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

SYNOPSIS

Title of Study:

A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of the Beta-3 Agonist Mirabegron (25 mg qd and 50 mg qd) in Subjects with Symptoms of Overactive Bladder; Protocol 178-CL-074 (CAPRICORN)

Coordinating Investigator:

[redacted], Prof. Dr., [redacted]

Responsible Medical Officers:

[redacted] MD, [redacted], Europe.

[redacted], MD, PharmD, FCP, [redacted]

Study Center(s):

This multinational, multicenter study was conducted at 151 sites in Europe (56 sites) and North America (95 sites). A total of 160 sites were initiated; 151 sites enrolled patients.

Publication (reference):

None

Study Period:

1 year

Date of first enrollment (Study initiation date):

28 Apr 2009

Date of last evaluation (Study completion date):

27 Apr 2010

Phase of Development:

Phase 3

Objectives:

The primary objective of the study was to assess the efficacy of mirabegron (25 mg qd and 50 mg qd) against placebo in the treatment of patients with symptoms of overactive bladder (OAB).

The secondary objective was to assess the safety and tolerability of mirabegron (25 mg qd and 50 mg qd) against placebo in the treatment of patients with symptoms of OAB.

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Methodology:

This was a phase 3, randomized, parallel group, placebo-controlled, double-blind, double-dummy, multicenter, multinational study conducted in female and male patients of at least 18 years of age with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) present for at least 3 months. 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). At baseline (visit 2), patients who met inclusion criteria and did not meet exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 25 mg, mirabegron 50 mg or a matching placebo once daily for a 12-week double-blind, placebo-controlled, treatment period that consisted of visits at weeks 4, 8 and 12 with a 2-week follow-up visit after end of treatment.

Number of Patients (planned, enrolled and analyzed):

Planned: 1821 enrolled, 1311 randomized

Actual: 2201 enrolled, 1306 randomized

Randomized Analysis Set: 1306 patients
- Placebo: 433 patients; mirabegron 25 mg: 433 patients; mirabegron 50 mg: 440 patients

Full Analysis Set (FAS): 1251 patients
- Placebo: 415 patients; mirabegron 25 mg: 410 patients; mirabegron 50 mg: 426 patients

Full Analysis Set Incontinence (FAS-I): 773 patients
- Placebo: 262 patients; mirabegron 25 mg: 254 patients; mirabegron 50 mg: 257 patients

Safety Analysis Set (SAF): 1305 patients
- Placebo: 433 patients; mirabegron 25 mg: 432 patients; mirabegron 50 mg: 440 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 were excluded if they had diabetic neuropathy; significant stress incontinence or mixed stress/urgency incontinence with stress as the predominant factor; an indwelling catheter; evidence of a 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 electrostimulation 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

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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 transpeptidase (GGT) > 3 times the ULN, as assessed in screening samples and considered clinically significant by the investigator; they had severe hypertension (as defined above); 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 if 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 (AEs) 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.

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

Mirabegron (oral controlled absorption system formulation) tablets: 25 mg and 50 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 25 mg or 50 mg.

Lot numbers:
25 mg tablet– [redacted] (North America), [redacted] (Europe)
50 mg tablet– [redacted] (North America), [redacted] (Europe)

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 2 weeks after the week 12 visit.

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

Two placebo tablets to match mirabegron 25 mg and 50 mg were administered each morning (qd) by mouth with a glass of water with or without food to patients randomized to placebo.

Lot numbers:
Placebo to match mirabegron 25 mg tablet– [redacted] (North America), [redacted] (Europe)

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Placebo to match mirabegron 50 mg tablet– [redacted] (North America), [redacted] (Europe)

Criteria for Evaluation:

The coprimary efficacy variables included:

Change from baseline to end of treatment (final visit) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary
Change from baseline to end of treatment (final visit) in mean number of micturitions per 24 hours based on a 3-day micturition diary

The key secondary efficacy variables (all based on the 3-day micturition diary) included:

Change from baseline to end of treatment (final visit) in mean volume voided per micturition
Change from baseline to week 4 in mean number of incontinence episodes per 24 hours
Change from baseline to week 4 in mean number of micturitions per 24 hours
Change from baseline to end of treatment (final visit) in mean level of urgency
Change from baseline to end of treatment (final visit) in mean number of urgency incontinence episodes per 24 hours
Change from baseline to end of treatment (final visit) in mean number of urgency episodes (grades 3 or 4) per 24 hours

Safety variables included:

Treatment-emergent adverse events (TEAEs)
Events adjudicated by the independent cardiovascular adjudication committee
TEAEs of interest (i.e., hypertension, corrected QT interval (QTc) prolongation, cardiac arrhythmias, urinary retention/acute urinary retention, hypersensitivity type events, syncope type events, seizure type events, hepatic type events and renal and urinary events)
Clinical laboratory evaluations (i.e., hematology, biochemistry, urinalysis and thyroid analytes)
Vital signs (sitting SBP, sitting DBP and pulse rate)
ECGs
Postvoid residual volume (PVR)
Physical examination

Statistical Methods:

Since there were 2 coprimary efficacy variables and 6 key secondary efficacy variables, the type I error rate was controlled at the alpha = 0.05 level using a stepwise parallel gatekeeping procedure. At each of the 8 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 final visit

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Stage 2: micturitions at final visit
Stage 3: volume voided per micturition at final visit
Stage 4: incontinence episodes at week 4
Stage 5: micturitions at week 4
Stage 6: level of urgency at final visit
Stage 7: urgency incontinence episodes at final visit
Stage 8: urgency episodes (grade 3 or 4) at final visit

Since 2 mirabegron 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

Change from baseline to final visit in mean number of incontinence episodes per 24 hours (coprimary efficacy variable) was analyzed using a 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. This stratified rank ANCOVA model was also used as the primary analysis for the key secondary efficacy variables of change from baseline to week 4 in mean number of incontinence episodes per 24 hours and change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours.

Change from baseline to final visit in mean number of micturitions per 24 hours (coprimary efficacy variable) was analyzed using an ANCOVA including treatment, sex and geographical region as fixed factors and baseline as a covariate. This ANCOVA model was also used as the primary analysis for the key secondary efficacy variables of change from baseline to final visit in mean volume voided per micturition, change from baseline to week 4 in mean number of micturitions per 24 hours, change from baseline to final visit in mean level of urgency, and change from baseline to final visit in mean number of urgency (grades 3 or 4) episodes per 24 hours.

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 were calculated.

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 were derived from the corresponding ANCOVA model with all treatment groups in the model.

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Summary of Results/Conclusions:

Population:

Demographic and baseline characteristics were consistent across treatment groups for patients in the SAF population. Overall, 68.7% of patients were female. The majority (63.1%) of patients were < 65 years of age and 90.4% were < 75 years of age. The mean body mass index (BMI) across all treatment groups was 29.5 kg/m^2.

Generally, demographic and baseline characteristics were similar across treatment groups in the FAS and FAS-I. Overall, approximately 69% and 80% of patients were female in the FAS and FAS-I, respectively. The higher proportion of female patients was the major difference in demographics and baseline characteristics observed between the FAS and FAS-I populations.

Efficacy Results:

The results from this study demonstrate:
For the coprimary efficacy endpoints:

The mirabegron 25 mg and 50 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: -0.40 and -0.42, mirabegron 25 mg and mirabegron 50 mg, respectively). The adjusted mean changes from baseline to final visit were -0.96, -1.36 and -1.38 for the placebo, mirabegron 25 mg and 50 mg groups, respectively. The mirabegron 25 mg and 50 mg groups demonstrated statistically significant greater reductions from baseline to final visit and in the mean number of micturitions per 24 hours (difference from placebo: -0.47 and -0.42, mirabegron 25 mg and mirabegron 50 mg). The adjusted mean changes from baseline to final visit were -1.18, -1.65 and -1.60 for the placebo, mirabegron 25 mg and 50 mg groups, respectively.

For the key secondary efficacy endpoints:

- The mirabegron 50 mg group had a statistically significant greater increase from baseline to final visit compared to placebo in the mean volume voided per micturition (difference from placebo: 12.4 mL); mirabegron 25 mg was not statistically significant compared to placebo (difference from placebo: 4.6 mL). Since the mirabegron 25 mg group did not meet significance for mean volume voided with multiplicity adjustment, subsequent endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level as part of the gatekeeping procedure. Subsequent endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing.
- The mirabegron 50 mg group had a statistically significant greater reduction from baseline to first measured time postdose at week 4 compared to placebo in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.51); the mean number of

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incontinence episodes per 24 hours in the mirabegron 25 mg group did not reach statistical significance (difference from placebo: -0.34).

- For all other key secondary efficacy variables, statistical significance was not achieved for either mirabegron treatment group due to the gatekeeping procedure which precluded further statistical testing on subsequent variables in the hierarchy once a dose group failed to reach statistical significance for an efficacy variable. The mirabegron 25 mg dose group failed to reach statistical significance versus placebo for mean volume voided per micturition and thus statistical testing was not performed on the remaining efficacy variables; change from baseline to week 4 in mean number of incontinence episodes per 24 hours, change from baseline to week 4 in the mean number of micturitions per 24 hours, and change from baseline to final visit in mean level of urgency, mean number of urgency incontinence episodes per 24 hours and mean number of urgency episodes (grade 3 or 4) per 24 hours. In accordance with the gatekeeping procedure described above the mirabegron 50 mg group was tested at a significance level of 0.025 for the remaining variables. Using this criterion for evaluation, the mirabegron 50 mg dose group failed to reach statistical significance for change from baseline to week 4 in mean number of micturitions per 24 hours thus precluding statistical testing for the remaining efficacy variables; change from baseline to final visit in mean level of urgency, mean number of urgency incontinence episodes per 24 hours and mean number of urgency episodes (grade 3 or 4) per 24 hours. For all of these variables however, there was a numeric trend toward a greater reduction from baseline with mirabegron 50 mg compared to mirabegron 25 mg.

For the additional secondary endpoints (the statistics for which were not subject to multiplicity adjustment):

- The mirabegron 25 mg and 50 mg treatment groups demonstrated statistically significantly greater reductions from baseline compared to placebo in mean number of incontinence episodes per 24 hours at weeks 8 and 12.
- The mirabegron 25 mg and 50 mg treatment groups demonstrated statistically significantly greater reductions from baseline compared to placebo at week 8 for mean number of micturitions per 24 hours. A numerical advantage was maintained in both groups at week 12 relative to placebo; however, the difference was not statistically significant, likely due to the magnitude of the placebo effect on micturition frequency at week 12.
- The mirabegron 50 mg treatment group demonstrated a statistically significant increase compared to placebo in mean volume voided per micturition at weeks 4, 8 and 12. A statistically significant difference compared to placebo in the mirabegron 25 mg group was not observed; the treatment by visit interaction was statistically significant (P = 0.030).
- The mirabegron 50 mg treatment group demonstrated statistically significantly greater improvements from baseline to weeks 4, 8 and 12 compared to placebo in mean level of urgency, mean number of urgency incontinence episodes per 24 hours and urgency episodes

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(grades 3 or 4) (weeks 4 and 8 only). The mirabegron 25 mg treatment group demonstrated numerically greater improvements on the 3 urgency assessments compared to placebo; statistical significance was achieved with mirabegron 25 mg for reduction from baseline to weeks 4, 8 and 12 in mean number of urgency incontinence episodes per 24 hours compared to placebo.

- For the TS-VAS, both the mirabegron 25 and 50 mg groups demonstrated statistically significantly greater increases from baseline to final visit compared to placebo.
- For the OAB-q, the mirabegron 50 mg group demonstrated statistically significantly greater improvements from baseline to final visit compared to placebo in the Symptom Bother scale.

Both doses of mirabegron examined in this study demonstrated efficacy based on the co-primary endpoints. Mirabegron 50 mg attained statistical significance at more secondary endpoints than mirabegron 25 mg.

Safety Results:

Based on the overall results of this study, mirabegron at doses of 25 and 50 mg were safe and well tolerated.

- The overall incidence of TEAEs was similar across the treatment groups (50.1%, 48.6% and 47.3% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively).
- No deaths were reported in this study.
- The overall incidence of treatment-emergent SAEs was 2.8%, 1.6% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.
- The overall incidence of patients who discontinued study drug due to a TEAE was 3.7%, 3.9% and 2.5% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

For events of interest:

- The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was 8.5%, 12.0% and 11.1% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Although the incidence of hypertension TEAEs was higher in mirabegron 25 mg treated patients relative to the placebo group, adjusted mean changes from baseline to final visit in SBP and DBP were comparable between the two groups.
- No TEAEs of QTc prolongation or its sequelae were observed. No proarrhythmic events of ventricular tachycardia, ventricular fibrillation or torsade de pointes were reported.
- The overall incidence of arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 2.5% in the placebo group and 3.0% in each of the mirabegron groups. Cases of atrial fibrillation of medical importance (based on predefined criteria) were noted in 1 (0.2%) patient treated with placebo, 1 (0.2%) patient treated with mirabegron 25 mg and 2 (0.5%) patients treated with mirabegron 50 mg.

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- The overall incidence of adjudicated APTC/MACE cardiovascular events was 0.5% in placebo-treated patients (2 patients experienced nonfatal strokes) and 0.0% in the mirabegron-treated groups.
- There was 1 event of urinary retention in a placebo-treated patient. Acute urinary retention was not observed in this study.
- The overall incidence of events indicative of potential hypersensitivity was similar across treatment groups. Medical evaluation identified 3 patients (2 placebo, 1 mirabegron 25 mg) with AEs in the category of "likely hypersensitivity". In the placebo patients, these events included dermatitis allergic in 1 patient and rash maculo-papular in the other patient. Rash and rash pruritic were reported in the patient who received mirabegron 25 mg
- No episodes of syncope were reported in this study.
- No events of seizure were reported in the mirabegron-treated patients; grand mal convulsion and petit mal epilepsy each occurred in 1 patient in the placebo group.
- For hepatic events:
  - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders – Comprehensive Search SMQ, was 1.2%, 1.4% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. All hepatic TEAEs, with the exception of 1 event in a patient treated with mirabegron 50 mg, were mild or moderate in intensity. This one patient, judged by the investigator as having a "severe liver test abnormal", had AST and GGT levels slightly above 1 x ULN.
  - No patient met laboratory criteria for Hy's law. The incidence of patients with hepatic parameters meeting PCS criteria was 0.5%, 0.7% and 0.2% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively (excluding patients that only met the isolated GGT PCS criterion as this laboratory evaluation is nonspecific for hepatic evaluations).
  - The incidence of any hepatic finding when TEAEs and PCS hepatic laboratory value criteria were assessed concurrently was 1.6%, 1.6% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg treatment groups, respectively.

- Changes in hematology and serum chemistry parameters, including renal parameters, were unremarkable and consistent across treatment groups.
- For AM measurements, the increases in mean pulse rate with mirabegron 25 mg and 50 mg relative to placebo were not dose-dependent (0.8 and 0.9 bpm, respectively, at final visit) but did appear to be dose-dependent for the PM measurement (0.6 and 1.1 bpm, respectively, at the final visit). These increases in pulse rate relative to baseline were not observed at the follow-up visit, at which point study drug had been discontinued for approximately 2 weeks.
- As described above adjusted mean changes from baseline in SBP and DBP measurements were comparable between the placebo and mirabegron 25 mg groups. The mirabegron 50 mg group experienced small

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increases in SBP relative to placebo (1.5 mm Hg for AM and PM measurements, respectively) and a small increase relative to placebo for AM DBP (1.0 mm Hg). Similar trends were observed in both the normotensive and hypertensive subgroups but the mean increases relative to placebo were smaller in hypertensive patients treated with mirabegron 50 mg. Smaller increases in blood pressure were noted in patients ≥65 years of age compared to patients < 65 years of age treated with mirabegron.

- Systolic and diastolic blood pressure measurements at the follow-up visit were consistent with baseline values at which point the study drug had been discontinued for approximately 2 weeks.
- Increases in heart rate noted on ECGs were consistent with increases in pulse rate based on diary data. No consistent ECG trends by treatment were identified.
- No trend in the incidence of notable shifts in PVR volume across treatment groups was observed. In cases where PVR shifts were noted, these did not result in reported adverse events that required intervention. Two patients in the placebo group and 1 patient in the mirabegron 50 mg group had a PVR volume ≥ 300 mL at the final visit.

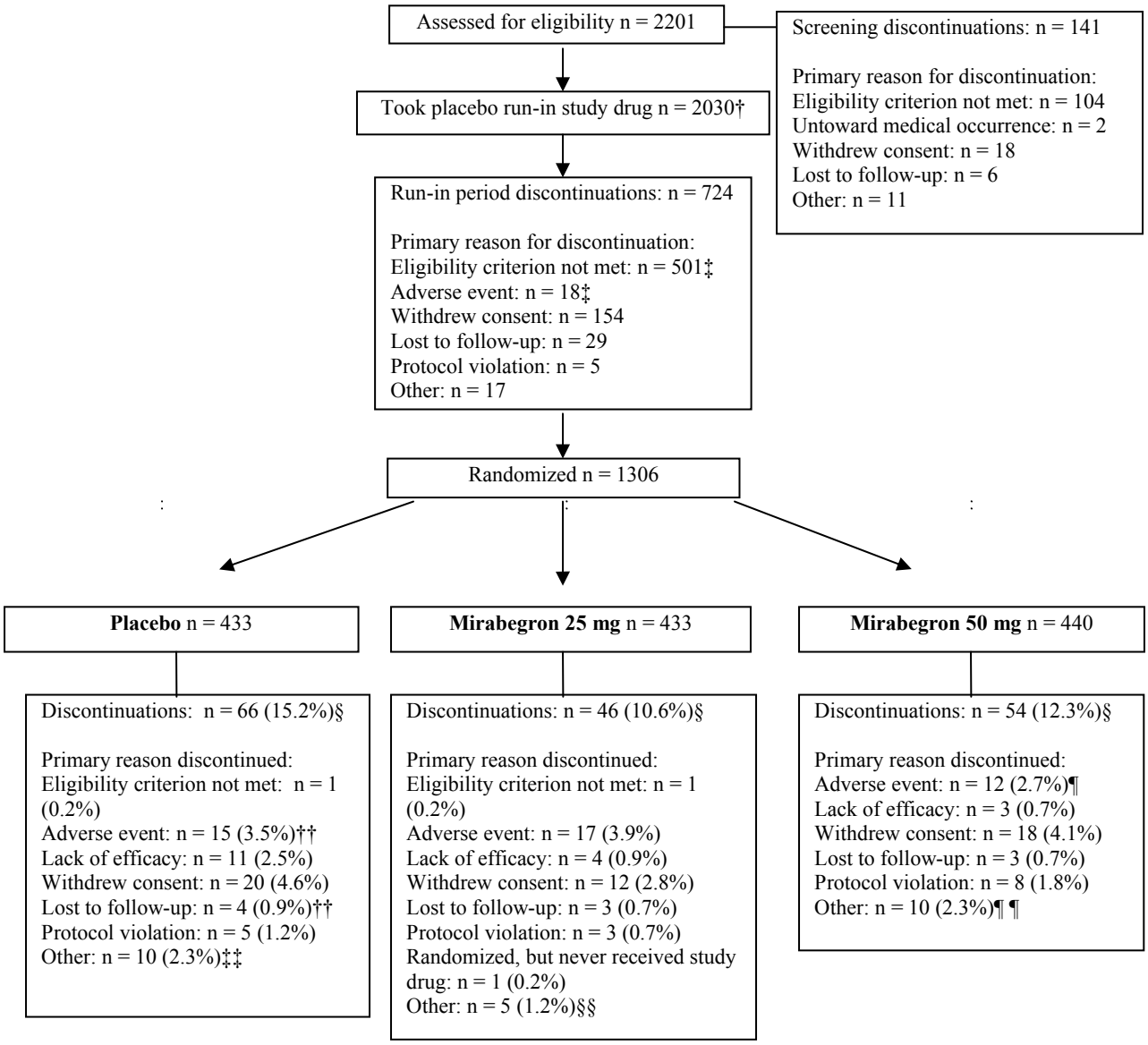
CONCLUSIONS:

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

- Mirabegron at doses of 25 and 50 mg once daily for 12 weeks demonstrated efficacy in the treatment of the symptoms of urinary frequency and incontinence that are characteristic of OAB. This study showed that while mirabegron 25 mg is efficacious, this dose does not represent a maximally effective dose.
- Mirabegron at doses of 25 and 50 mg once daily for 12 weeks was safe and well tolerated.

Date of Report: 01 February 2011

Figure 1 Patient Disposition



All patients.

AE: adverse event; ECG: electrocardiogram; TEAE: treatment-emergent adverse event; UTI: urinary tract infection.

† Thirty patients returned full medication kits at baseline visit (visit 2) indicating that they did not take any study medication and thus were considered run-in failures.

‡ One patient in the run-in period (Patient No. [redacted]) experienced a AE of urinary tract infection that led to permanent discontinuation of study drug [Appendix 13.2.7.6]. This patient is included in Figure 1 as discontinued due to eligibility criterion not met.

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

¶ One patient in the mirabegron 50 mg group (Patient No. [redacted]) reported an AE prior to start of double-blind study drug that led to permanent discontinuation of study drug; therefore, this patient is not included in the summary of patients who discontinued due to TEAEs.

Footnotes continued on next page

†† One patient in the placebo group (Patient No. [redacted]) experienced a TEAE of chest pain that led to permanent discontinuation of study drug. This patient is included as discontinued due to lost to follow-up in Figure 1.

‡‡ Other reasons for discontinuation in the placebo group were medications that were considered exclusionary by the medical monitor, early termination due to medical history, possibility of patient missing safety assessments at visits 5 and 6, and initial ECG conducted on wrong machine which was initially read as abnormal (and was later reread and assessed as normal after the patient was discontinued).

§§ Other reasons for discontinuation in the mirabegron 25 mg group were medications that were considered exclusionary, either by the protocol or by the medical monitor and concomitant leukopenia and thrombocytopenia.

¶¶ Other reasons for discontinuation in the mirabegron 50 mg group were medications that were considered exclusionary either by the protocol or the medical monitor, cannabis use and multiple prior UTIs.

Source: Tables 12.1.1.1, 12.1.1.3.1, 12.1.1.3.2, 12.1.1.3.3 and Appendix 13.2.1.2

Table 1 Summary of Patient Demographics and Baseline Characteristics, SAF

Parameter	Placebo (n = 433)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 440)	Total (n = 1305)
Sex (n, %)				
Male	132 (30.5%)	139 (32.2%)	137 (31.1%)	408 (31.3%)
Female	301 (69.5%)	293 (67.8%)	303 (68.9%)	897 (68.7%)
Age (years)	58.2	58.5	60.3	59.0
Mean (SD)	(13.73)	(12.85)	(12.22)	(12.97)
Age group (years) (n, %)				
< 65	273 (63.0%)	278 (64.4%)	272 (61.8%)	823 (63.1%)
≥ 65	160 (37.0%)	154 (35.6%)	168 (38.2%)	482 (36.9%)
< 75	388 (89.6%)	400 (92.6%)	392 (89.1%)	1180 (90.4%)
≥ 75	45 (10.4%)	32 (7.4%)	48 (10.9%)	125 (9.6%)
Race (n, %)				
White	389 (89.8%)	394 (91.2%)	400 (90.9%)	1183 (90.7%)
Black or African American	35 (8.1%)	32 (7.4%)	33 (7.5%)	100 (7.7%)
Asian	7 (1.6%)	5 (1.2%)	5 (1.1%)	17 (1.3%)
Other	2 (0.5%)†	1 (0.2%)‡	2 (0.5%)§	5 (0.4%)
Ethnicity (n, %)				
Hispanic/Latino	23 (5.3%)	24 (5.6%)	21 (4.8%)	68 (5.2%)
Non-Hispanic/Non-Latino	410 (94.7%)	408 (94.4%)	419 (95.2%)	1237 (94.8%)
BMI (kg/m^2)				
n	433	432	440	1305
Mean (SD)	29.2 (6.29)	29.8 (6.50)	29.5 (6.54)	29.5 (6.45)
Geographical region (n, %)				
Eastern Europe	75 (17.3%)	76 (17.6%)	75 (17.0%)	226 (17.3%)
Western Europe	126 (29.1%)	121 (28.0%)	120 (27.3%)	367 (28.1%)
Northeastern US	42 (9.7%)	40 (9.3%)	44 (10.0%)	126 (9.7%)
Midwestern US	23 (5.3%)	25 (5.8%)	23 (5.2%)	71 (5.4%)
Southern US	70 (16.2%)	74 (17.1%)	76 (17.3%)	220 (16.9%)
Western US	66 (15.2%)	71 (16.4%)	70 (15.9%)	207 (15.9%)
Canada	31 (7.2%)	25 (5.8%)	32 (7.3%)	88 (6.7%)

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 were the number of patients with nonmissing values. BMI = weight (kg)/height (m^2).

BMI: body mass index; US: United States.

† Other races in the placebo group included White and Black and Caucasian/African American/Native American (n=1 each).

‡ Other races in the mirabegron 25 mg group included Aboriginal (n=1).

§ Other races in the mirabegron 50 mg group included American Indian/Alaska Native and Caucasian/Black American (n=1 each).

Source: Table 12.1.2.1.1 and Appendix 13.2.4.1

Table 2 Summary of Patient Demographics and Baseline Characteristics, FAS and FAS-I

Parameter	FAS			FAS-I		
		Mirabegron			Mirabegron	
	Placebo (n = 415)	25 mg (n = 410)	50 mg (n = 426)	Placebo (n = 262)	25 mg (n = 254)	50 mg (n = 257)
Sex (n, %)						
Male	127 (30.6%)	134 (32.7%)	133 (31.2%)	51 (19.5%)	55 (21.7%)	52 (20.2%)
Female	288 (69.4%)	276 (67.3%)	293 (68.8%)	211 (80.5%)	199 (78.3%)	205 (79.8%)
Age (years)						
Mean	58.2	58.8	60.4	58.8	59.9	61.4
SD	13.83	12.68	12.26	13.54	12.08	11.97
Age group (years) (n, %)						
< 65	261 (62.9%)	263 (64.1%)	262 (61.5%)	165 (63.0%)	155 (61.0%)	149 (58.0%)
≥ 65	154 (37.1%)	147 (35.9%)	164 (38.5%)	97 (37.0%)	99 (39.0%)	108 (42.0%)
< 75	371 (89.4%)	378 (92.2%)	378 (88.7%)	231 (88.2%)	234 (92.1%)	225 (87.5%)
≥ 75	44 (10.6%)	32 (7.8%)	48 (11.3%)	31 (11.8%)	20 (7.9%)	32 (12.5%)
Race (n, %)						
White	372 (89.6%)	373 (91.0%)	389 (91.3%)	229 (87.4%)	231 (90.9%)	236 (91.8%)
Black or African American	34 (8.2%)	31 (7.6%)	31 (7.3%)	27 (10.3%)	19 (7.5%)	19 (7.4%)
Asian	7 (1.7%)	5 (1.2%)	4 (0.9%)	5 (1.9%)	3 (1.2%)	2 (0.8%)
Other	2 (0.5%)†	1 (0.2%)‡	2 (0.5%)§	1(0.4%)¶	1(0.4%)††	0
Ethnicity (n, %)						
Hispanic/Latino	21 (5.1%)	22 (5.4%)	21 (4.9%)	14 (5.3%)	17 (6.7%)	18 (7.0%)
Non-Hispanic/ Non-Latino	394 (94.9%)	388 (94.6%)	405 (95.1%)	248 (94.7%)	237 (93.3%)	239 (93.0%)
BMI (kg/m^2)						
n	415	410	426	262	254	257
Mean (SD)	29.1 (6.27)	29.6 (6.32)	29.5 (6.52)	29.3 (6.51)	30.5 (6.70)	29.8 (6.71)
Geographical region (n, %)						
Eastern Europe	73 (17.6%)	75 (18.3%)	74 (17.4%)	37 (14.1%)	38 (15.0%)	40 (15.6%)
Western Europe	123 (29.6%)	117 (28.5%)	119 (27.9%)	77 (29.4%)	70 (27.6%)	72 (28.0%)
Northeastern US	39 (9.4%)	38 (9.3%)	41 (9.6%)	27 (10.3%)	29 (11.4%)	27 (10.5%)
Midwestern US	22 (5.3%)	24 (5.9%)	22 (5.2%)	13 (5.0%)	16 (6.3%)	13 (5.1%)
Southern US	67 (16.1%)	68 (16.6%)	74 (17.4%)	51 (19.5%)	47 (18.5%)	44 (17.1%)
Western US	60 (14.5%)	64 (15.6%)	65 (15.3%)	36 (13.7%)	42 (16.5%)	43 (16.7%)
Canada	31 (7.5%)	24 (5.9%)	31 (7.3%)	21 (8.0%)	12 (4.7%)	18 (7.0%)

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]). The denominators for the percentage calculations of the categorical variables were the number of patients with nonmissing values. BMI = weight (kg)/height (m^2).

BMI: body mass index; US: United States.

† Other races in the placebo (FAS) group included White/Black and Caucasian/African American/Native American (n=1 each).

‡ Other races in the mirabegron 25 mg (FAS) group included Aboriginal (n=1).

§ Other races in the mirabegron 50 mg (FAS) group included American Indian/Alaska Native and Caucasian/Black American (n=1 each).

¶ Other races in the placebo (FAS-I) group included White and Black (n=1).

†† Other races in the mirabegron 25 mg (FAS-I) group included Aboriginal (n=1).

Source: Table 12.1.2.1.2, Table 12.1.2.1.3, Appendix 13.1.7 and Appendix 13.2.4.1

Table 3 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 25 mg (n = 254)	**Mirabegron 50 mg (n = 257)**
Mean difference from placebo (SE) 95% 2-sided CI	-0.40 (0.174) (-0.74, -0.06)	-0.42 (0.173) (-0.76, -0.08)
P-values†	0.005#	0.001#
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
Mean difference from placebo (SE) 95% 2-sided CI	-0.47 (0.176) (-0.82, -0.13)	-0.42 (0.174) (-0.76, -0.08)
P-values‡	0.007#	0.015#

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]).

ANCOVA: analysis of covariance.

† P-values were from pairwise comparison vs placebo within the stratified rank ANCOVA.

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

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

Source: Table 12.3.1.1 and Table 12.3.1.2

Table 4 Overview of Key Secondary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Volume Voided per Micturition (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	410 4.6 (3.16) (-1.6, 10.8)	426 12.4 (3.13) (6.3, 18.6)
P-values†	0.15	<0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)		
	Mirabegron 25 mg (n = 254)	**Mirabegron 50 mg (n = 257)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	254 -0.34 (0.172) (-0.68, -0.01)	255 -0.51 (0.171) (-0.85, -0.17)
P-values‡	0.039	<0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	410 -0.18 (0.176) (-0.53, 0.16)	424 -0.37 (0.174) (-0.71, -0.03)
P-values†	0.30	0.035
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	410 -0.07 (0.040) (-0.15, 0.01)	426 -0.14 (0.040) (-0.22, -0.06)
P-values†	0.083	<0.001
Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I)		
	Mirabegron 25 mg (n = 254)	**Mirabegron 50 mg (n = 257)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	247 -0.36 (0.157) (-0.67, -0.05)	251 -0.39 (0.156) (-0.69, -0.08)
P-values‡	0.004	0.002
Change from Baseline to Final Visit in Mean Number of Episodes with Urgency (Grade 3 or Grade 4) per 24 Hours (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n Adjusted mean difference from placebo (SE) 95% 2-sided CI	410 -0.33 (0.219) (-0.76, 0.10)	426 -0.59 (0.217) (-1.01, -0.16)
P-values†	0.13	0.007

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]).

Footnotes continued on the next page

ANCOVA: analysis of covariance.

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

‡ P-values were from pairwise comparison vs placebo within the stratified rank ANCOVA.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment(Hochberg Procedure).

Source: Table 12.3.4.1, Table 12.3.4.2, Table 12.3.4.3, Table 12.3.4.4, Table 12.3.4.5 and Table 12.3.4.6

Table 5 Common (≥ 2% of Patients in Any Treatment Group) Treatment-emergent Adverse Events

MedDRA (v9.1) Preferred Term	Placebo (n = 433) n (%)	Mirabegron 25 mg (n = 432) n (%)	Mirabegron 50 mg (n = 440) n (%)	Mirabegron Total (n = 872) n (%)
Hypertension	37 (8.5%)	49 (11.3%)	47 (10.7%)	96 (11.0%)
Nasopharyngitis	14 (3.2%)	15 (3.5%)	25 (5.7%)	40 (4.6%)
Urinary tract infection	10 (2.3%)	18 (4.2%)	21 (4.8%)	39 (4.5%)
Headache	19 (4.4%)	9 (2.1%)	12 (2.7%)	21 (2.4%)
Upper respiratory tract infection	8 (1.8%)	9 (2.1%)	7 (1.6%)	16 (1.8%)
Dry mouth	9 (2.1%)	8 (1.9%)	7 (1.6%)	15 (1.7%)
Dizziness	2 (0.5%)	10 (2.3%)	4 (0.9%)	14 (1.6%)
Nausea	10 (2.3%)	5 (1.2%)	6 (1.4%)	11 (1.3%)
Back pain	9 (2.1%)	6 (1.4%)	4 (0.9%)	10 (1.1%)

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 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 6 Serious Treatment-emergent Adverse Events

MedDRA (v9.1) System Organ Class Preferred Term	Placebo (n = 433) n (%)	Mirabegron 25 mg (n = 432) n (%)	Mirabegron 50 mg (n = 440) n (%)	Mirabegron Total (n = 872) n (%)
Any serious adverse event	**12 (2.8%)**	**7 (1.6%)**	**4 (0.9%)**	**11 (1.3%)**
Infections and Infestations	**1 (0.2%)**	**2 (0.5%)**	**1 (0.2%)**	**3 (0.3%)**
Bronchitis acute	0	0	1 (0.2%)	1 (0.1%)
Diverticulitis	0	1 (0.2%)	0	1 (0.1%)
Pyelonephritis acute	0	1 (0.2%)	0	1 (0.1%)
Viral upper respiratory tract infection	1 (0.2%)	0	0	0
Cardiac Disorders	**1 (0.2%)**	**0**	**1 (0.2%)**	**1 (0.1%)**
Atrial fibrillation	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Gastrointestinal Disorders	**2 (0.5%)**	**1 (0.2%)**	**0**	**1 (0.1%)**
Inguinal hernia	0	1 (0.2%)	0	1 (0.1%)
Abdominal pain	1 (0.2%)	0	0	0
Pancreatitis	1 (0.2%)	0	0	0
General Disorders and Administration Site Conditions	**1 (0.2%)**	**1 (0.2%)**	**0**	**1 (0.1%)**
Chest pain	1 (0.2%)	1 (0.2%)	0	1 (0.1%)
Non-cardiac chest pain	0	1 (0.2%)	0	1 (0.1%)
Injury, Poisoning and Procedural Complications	**1 (0.2%)**	**0**	**1 (0.2%)**	**1 (0.1%)**
Radius fracture	0	0	1 (0.2%)	1 (0.1%)
Ligament rupture	1 (0.2%)	0	0	0
Investigations	**1 (0.2%)**	**1 (0.2%)**	**0**	**1 (0.1%)**
Liver function test abnormal	0	1 (0.2%)	0	1 (0.1%)
Laparoscopy	1 (0.2%)	0	0	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**
Breast cancer	0	1 (0.2%)	0	1 (0.1%)
Psychiatric Disorders	**2 (0.5%)**	**0**	**1 (0.2%)**	**1 (0.1%)**
Bipolar disorder	0	0	1 (0.2%)	1 (0.1%)
Delirium	1 (0.2%)	0	0	0
Depression	1 (0.2%)	0	0	0
Vascular Disorders	**0**	**1 (0.2%)**	**0**	**1 (0.1%)**
Orthostatic hypotension	0	1 (0.2%)	0	1 (0.1%)
Nervous System Disorders	**5 (1.2%)**	**0**	**0**	**0**
Carotid artery stenosis	1 (0.2%)	0	0	0
Cerebral ischaemia	1 (0.2%)	0	0	0
Cerebrovascular accident	2 (0.5%)	0	0	0
Grand mal convulsion	1 (0.2%)	0	0	0
Hemianopia homonymous	1 (0.2%)	0	0	0
Petit mal epilepsy	1 (0.2%)	0	0	0
Surgical and Medical Procedures	**1 (0.2%)**	**0**	**0**	**0**
Appendicectomy	1 (0.2%)	0	0	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 system organ class and within that in descending order by preferred term.

Source: Table 12.6.1.6

Table 7 Overview of Change from Baseline to Final Visit in Vital Signs Measured by Patient's Diary, Overall Population

Parameter	Placebo (n = 433)		Mirabegron 25 mg (n = 432)		Mirabegron 50 mg (n = 440)	
Pulse Rate (bpm)						
AM						
n	415		410		427	
Baseline mean (SE)	70.3 (0.50)		71.0 (0.50)		70.3 (0.52)	
Adjusted mean change from baseline (SE)	-0.0 (0.31)		0.8 (0.31)		0.9 (0.30)	
Mean difference vs placebo (SE)			0.8 (0.44)		0.9 (0.43)	
95% 2-sided CI			(-0.1, 1.6)		(0.0, 1.7)	
PM						
n	414		410		427	
Baseline mean (SE)	74.8 (0.50)		75.5 (0.51)		74.8 (0.50)	
Adjusted mean change from baseline (SE)	-0.7 (0.33)		-0.1 (0.33)		0.4 (0.32)	
Mean difference vs placebo (SE)			0.6 (0.47)		1.1 (0.46)	
95% 2-sided CI			(-0.3, 1.5)		(0.2, 2.0)	
Blood Pressure (mm Hg)	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
AM						
n	415	415	410	410	427	427
Baseline mean (SE)	128.3 (0.82)	76.5 (0.45)	129.2 (0.81)	78.2 (0.48)	131.1 (0.85)	77.4 (0.46)
Adjusted mean change from baseline (SE)	-0.5 (0.45)	-0.6 (0.27)	-0.5 (0.46)	-0.4 (0.27)	1.1 (0.45)	0.4 (0.27)
Mean difference vs placebo (SE)			-0.1 (0.64)	0.2 (0.39)	1.5 (0.64)	1.0 (0.38)
95% 2-sided CI			(-1.3, 1.2)	(-0.6, 1.0)	(0.3, 2.8)	(0.3, 1.8)
PM						
n	414	414	410	410	427	427
Baseline mean (SE)	127.9 (0.74)	74.7 (0.43)	129.0 (0.71)	76.1 (0.46)	129.5 (0.75)	75.3 (0.47)
Adjusted mean change from baseline (SE)	-0.1 (0.46)	0.1 (0.29)	-0.6 (0.46)	-0.1 (0.29)	1.4 (0.45)	0.6 (0.28)
Mean difference vs placebo (SE)			-0.5 (0.65)	-0.2 (0.41)	1.5 (0.64)	0.5 (0.40)
95% 2-sided CI			(-1.7, 0.8)	(-1.0, 0.6)	(0.3, 2.8)	(-0.3, 1.3)

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