 50 mg and mirabegron 100 mg).
- Both mirabegron 50 mg and 100 mg groups had statistically significant greater reductions from baseline to week 4 compared to placebo in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.39 and -0.38, mirabegron 50 mg and mirabegron 100 mg) and the mean number of micturitions per 24 hours (difference from placebo: -0.40 and -0.52, mirabegron 50 mg and mirabegron 100 mg).
- The tolterodine SR 4 mg group had a statistically significant greater increase from baseline to Final Visit compared to placebo in mean volume voided per micturition (difference from placebo: 12.6 mL). The tolterodine SR 4 mg group also had statistically significant greater reductions from baseline to week 4 compared to placebo in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.35) and in the mean number of micturitions per 24 hours (difference from placebo: -0.33). For the tolterodine SR 4 mg group, the analyses of these key secondary efficacy endpoints were not adjusted for multiplicity.

For the additional secondary efficacy endpoints:

- Statistically significant greater reductions from baseline to week 4, week 8 and week 12 compared to placebo in the mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours were observed for mirabegron 50 mg and

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100 mg. The tolterodine SR 4 mg group only demonstrated statistically significant greater reductions from baseline to week 4 compared to placebo for these parameters.

- Statistically significant greater reductions from baseline to week 4, week 8 and week 12 compared to placebo in the mean volume voided per micturition were observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg.
- The mirabegron 50 mg group demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the mean number of urgency episodes (grade 3 or 4) per 24 hours (using the patient Perception of Intensity of Urgency Scale) and mean number of nocturia episodes per 24 hours for mirabegron 50 mg.
- The tolterodine SR 4 mg group also demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the mean number of urgency episodes (grade 3 or 4) per 24 hours.
- For the TS-VAS, the mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups demonstrated statistically significant greater increases from baseline to Final Visit compared to placebo.
- For the OAB-q:
    - The mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the Symptom Bother scale.
    - The mirabegron 50 mg and 100 mg groups demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the HRQL dimensions of Coping, Concern and in mean total HRQL score. The mirabegron 100 mg group also demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the HRQL dimension of Sleep and Social Interaction.
    - The tolterodine SR 4 mg group did not demonstrate statistically significant improvement from baseline to Final Visit compared to placebo for any of these OAB-q parameters.

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Safety Results:

Based on the overall results of this study, mirabegron at doses of 50 and 100 mg was well tolerated:

- The overall incidence of patients with TEAEs was similar across the treatment groups (43.3%, 42.8%, 40.1% and 46.7%; placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg, respectively).
- One death, due to a cerebral aneurysm, occurred in a tolterodine SR 4 mg-treated patient 10 days after the last dose of study drug.
- The overall incidence of patients with treatment-emergent SAEs was 1.6%, 2.8%, 2.4% and 2.2% in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively. The overall incidence patients who discontinued study drug due to a TEAE was 2.6%, 4.9%, 3.2% and 4.4% % in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively.
- For events of interest:
    - The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was higher in the tolterdine SR 4 mg (9.5%) and placebo (9.3%) groups than in the mirabegron 50 mg (7.7%) and 100 mg (6.3%) groups.
    - TEAEs of QTc prolongation in the Torsades de pointes/QT prolongation SMQ were observed only in the tolterodine SR 4 mg group (2 patients, 0.4%). No proarrhythmic findings of ventricular tachycardia, ventricular fibrillation or torsades were reported.
    - The overall incidence of arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 1.0% in the placebo group, 2.2% in the mirabegron 50 mg group, 1.8% in the mirabegron 100 mg group, and 3.2% in the tolterodine SR 4 mg group. Cases of atrial fibrillation of medical importance were noted in 1 (0.2%) patient in the placebo group, 2 (0.4%) patients in the mirabegron 50 mg group, 2 (0.4%) patients in the mirabegron 100 mg group, and 5 (1.0%) patients in the tolterodine SR 4 mg group.
    - Only 1 patient had a TEAE adjudicated as an APTC/MACE cardiovascular event; Patient [redacted] in the tolterodine SR 4 mg group experienced cardiovascular death due to a ruptured cerebral aneurysm. The overall incidence of adjudicated non-APTC/MACE cardiovascular TEAEs was 0.2%, 0.4%, 0.4% and 0.4% in the placebo, mirabegron 50 mg, mirabegon 100 mg and tolterodine SR 4 mg groups, respectively.

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  - TEAEs of acute urinary retention were reported for 1 patient in the placebo group, 1 patient in the mirabegron 50 mg group, and 3 patients in the tolterodine SR 4 mg group. No patients had a PVR > 500 mL.
  - The overall incidence of TEAEs indicative of potential hypersensitivity was similar across treatment groups (3.2%, 4.5%, 4.0%, and 4.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively).
  - No episodes of syncope were observed in the study.
  - A TEAE of seizure was reported for 1 (0.2%) patient in the tolterodine SR 4 mg group and no patients in the placebo or mirabegron groups.
  - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders – Comprehensive Search SMQ, was similar across treatment groups (1.4%, 2.2%, 1.4% and 2.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively). Most hepatic TEAEs were mild or moderate in intensity.
  - No patients met laboratory criteria for Hy's law. The incidence of patients with hepatic parameters meeting PCS criteria was 2.2%, 1.2%, 1.4% and 1.0% in the placebo, mirabegron 50 mg, mirabegon 100 mg and tolterodine SR 4 mg groups, respectively (excluding patients with GGT values that met the PCS criterion for GGT only).
  - The incidence of hepatic events when TEAEs and PCS criteria were assessed concurrently was 0, 0.2%, 0.8%, and 1.0% in the placebo, mirabegron 50 mg, mirabegon 100 mg and tolterodine SR 4 mg groups, respectively.
- Changes in hematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups.
- Dose-dependent increases in adjusted mean change from baseline to Final Visit for AM and PM pulse rates were observed with mirabegron treatment compared to placebo (AM: 0.8 and 1.6 bpm; PM: 0.7 and 2.0 bpm for mirabegron 50 mg and 100 mg, respectively). Treatment with tolterodine SR 4 mg resulted in an increase compared to placebo of 0.8 bpm in mean AM pulse rate and 1.9 bpm in mean PM pulse rate.
- Adjusted mean changes from baseline in systolic and diastolic blood pressure measurements were similar across treatment groups and between normotensive and hypertensive population.
- Increases in heart rate noted on ECGs were consistent with increases in pulse rate. No consistent ECG trends were identified.
- The incidence of notable shifts in PVR was comparable across treatment groups. One patient (0.2%) in the mirabegron 50 mg group, 2 (0.4%) patients in the mirabegron

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100 mg group, and 1 (0.2%) patient in the tolterodine SR 4 mg group had PVR values > 300 mL at the Final Visit.

CONCLUSIONS:

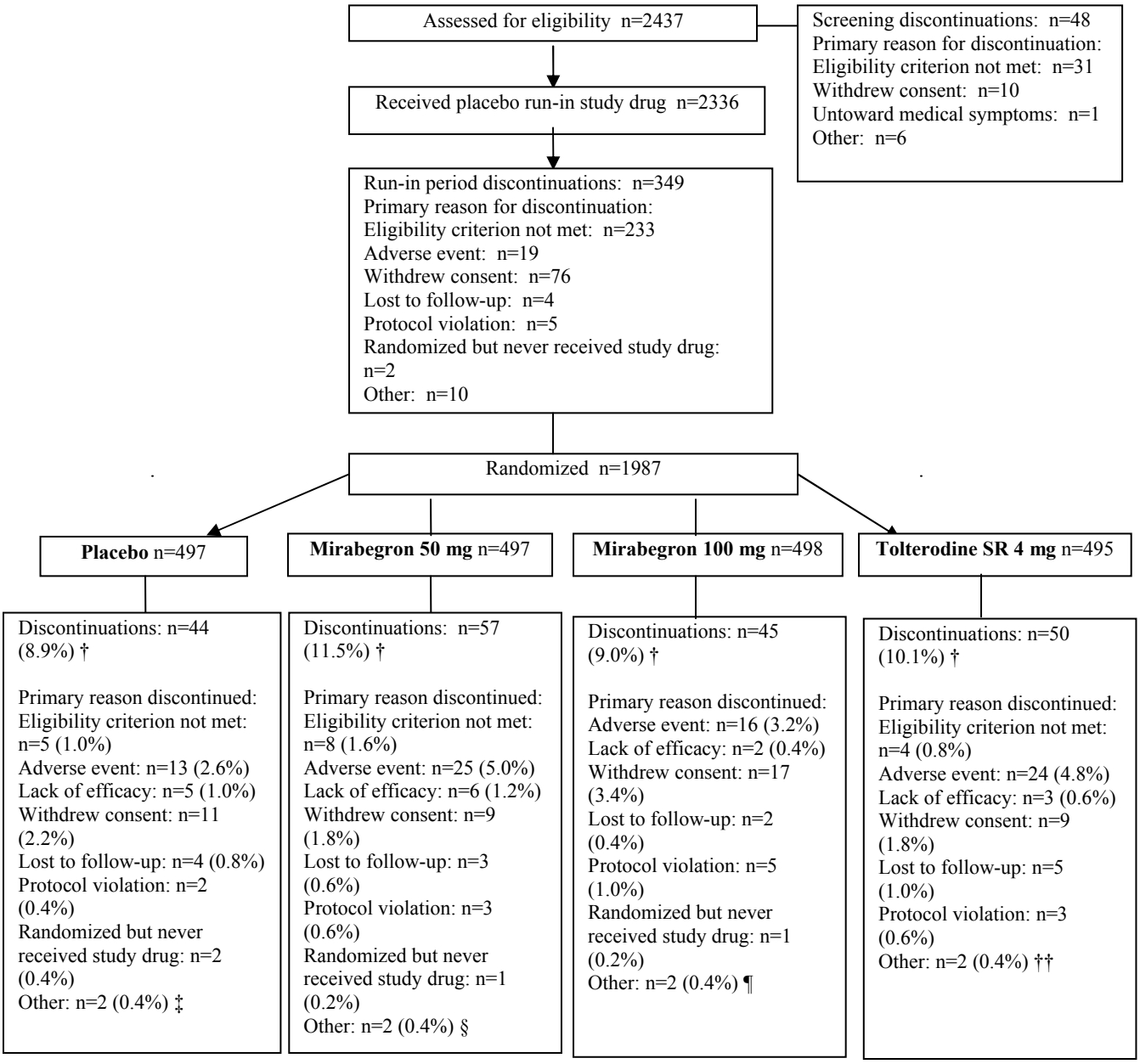
Based on the results of this study, it is concluded that:

- Mirabegron at doses of 50 and 100 mg once daily for 12 weeks demonstrated efficacy in the treatment of the symptoms of urinary incontinence, frequency and urgency that are characteristic of OAB.
- Mirabegron at doses of 50 and 100 mg once daily for 12 weeks was safe and well tolerated with the tolerability profile anticipated based on prior nonclinical and clinical studies.

Date of Report:

22 Apr 2010

Figure 1 Patient Disposition



All patients.

† Discontinuations are those reported for patients in the Randomized Analysis Set.

‡ Other reasons for discontinuation in the placebo group were personal reasons and blood pressure was too difficult to measure.

§ Other reasons for discontinuation in the mirabegron 50 mg group were unable to commit to study schedule due to work commitments and patient wanted to go to Italy for family reasons and could not return in time to begin the study.

¶ Other reasons for discontinuation in the mirabegron 100 mg group were patient was excluded in error and patient had to move to another town in Spain.

Table footnote continued on next page

†† Other reasons for discontinuation in the tolterodine SR 4 mg group were personal reasons and familial troubles.

Source: Tables 12.1.1.3.1, 12.1.1.3.2, 12.1.1.3.3 and 12.1.1.3.4; Appendix 13.2.1.2

Table 1 Summary of Patient Demographics and Baseline Characteristics, SAF

Parameter	Placebo (n=494)	Mirabegron 50 mg (n=493)	Mirabegron 100 mg (n=496)	Tolterodine SR 4 mg (n=495)	Total (n=1978)
Sex (n, %)					
Male	138 (27.9%)	136 (27.6%)	141 (28.4%)	134 (27.1%)	549 (27.8%)
Female	356 (72.1%)	357 (72.4%)	355 (71.6%)	361 (72.9%)	1429 (72.2%)
Age (years)					
Mean (SD)	59.2 (12.30)	59.1 (12.36)	59.0 (12.71)	59.1 (12.89)	59.1 (12.56)
Age group (years) (n, %)					
< 65	313 (63.4%)	315 (63.9%)	313 (63.1%)	303 (61.2%)	1244 (62.9%)
≥ 65	181 (36.6%)	178 (36.1%)	183 (36.9%)	192 (38.8%)	734 (37.1%)
< 75	450 (91.1%)	447 (90.7%)	450 (90.7%)	458 (92.5%)	1805 (91.3%)
≥ 75	44 (8.9%)	46 (9.3%)	46 (9.3%)	37 (7.5%)	173 (8.7%)
Race (n, %)					
White	490 (99.2%)	488 (99.0%)	492 (99.2%)	490 (99.0%)	1960 (99.1%)
Black or African American	2 (0.4%)	1 (0.2%)	1 (0.2%)	3 (0.6%)	7 (0.4%)
Asian	0	2 (0.4%)	2 (0.4%)	2 (0.4%)	6 (0.3%)
Other †	2 (0.4%)	2 (0.4%)	1 (0.2%)	0	5 (0.3%)
BMI (kg/m^2)					
n	493	493	495	495	1976
Mean (SD)	27.8 (4.96)	27.5 (4.86)	28.0 (4.95)	27.8 (4.96)	27.8 (4.93)
Geographical region (n, %)					
Eastern Europe	225 (45.5%)	222 (45.0%)	224 (45.2%)	226 (45.7%)	897 (45.3%)
Western Europe‡	269 (54.5%)	271 (55.0%)	272 (54.8%)	269 (54.3%)	1081 (54.7%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). The denominators for the percentage calculations of categorical variables are the number of patients with nonmissing values. Body mass index (BMI) = weight (kg)/height (m^2).

† Other race: placebo: Romanian and Ghanaian; mirabegron 50 mg: Pakistani and American Indian; mirabegron 100 mg: Latin.

‡ For the purposes of this summary, Australia was included within the Western Europe category. A list of countries included in each geographical region (Eastern Europe or Western Europe) is provided [see Appendix 1 of the SAP, Appendix 13.1.9].

Source: Table 12.1.2.1.1 and Appendix 13.2.4.1

Table 2 Summary of Patient Demographics and Baseline Characteristics, FAS

Parameter	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)	Total (n=1906)
Sex (n, %)					
Male	134 (27.9%)	133 (28.1%)	138 (28.9%)	129 (27.2%)	534 (28.0%)
Female	346 (72.1%)	340 (71.9%)	340 (71.1%)	346 (72.8%)	1372 (72.0%)
Age (years)					
Mean (SD)	59.3 (12.15)	59.2 (12.15)	58.9 (12.69)	59.1 (12.75)	59.1 (12.43)
Age group (years) (n, %)					
< 65	302 (62.9%)	302 (63.8%)	306 (64.0%)	291 (61.3%)	1201 (63.0%)
≥ 65	178 (37.1%)	171 (36.2%)	172 (36.0%)	184 (38.7%)	705 (37.0%)
< 75	437 (91.0%)	430 (90.9%)	435 (91.0%)	442 (93.1%)	1744 (91.5%)
≥ 75	43 (9.0%)	43 (9.1%)	43 (9.0%)	33 (6.9%)	162 (8.5%)
Race (n, %)					
White	477 (99.4%)	468 (98.9%)	474 (99.2%)	472 (99.4%)	1891 (99.2%)
Black or African American	2 (0.4%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	6 (0.3%)
Asian	0	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (0.3%)
Other †	1 (0.2%)	2 (0.4%)	1 (0.2%)	0	4 (0.2%)
BMI (kg/m^2)					
n	480	473	477	475	1905
Mean (SD)	27.8 (4.97)	27.5 (4.90)	28.0 (4.87)	27.9 (4.97)	27.8 (4.93)
Geographical region (n, %)					
Eastern Europe	221 (46.0%)	210 (44.4%)	221 (46.2%)	221 (46.5%)	873 (45.8%)
Western Europe‡	259 (54.0%)	263 (55.6%)	257 (53.8%)	254 (53.5%)	1033 (54.2%)

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). The denominators for the percentage calculations of the categorical variables are the number of patients with nonmissing values. Body mass index (BMI) = weight (kg)/height (m^2).

† Other race: placebo: Romanian; mirabegron 50 mg: Pakistani and American Indian; mirabegron 100 mg: Latin.

‡ For the purposes of this summary, Australia was included within the Western Europe category. A list of countries included in each geographical region (Eastern Europe or Western Europe) is provided [see Appendix 1 of the SAP, Appendix 13.1.9].

Source: Tables 12.1.2.1.2 and Appendix13.2.4.1

Table 3 Summary of Patient Demographics and Baseline Characteristics, FAS-I

Parameter	Placebo (n=291)	Mirabegron 50 mg (n=293)	Mirabegron 100 mg (n=281)	Tolterodine SR 4 mg (n=300)	Total (n=1165)
Sex (n, %)					
Male	48 (16.5%)	55 (18.8%)	42 (14.9%)	48 (16.0%)	193 (16.6%)
Female	243 (83.5%)	238 (81.2%)	239 (85.1%)	252 (84.0%)	972 (83.4%)
Age (years)					
Mean (SD)	59.9 (11.86)	60.1 (11.84)	59.8 (12.48)	60.1 (12.39)	60.0 (12.13)
Age group (years) (n, %)					
< 65	177 (60.8%)	179 (61.1%)	173 (61.6%)	175 (58.3%)	704 (60.4%)
≥ 65	114 (39.2%)	114 (38.9%)	108 (38.4%)	125 (41.7%)	461 (39.6%)
< 75	265 (91.1%)	262 (89.4%)	250 (89.0%)	274 (91.3%)	1051 (90.2%)
≥ 75	26 (8.9%)	31 (10.6%)	31 (11.0%)	26 (8.7%)	114 (9.8%)
Race (n, %)					
White	288 (99.0%)	290 (99.0%)	278 (98.9%)	297 (99.0%)	1153 (99.0%)
Black or African American	2 (0.7%)	0	1 (0.4%)	2 (0.7%)	5 (0.4%)
Asian	0	2 (0.7%)	1 (0.4%)	1 (0.3%)	4 (0.3%)
Other †	1 (0.3%)	1 (0.3%)	1 (0.4%)	0	3 (0.3%)
BMI (kg/m^2)					
Mean (SD)	28.3 (5.01)	27.8 (5.05)	28.4 (5.18)	28.4 (5.39)	28.2 (5.16)
Geographical region (n, %)					
Eastern Europe	127 (43.6%)	130 (44.4%)	115 (40.9%)	135 (45.0%)	507 (43.5%)
Western Europe‡	164 (56.4%)	163 (55.6%)	166 (59.1%)	165 (55.0%)	658 (56.5%)

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set Incontinence [FAS-I]). The denominators for the percentage calculations of the categorical variables are the number of patients with nonmissing values. Body mass index (BMI) = weight (kg)/height (m^2).

† Other race: placebo: Romanian; mirabegron 50 mg: Pakistani; mirabegron 100 mg: Latin.

‡ For the purposes of this summary, Australia was included within the Western Europe category. A list of countries included in each geographical region (Eastern Europe or Western Europe) is provided [see Appendix 1 of the SAP, Appendix 13.1.9].

Source: Tables 12.1.2.1.3 and Appendix 13.2.4.1

Table 4 Overview of Coprimary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)			
	Mirabegron 50 mg (n=293)	**Mirabegron 100 mg (n=281)**	**Tolterodine SR 4 mg (n=300)**
Mean difference from placebo (SE) 95% CI	-0.41 (0.160) (-0.72, -0.09)	-0.29 (0.162) (-0.61, 0.03)	-0.10 (0.159) (-0.42, 0.21)
P-values†	0.003#	0.010#	0.11
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours (FAS)			
	Mirabegron 50 mg (n=473)	**Mirabegron 100 mg (n=478)**	**Tolterodine SR 4 mg (n=475)**
Mean difference from placebo (SE) 95% CI	-0.60 (0.156) (-0.90, -0.29)	-0.44 (0.156) (-0.74, -0.13)	-0.25 (0.156) (-0.55, 0.06)
P-values‡	<0.001#	0.005#	0.11

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

† Nominal P-values were from pairwise comparisons vs placebo within the stratified rank analysis of covariance (ANCOVA).

‡ Nominal P-values were from pairwise comparisons vs placebo within the ANCOVA model.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustments.

Source: Tables 12.3.1.1 and Table 12.3.1.2

Table 5 Overview of Key Secondary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition (FAS)			
	Mirabegron 50 mg (n=472)	**Mirabegron 100 mg (n=478)**	**Tolterodine SR 4 mg (n=475)**
Mean difference from placebo (SE) 95% CI	11.9 (2.83) (6.3, 17.4)	13.2 (2.82) (7.7, 18.7)	12.6 (2.83) (7.1, 18.2)
P-values‡	<0.001#	<0.001#	<0.001&
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)			
	Mirabegron 50 mg (n=293)	**Mirabegron 100 mg (n=281)**	**Tolterodine SR 4 mg (n=299)**
Mean difference from placebo (SE) 95% CI	-0.39 (0.167) (-0.71, -0.06)	-0.38 (0.169) (-0.71, -0.05)	-0.35 (0.166) (-0.68, -0.03)
P-values†	0.002#	0.002#	0.019&
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)			
	Mirabegron 50 mg (n=471)	**Mirabegron 100 mg (n=477)**	**Tolterodine SR 4 mg (n=474)**
Mean difference from placebo (SE) 95% CI	-0.40 (0.136) (-0.66, -0.13)	-0.52 (0.136) (-0.79, -0.26)	-0.33 (0.136) (-0.60, -0.06)
P-values‡	0.004#	<0.001#	0.016&

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

† Nominal P-values were from pairwise comparisons vs placebo within the stratified rank analysis of covariance (ANCOVA).

‡ Nominal P-values were from pairwise comparisons vs placebo within the ANCOVA model.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustments.

& Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustments.

Source: Table 12.3 4.1, Table 12.3.4.2 and Table 12.3.4.3

Table 6 Common (≥ 2 % of Patients in Any Treatment Group) Treatment-emergent Adverse Events

MedDRA (v9.1) Preferred Term, n (%)	Placebo (n=494) n (%)	Mirabegron			Tolterodine SR 4 mg (n=495) n (%)
		50 mg (n=493) n (%)	100 mg (n=496) n (%)	Total (n=989) n (%)	
Hypertension	38 (7.7%)	29 (5.9%)	27 (5.4%)	56 (5.7%)	40 (8.1%)
Nasopharyngitis	8 (1.6%)	14 (2.8%)	14 (2.8%)	28 (2.8%)	14 (2.8%)
Dry mouth	13 (2.6%)	14 (2.8%)	14 (2.8%)	28 (2.8%)	50 (10.1%)
Headache	14 (2.8%)	18 (3.7%)	9 (1.8%)	27 (2.7%)	18 (3.6%)
Influenza	8 (1.6%)	11 (2.2%)	10 (2.0%)	21 (2.1%)	7 (1.4%)
Urinary tract infection	7 (1.4%)	7 (1.4%)	9 (1.8%)	16 (1.6%)	10 (2.0%)
Constipation	7 (1.4%)	8 (1.6%)	8 (1.6%)	16 (1.6%)	10 (2.0%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set). 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. Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level. Adverse events were sorted in descending incidence of the Total mirabegron column by preferred term.

Source: Table 12.6.1.5

Table 7 Summary of Serious Treatment-emergent Adverse Events

MedDRA (v9.1) System Organ Class Preferred Term	Placebo (n=494) n (%)	Mirabegron 50 mg (n=493) n (%)	Mirabegron 100 mg (n=496) n (%)	Mirabegron Total (n=989) n (%)	Tolterodine SR 4 mg (n=495) n (%)
Any serious adverse event	**8 (1.6%)**	**14 (2.8%)**	**12 (2.4%)**	**26 (2.6%)**	**11 (2.2%)**
Infections and Infestations	**0**	**3 (0.6%)**	**1 (0.2%)**	**4 (0.4%)**	**1 (0.2%)**
Erysipelas	0	0	1 (0.2%)	1 (0.1%)	1 (0.2%)
Hepatitis A	0	1 (0.2%)	0	1 (0.1%)	0
Postoperative infection	0	1 (0.2%)	0	1 (0.1%)	0
Urinary tract infection	0	1 (0.2%)	0	1 (0.1%)	0
Injury, Poisoning and Procedural Complications	**2 (0.4%)**	**2 (0.4%)**	**2 (0.4%)**	**4 (0.4%)**	**1 (0.2%)**
Fall	0	0	1 (0.2%)	1 (0.1%)	1 (0.2%)
Humerus fracture	0	1 (0.2%)	0	1 (0.1%)	0
Limb injury	0	1 (0.2%)	0	1 (0.1%)	0
Open wound	0	0	1 (0.2%)	1 (0.1%)	0
Gas poisoning	1 (0.2%)	0	0	0	0
Lower limb fracture	1 (0.2%)	0	0	0	0
Cardiac Disorders	**3 (0.6%)**	**2 (0.4%)**	**1 (0.2%)**	**3 (0.3%)**	**1 (0.2%)**
Atrial fibrillation	0	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
Acute coronary syndrome	0	1 (0.2%)	0	1 (0.1%)	0
Cardiac failure acute	0	0	1 (0.2%)	1 (0.1%)	0
Arrhythmia	0	0	0	0	1 (0.2%)
Atrioventricular block first degree	1 (0.2%)	0	0	0	0
Coronary artery disease	1 (0.2%)	0	0	0	0
Myocardial infarction	1 (0.2%)	0	0	0	0
Gastrointestinal Disorders	**0**	**1 (0.2%)**	**2 (0.4%)**	**3 (0.3%)**	**1 (0.2%)**
Abdominal pain	0	1 (0.2%)	0	1 (0.1%)	0
Enterocele	0	0	1 (0.2%)	1 (0.1%)	0
Pancreatitis chronic	0	0	1 (0.2%)	1 (0.1%)	0
Reflux oesophagitis	0	0	1 (0.2%)	1 (0.1%)	0
Gastritis	0	0	0	0	1 (0.2%)
Renal and Urinary Disorders	**0**	**2 (0.4%)**	**1 (0.2%)**	**3 (0.3%)**	**0**
Calculus urinary	0	0	1 (0.2%)	1 (0.1%)	0
Nephrolithiasis	0	1 (0.2%)	0	1 (0.1%)	0
Urinary retention	0	1 (0.2%)	0	1 (0.1%)	0
Investigations	**0**	**1 (0.2%)**	**1 (0.2%)**	**2 (0.2%)**	**1 (0.2%)**
Cardiovascular evaluation	0	0	1 (0.2%)	1 (0.1%)	0
Hepatic enzyme increased	0	1 (0.2%)	0	1 (0.1%)	0
Catheterisation cardiac	0	0	0	0	1 (0.2%)
Nervous System Disorders	**1 (0.2%)**	**1 (0.2%)**	**1 (0.2%)**	**2 (0.2%)**	**2 (0.4%)**
Cerebral ischaemia	0	0	1 (0.2%)	1 (0.1%)	0
Neuralgia	0	1 (0.2%)	0	1 (0.1%)	0
Balance disorder	1 (0.2%)	0	0	0	0
Epilepsy	0	0	0	0	1 (0.2%)
Ruptured cerebral aneurysm	0	0	0	0	1 (0.2%)
Surgical and Medical Procedures	**1 (0.2%)**	**0**	**2 (0.4%)**	**2 (0.2%)**	**1 (0.2%)**
Bunion operation	0	0	2 (0.4%)	2 (0.2%)	0
Papilloma excision	0	0	0	0	1 (0.2%)
Polypectomy	1 (0.2%)	0	0	0	0
Eye Disorders	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**	**0**
Retinitis	0	1 (0.2%)	0	1 (0.1%)	0

Table continued on next page

MedDRA (v9.1) System Organ Class Preferred Term	Placebo (n=494) n (%)	Mirabegron 50 mg (n=493) n (%)	Mirabegron 100 mg (n=496) n (%)	Mirabegron Total (n=989) n (%)	Tolterodine SR 4 mg (n=495) n (%)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**	**1 (0.2%)**
Rotator cuff syndrome	0	1 (0.2%)	0	1 (0.1%)	0
Sympathetic posterior cervical syndrome	0	0	0	0	1 (0.2%)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**	**1 (0.2%)**
Bowen's disease	0	0	1 (0.2%)	1 (0.1%)	0
Leukaemia	0	0	0	0	1 (0.2%)
Pregnancy, Puerperium and Perinatal Conditions	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**	**0**
Pregnancy	0	1 (0.2%)	0	1 (0.1%)	0
Reproductive System and Breast Disorders	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**	**0**
Rectocele	0	0	1 (0.2%)	1 (0.1%)	0
Vaginal erosion	0	0	1 (0.2%)	1 (0.1%)	0
Vascular Disorders	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**	**1 (0.2%)**
Hypertensive crisis	0	1 (0.2%)	0	1 (0.1%)	0
Hypertension	0	0	0	0	1 (0.2%)
General Disorders and Administration Site Conditions	**2 (0.4%)**	**0**	**0**	**0**	**0**
Asthenia	1 (0.2%)	0	0	0	0
Chest pain	1 (0.2%)	0	0	0	0
Pyrexia	1 (0.2%)	0	0	0	0
Hepatobiliary Disorders	**0**	**0**	**0**	**0**	**1 (0.2%)**
Hepatitis	0	0	0	0	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**0**	**1 (0.2%)**
Asthma	0	0	0	0	1 (0.2%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set). 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. Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level.

Source: Table 12.6.1.6

Table 8 Overview of Change from Baseline to Final Visit in Vital Signs Measured by Patient's Diary, Overall Population

	Placebo (n=494)		Mirabegron 50 mg (n=493)		Mirabegron 100 mg (n=496)		Tolterodine SR 4 mg (n=495)	
Pulse Rate (bpm)								
AM								
n	481		474		479		476	
Baseline mean (SE)	70.0 (0.43)		69.5 (0.42)		69.3 (0.45)		69.8 (0.44)	
Adjusted mean change from baseline (SE)	0.8 (0.28)		1.6 (0.28)		2.4 (0.28)		1.6 (0.28)	
Mean difference vs placebo (SE)			0.8 (0.39)		1.6 (0.39)		0.8 (0.39)	
95% two-sided CI			0.0, 1.6		0.8, 2.4		0.0, 1.6	
PM								
n	479		474		478		476	
Baseline mean (SE)	74.5 (0.46)		73.9 (0.43)		73.0 (0.45)		73.9 (0.45)	
Adjusted mean change from baseline (SE)	0.1 (0.29)		0.8 (0.29)		2.1 (0.29)		2.0 (0.29)	
Mean difference vs placebo (SE)			0.7 (0.40)		2.0 (0.40)		1.9 (0.40)	
95% two-sided CI			-0.1, 1.5		1.2, 2.8		1.1, 2.7	
Blood Pressure (mm Hg)	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
AM								
n	481	481	474	474	479	478	476	476
Baseline mean (SE)	128.4 (0.77)	76.8 (0.42)	127.2 (0.75)	76.0 (0.38)	127.5 (0.72)	76.6 (0.39)	128.2 (0.75)	76.8 (0.40)
Adjusted mean change from baseline (SE)	0.7 (0.40)	0.4 (0.26)	0.6 (0.40)	0.3 (0.26)	1.0 (0.40)	0.5 (0.26)	0.1 (0.40)	0.9 (0.26)
Mean difference vs placebo (SE)			-0.1 (0.56)	-0.1 (0.36)	0.4 (0.56)	0.2 (0.36)	-0.5 (0.56)	0.5 (0.36)
95% two-sided CI			-1.2, 1.0	-0.8, 0.6	-0.7, 1.5	-0.5, 0.9	-1.6, 0.6	-0.2, 1.2
PM								
n	479	479	474	474	478	478	476	476
Baseline mean (SE)	127.4 (0.64)	75.4 (0.38)	127.2 (0.69)	74.6 (0.39)	126.8 (0.64)	74.9 (0.37)	127.4 (0.64)	75.4 (0.38)
Adjusted mean change from baseline (SE)	1.2 (0.41)	0.3 (0.26)	0.3 (0.41)	0.3 (0.26)	1.7 (0.41)	1.2 (0.26)	0.4 (0.41)	1.3 (0.26)
Mean difference vs placebo (SE)			-0.9 (0.58)	-0.0 (0.37)	0.5 (0.58)	0.9 (0.37)	-0.8 (0.58)	1.0 (0.37)
95% two-sided CI			-2.1, 0.2	-0.8, 0.7	-0.7, 1.6	0.1, 1.6	-1.9, 0.4	0.2, 1.7

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set). The adjusted mean change from baseline, mean difference vs placebo and 95% CI are from an analysis of covariance (ANCOVA) model that included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

bpm: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Source: Table 12.6.3.4.1