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 Randomized, Double-Blind, Parallel Group, Active Controlled, Multi center Long-term Study to Assess the Safety and Efficacy of the Beta-3 Agonist Mirabegron (YM178) 50 mg qd and 100 mg qd in Subjects With Symptoms of Overactive Bladder

Responsible Medical Officers/Investigators:

Coordinating Investigator: Prof. [redacted], B.Sc, MD, FRCS, (Urol), FEBU, [redacted] United Kingdom

[redacted], MD, PhD, [redacted]

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

Study Center(s): This multinational, multicenter study was conducted at 306 sites across Europe (181 sites), the United States (US) (97 sites), Canada (18 sites), South Africa (6 sites) and Australia/New Zealand (4 sites). A total of 334 sites were initiated; 306 sites enrolled patients.

Publication (reference): None

Study Period: 1 year

Date of first enrollment (Study initiation date): 25 Apr 2008

Date of last evaluation (Study completion date): 06 May 2010

Phase of Development: Phase 3

Objectives:

The primary objective of the study was to assess the safety and tolerability of long-term treatment with mirabegron (50 mg qd and 100 mg qd) in patients with symptoms of overactive bladder (OAB).

The secondary objectives of the study were to assess the efficacy of long-term treatment with mirabegron (50 mg qd and 100 mg qd) in patients with symptoms of OAB and to compare the long-term safety and efficacy of mirabegron with tolterodine extended release (ER) 4 mg qd in the treatment of patients with symptoms of OAB.

Methodology:

This was a randomized, parallel group, active-controlled, double-blind, multicenter, multinational study conducted in male and female patients of at least 18 years of age, with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) 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

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

criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg or tolterodine ER 4 mg once daily for 12 months. The randomized, double-blind, active-controlled treatment period consisted of visits at months 1, 3, 6, 9 and 12.

Patients who completed the 12-week treatment and safety follow-up periods of studies 178-CL-046 or 178-CL-047 in any treatment group (placebo, mirabegron or tolterodine ER 4 mg) could enroll in 178-CL-049 after being off study medication for at least 30 days, as well as patients that did not participate in the 178-CL-046 or 178-CL-047 studies could be enrolled into this study, if they met all inclusion criteria and none of the exclusion criteria at visit 1 and visit 2.

Number of Patients (planned, enrolled and analyzed):

Planned: 2500 enrolled

Actual: 2849 enrolled, 2452 randomized

- Randomized Analysis Set: 2452 patients
    - mirabegron 50 mg: 815 patients; mirabegron 100 mg: 824 patients; tolterodine ER 4 mg 813 patients
- Full Analysis Set (FAS): 2382 patients
    - mirabegron 50 mg: 789 patients; mirabegron 100 mg: 802 patients; tolterodine ER 4 mg 791 patients
- Full Analysis Set Incontinence (FAS-I): 1450 patients
    - mirabegron 50 mg: 479 patients; mirabegron 100 mg: 483 patients; tolterodine ER 4 mg 488 patients
- Safety Analysis Set (SAF): 2444 patients
    - mirabegron 50 mg: 812 patients; mirabegron 100 mg: 820 patients; tolterodine ER 4 mg 812 patients

Diagnosis and Main Criteria for Inclusion:

Patients could be included if they fulfilled all of the following inclusion criteria at screening:

- male and female patients at least 18 years of age
- provided written informed consent
- were willing and able to complete the micturition diary and questionnaires correctly
- were required to have had symptoms of OAB for ≥ 3 months

Patients were excluded if they fulfilled any of the following exclusion criteria at screening:

- had diabetic neuropathy
- significant stress incontinence or mixed stress/urgency incontinence with stress as the predominant factor

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

- evidence of a symptomatic urinary tract infection, chronic inflammation of the bladder, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs
- severe hypertension (defined as a sitting average systolic blood pressure (SBP) ≥ 180 mm Hg and/or average diastolic blood pressure (DBP) ≥ 110 mm Hg)
- an indwelling catheter; practiced intermittent self-catheterization
- received nondrug treatment including electro-stimulation therapy
- used medications intended to treat OAB, prohibited medications, or restricted medications without meeting conditions for use

Patients were included if they fulfilled all of the following inclusion criteria at baseline:

- experienced a micturition frequency on average ≥ 8 times per 24-hour period during the 3-day micturition diary period and at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period.
- continued to meet all screening eligibility criteria

Patients were excluded if they fulfilled any of the following exclusion criteria at baseline:

- had an average total daily urine volume > 3000 mL as recorded in the 3-day micturition diary period
- 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 ULN, as assessed in screening samples and considered clinically significant by the investigator
- had severe hypertension (as defined above) or a clinically significant abnormal electrocardiogram (ECG)

Medications prohibited during the placebo run-in period and the double-blind treatment period included anticholinergics, antispasmodics, CYP2D6 substrates with narrow therapeutic indices and medication not recommended to be used with tolterodine.

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.

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

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

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

Lot numbers (North America): [redacted] and [redacted] (mirabegron 50 mg tablet); [redacted] (mirabegron 100 mg tablet)

Lot numbers (all other countries): [redacted] and [redacted] (mirabegron 50 mg tablet); [redacted] and [redacted] (mirabegron 100 mg tablet)

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

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

Double-blind, active-controlled treatment period: 12 months

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

One tolterodine ER 4 mg capsule (in addition to 2 matching placebo tablets for mirabegron 50 mg and 100 mg) was administered each morning by mouth with a glass of water with or without food to patients randomized to receive tolterodine 4 mg ER.

Lot numbers (North America): [redacted], [redacted], [redacted] (tolterodine ER 4 mg capsule, overencapsulated); [redacted] and [redacted] (placebo to match mirabegron 50 mg tablet); [redacted] and [redacted] (placebo to match mirabegron 100 mg tablet); [redacted] (placebo to match overencapsulated tolterodine 4 mg capsule)

Lot numbers (all other countries): [redacted], [redacted], [redacted] (tolterodine ER 4 mg capsule, overencapsulated); [redacted], and [redacted] (placebo to match mirabegron 50 mg tablet); [redacted] and [redacted] (placebo to match mirabegron 100 mg tablet); [redacted], [redacted], [redacted], [redacted] and [redacted] (placebo to match overencapsulated tolterodine 4 mg capsule)

Criteria for Evaluation:

Efficacy variables were secondary in this study and included:

- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of micturitions per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of incontinence episodes per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean volume voided per micturition
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency incontinence episodes per 24 hours

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

- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency episodes (grade 3 and/or 4) per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean level of urgency
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in the mean number of pads used per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of nocturia episodes per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in Symptom Bother and health related quality of life scores as assessed by the OAB questionnaire (OAB-q)
- Change from baseline to months 3, 6, 12 and Final Visit in scores as assessed by Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP)
- Change from baseline to month 1, 3, 6, 9, 12 and Final Visit in scores as assessed by European Quality of Life-5 Dimensions (EQ-5D) questionnaire
- Change from baseline to months 12 and Final Visit in Patient Perception of Bladder Condition (PPBC)
- Change from baseline to months 12 and Final Visit in the Treatment Satisfaction Visual Analog Scale (TS-VAS)
- Change from baseline to months 3, 6, 12 and Final Visit in the number of physician visits for the patient's bladder condition (excluding study related visits)

Efficacy responder analyses included:

- Zero Incontinence Episodes: A responder was defined as a patient with 0 incontinence episodes postbaseline
- Reduction in Incontinence Episodes: A responder was defined as a patient with a $\geq$ 50% decrease from baseline in mean number of incontinence episodes per 24 hours

The primary safety variable was the incidence and severity of treatment-emergent adverse events (TEAEs). Secondary safety variables included:

- Vital signs (sitting SBP, sitting DBP and pulse rate)
- Ambulatory Blood Pressure Monitoring (ABPM) (performed on a subset of patients)
- Laboratory tests (hematology, biochemistry and urinalysis)
- Physical examination
- ECG parameters

Statistical Methods:

Efficacy Analyses

Efficacy analyses were secondary in this study. No comparisons were made between mirabegron and tolterodine ER 4 mg.

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

All efficacy analyses were based on the FAS with the exception of incontinence episodes and urgency incontinence episodes, for which the FAS-I was used. For the efficacy variables derived from the micturition diary, both the actual values as well as the changes from baseline were summarized descriptively by treatment and visit (including Final Visit) using mean, SE, median, minimum, and maximum.

Two models were used to analyze efficacy variables: a repeated measures model and an analysis of covariance (ANCOVA) model. Factors in the repeated measures model included previous study history, sex, geographical region, randomized treatment group, time, randomized treatment by time interaction and sex by time interaction. Covariates in the model included baseline and baseline by time interaction. Factors in the ANCOVA model included previous study history, sex, geographical region and randomized treatment group. Baseline was the only covariate in the ANCOVA model. Both models were used to obtain adjusted mean changes from baseline along with 95% CIs. No comparisons between treatments were performed.

The changes from baseline to months 1, 3, 6, 9 and 12 for micturitions, incontinence episodes, mean volume voided, urgency incontinence episodes and nocturia were analyzed using the repeated measures model. The ANCOVA model was also used to analyze these variables for each visit, including Final Visit.

The changes from baseline to months 1, 3, 6, 9, 12 and Final Visit for urgency episodes, level of urgency, pads used, OAB-q, PPBC and TS-VAS (month 12 and Final Visit only) were analyzed using the ANCOVA.

The changes from baseline in WPAI:SHP, physician visits for bladder condition and EQ-5D VAS were summarized by treatment group at each relevant visit using descriptive statistics. The descriptive system of the EQ-5D was summarized for the number and percentage of patients at each severity level for each EQ-5D symptom at months 1, 3, 6, 9, 12 and Final Visit by treatment group and baseline severity.

Responder analyses were conducted based on incontinence episodes. The number and percentage of patients who were responders for incontinence episodes at months 1, 3, 6, 9, 12 and Final Visit for each treatment group were summarized using absolute and relative frequencies. The number and percentage of patients who had any improvement or who had a major improvement at month 12 and Final Visit in PPBC were similarly summarized.

Safety Analyses

All common (≥ 2%) TEAEs and related TEAEs were analyzed by means of a life table analysis, with exposure to treatment to be divided into the following intervals: < 1 month, 1 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12-14 months and ≥ 14 months.

AEs of interest were summarized using standardized MedDRA queries (SMQs), if available, or a comprehensive list of preferred terms (PTs) and lower level terms.

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

With the exception of ABPM measurements, the average change from baseline for each vital sign variable and for each population (overall, normotensive, past history of hypertension and hypertensive) were analyzed using the same repeated measures and ANCOVA models described for the efficacy analyses.

Summary of Results/Conclusions:

Population:

A total of 2444 patients were evaluated for safety; of these, 81.3% of patients had been previously enrolled in studies 178-CL-046 or 178-CL-047. A similar proportion of patients (approximately 21% to 24%) had previously received either placebo, mirabegron 50 mg or mirabegron 100 mg. Fewer patients (14.1%) were previously treated with tolterodine in 178-CL-046. There was no meaningful difference between the treatment groups in the current study with regard to prior treatment in either 178-CL-046 or 178-CL-047.

Demographic and baseline characteristics were consistent across treatment groups for patients in the SAF population. Overall, 74.1% of patients were female. The majority (62.8%) of patients were < 65 years of age and 90.2% were < 75 years of age.

Generally, demographic and baseline characteristics were similar across treatment groups in the FAS and FAS-I. Overall, 74.2% and 85.3% of patients were female (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 the FAS-I populations.

Efficacy Results:

This was not a placebo-controlled study and all efficacy analyses were secondary. Additionally, there were no direct comparisons of efficacy between treatment groups, including the active control.

Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturitions per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours (adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables.

Numerically similar results and a similar course of improvement over time were observed with tolterodine ER 4 mg.

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

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 comparable across treatment groups with reported incidence of 59.7% in the mirabegron 50 mg group, 61.3% in the mirabegron 100 mg group and 62.6% in the tolterodine ER 4 mg group.
- A time to event evaluation on the most common TEAEs demonstrated:
    - The time to first occurrence of hypertension (based on PT) was consistent across the treatment groups and manifest within the first 3 months of treatment, however, onset of events were observed throughout the 1 year duration of the study.
    - The time to first occurrence of dry mouth was reported with a higher incidence in the tolterodine ER 4 mg group relative to the mirabegron treatment groups and manifest within the first month of treatment, however, onset of events were observed throughout the 1 year duration of the study.
    - Time to first onset of UTI, cystitis and tachycardia occurred evenly throughout the duration of the study across all treatment groups.
- Five deaths were reported, of which 4 were considered treatment-emergent:
    - Two treatment-emergent deaths occurred in the mirabegron 50 mg treatment group.
        - One patient had a fatal AE of cardiac failure on day 190 (last dose: day 190) which was not considered to be related to study medication.
        - One patient died on day 108 after experiencing multiple organ failure secondary to sepsis with onsets ranging from day 104 to day 107. Pneumonia was the only event considered to be possibly related to study medication. The last dose of study drug was unknown (estimated to be day 86).
    - Two treatment-emergent deaths occurred in the tolterodine ER 4 mg treatment group:
        - One patient had a fatal AE of coronary artery disease on day 208 (last dose: day 208) which was not considered to be related to study medication.
        - One patient died on day 72 after experiencing fatal AEs of cerebrovascular accident and pneumonia aspiration which began on day 62. The last dose of study medication was on day 62. The events were not considered to be related to study medication.
    - A non-treatment-emergent death (completed suicide) occurred in a mirabegron 50 mg-treated patient; the patient died on day 359, 93 days after the last study drug kit (containing 105 days-worth of study drug) was dispensed. The actual last dose date for this patient was unknown but was estimated to be day 267 (per imputation rules in the SAP). The investigator considered the completed suicide as possibly related to study drug.
- The overall incidence of patients with treatment-emergent SAEs was 5.2%, 6.2% and 5.4% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.

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

  - A higher incidence of SAEs in the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) was observed in the mirabegron 100 mg group (1.3%) compared to mirabegron 50 mg (0.1%) or tolterodine ER 4 mg (0.5%). The reported neoplasms were heterogeneous in tissue of origin and were not considered related to study drug treatment per the investigator's assessment.
- The overall incidence of patients who discontinued study drug due to a TEAE was 5.9%, 6.1% and 5.7% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.
- For events of interest:
  - The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was similar across treatment groups: 11.0% in the mirabegron 50 mg group, 10.1% in the mirabegron 100 mg group and 10.6% in the tolterodine ER 4 mg group.
  - TEAEs of QTc prolongation in the Torsades de pointes/QT prolongation SMQ were observed in 8 patients, including 3 patients (0.4%) in the mirabegron 50 mg group, 2 patients (0.2%) in the mirabegron 100 mg group and 3 patients (0.4%) in the tolterodine ER 4 mg group. Of these, 1 patient in the mirabegron 50 mg group experienced SAEs of cardiac arrest, myocardial infarction, ventricular tachycardia and ventricular fibrillation which led to permanent discontinuation of study drug. The cardiovascular adjudication committee adjudicated all of these concurrent cardiovascular events as a nonfatal myocardial infarction in this patient. There was no evidence of Torsades de pointes among the events retrieved by the Torsades de pointes/QT prolongation SMQ.
  - The overall incidence of cardiac arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 3.9% in the mirabegron 50 mg group, 4.1% in the mirabegron 100 mg group and 6.0% in the tolterodine ER 4 mg group. Cases of atrial fibrillation of medical importance (based on predefined criteria) were noted in 7 (0.9%) patients in the mirabegron 50 mg group, 4 (0.5%) patients in the mirabegron 100 mg group and 9 (1.1%) patients in the tolterodine ER 4 mg group.
  - The overall incidence of TEAEs adjudicated as an APTC/MACE cardiovascular event was 0.7% in the mirabegron 50 mg group, 0% in the mirabegron 100 mg group and 0.5% in the tolterodine ER 4 mg group.
  - TEAEs of urinary retention (PT) were reported for 1 patient in the mirabegron 50 mg group, 1 patient in the mirabegron 100 mg group, and 3 patients in the tolterodine ER 4 mg group. Two of these patients reported acute urinary retention requiring catheterization: 1 patient (0.1%) in the mirabegron 100 mg group and 1 patient (0.1%) in the tolterodine ER 4 mg group.
  - The overall incidence of TEAEs indicative of potential hypersensitivity (identified through a comprehensive MedDRA search of PTs indicative of hypersensitivity) was 5.5% in the mirabegron 50 mg group, 5.4% in the mirabegron 100 mg group and 5.2% in the tolterodine

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

ER 4 mg group. Medical evaluation identified 14 patients with events of "likely hypersensitivity". These patients experienced (1) symptoms and course consistent with drug hypersensitivity reaction, although drugs other than mirabegron could have been implicated, and (2) no explanation other than drug hypersensitivity was documented. Seven patients were considered to have had a hypersensitivity reaction attributable to a source other than study drug, such as concomitant medication. The remaining patients with "likely hypersensitivity" where study drug may have been a precipitating factor, include 3 patients in the mirabegron 50 mg group, 3 patients in the mirabegron 100 mg group and 1 patient in the tolterodine ER 4 mg group

- Syncope was observed in 1 (0.1%) patient in the mirabegron 50 mg group and 1 (0.1%) patient in the tolterodine ER 4 mg group. In both subjects there were confounding factors, which may have caused the syncope.
- No episodes of seizure were observed during the study.
- Hepatic events:
  - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders – Comprehensive Search SMQ, was 2.1% in the mirabegron 50 mg group, 2.3% in the mirabegron 100 mg group and 1.8% in the tolterodine ER 4 mg group. Most hepatic TEAEs were mild or moderate in intensity.
  - One patient in the mirabegron 50 mg group met laboratory criteria for Hy's law; this patient had ongoing hepatitis B and a history of alcoholism. The case was definitively ruled out as a confirmed case of Hy's law due to the ongoing viral hepatitis as an alternate etiology.
  - The incidence of patients with hepatic parameters meeting PCS criteria was 1.0%, 1.3% and 0.9% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively (excluding patients who met the PCS criterion for isolated elevations in GGT only). The incidence of hepatic events based TEAEs and/or meeting hepatic PCS criteria (excluding events/elevations in GGT only) was 2.6%, 3.3% and 2.2% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.

- Changes in hematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups except for leukocyte count.
  - In both mirabegron groups a decrease in leukocyte counts was observed at month 1 and month 6 but was followed by an observed increase for subsequent measurements. The number of patients with an ANC < 1000 x 10^6/L was comparable between treatment groups.
- Dose-dependent increases in adjusted mean change from baseline to Final Visit for AM and PM pulse rates were observed in all treatment groups (AM: 0.9, 1.6 and 1.5 bpm; PM: 0.4, 1.3 and 1.9 bpm for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively).

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

- For SBP, the adjusted mean changes from baseline to Final Visit for the mirabegron 50 mg group, mirabegron 100 mg group, and tolterodine ER 4 mg group respectively, were 0.2, 0.4 and -0.5 mm Hg for AM SBP and -0.3, 0.1 and -0.0 mm Hg for PM SBP. For DBP, the adjusted mean changes from baseline to Final Visit for the mirabegron 50 mg group, 100 mg group and tolterodine ER 4 mg groups, respectively, were -0.3, 0.4 and 0.1 mm Hg for AM DBP and -0.0, 0.1 and 0.6 mm Hg for PM DBP.
- ABPM data were consistent with cuff measurements recorded in the patient diary.
- Across the mirabegron and tolterodine treatment groups, increases in heart rate noted on ECGs were consistent with increases in pulse rate. No consistent ECG trends were identified.

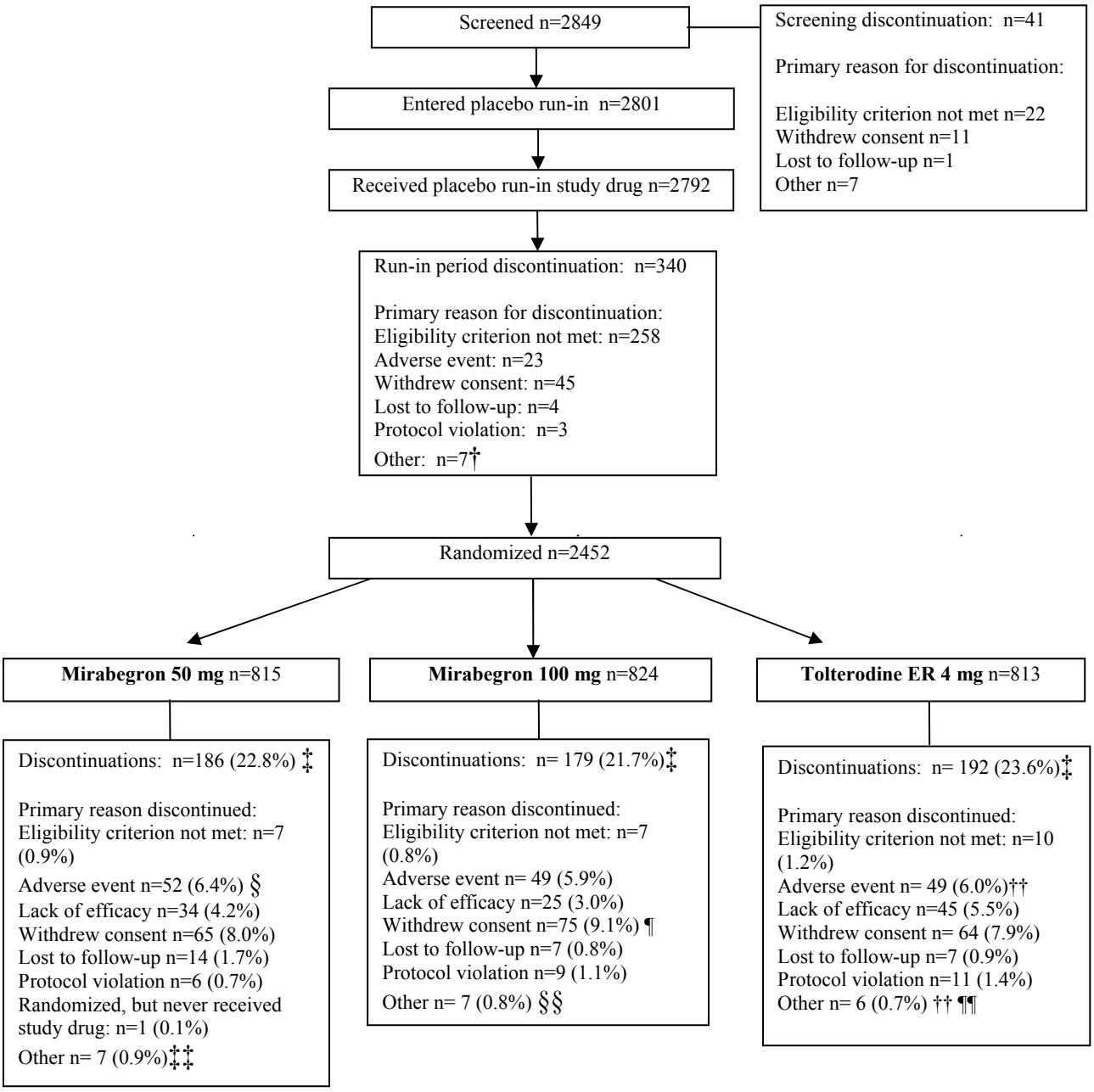
CONCLUSIONS:

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

- Mirabegron at doses of 50 and 100 mg once daily for 12 months was safe and well tolerated.
- Mirabegron at doses of 50 and 100 mg once daily for 12 months resulted in numeric improvements in the symptoms of urinary incontinence, frequency and urgency that are characteristic of OAB.

Date of Report: 08 December 2010

Figure 1 Patient Disposition



All patients.

AE: adverse event; ER: extended release; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

† Other reasons for discontinuation during the run-in period included unreliable diary, noncompliance with study drug medication, not randomized per Sponsor's decision, unable to respect study calendar, did not want to continue in trial, withdrew due to history of irritated mucous membranes in the mouth and Investigator's decision.

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

Footnotes continued on next page.

§ Four patients in the mirabegron 50 mg group (Patient No. [redacted], Patient No [redacted], Patient No [redacted] and Patient No [redacted]) are included in Figure 1 as discontinued due to an AE but are not included in the summary of patients who discontinued due to TEAEs: 2 patients discontinued due to non-TEAEs and 2 patients experienced AEs which led to temporary study drug interruption but did not permanently discontinue study drug until several weeks later.

¶ One patient in the mirabegron 100 mg group (Patient No. [redacted]) experienced several TEAEs that led to permanent discontinuation of study drug. This patient is listed as "withdrew consent" in Figure 1 but is included in the summary of patients who discontinued due to TEAEs.

†† Four patients in the tolterodine ER 4 mg group (Patient No. [redacted], Patient No. [redacted], Patient No. [redacted] and Patient No. [redacted]) are included in Figure 1 as discontinued due to an AE but are not included in the summary of patients who discontinued due to TEAEs since the events were non-treatment-emergent. One patient (Patient No. [redacted]) experienced SAEs of aortic valve incompetence and aortic stenosis that led to permanent discontinuation of study drug. This patient is included in summary of patients who discontinued due to a TEAE but is included as discontinued to "other" reasons in Figure 1.

‡‡ Other reasons for discontinuation in the mirabegron 50 mg group were: noncompliance with study visits, patient did not show up for appointment, lack of efficacy and prohibited medication usage, patient missed visit 6 due to family illness, patient was dissatisfied, not 3 consecutive days in visit 2 diary and patient noncompliant from visit 2.

§§ Other reasons for discontinuation in the mirabegron 100 mg group were patient irritability, site closure, persistent tachycardia, blood pressure cuff errors and study drug dispensing at visit 3 and use, QT prolongation(at baseline, therefore the patient was discontinued), missed scheduled visit and, consequently, was out of window and noncompliance with visit window.

¶¶ Other reasons for discontinuation in the tolterodine ER 4 mg group were SAE of abnormal cardiac catheterization, blood pressure machine issues, noncompliant with visit windows, unable to come for visit 7 per protocol window, patient stopped medication due to erectile dysfunction in medical history and missed visit 2 questionnaire.

Source: Table 12.1.1.1, Table 12.1.1.3.1, Table 12.1.1.3.2, Table 12.1.1.3.3, Appendix 13.2.1.2 and Appendix 13.2.7.1

Table 1 Summary of Patient Demographics and Baseline Characteristics, SAF

Parameter	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)	Tolterodine ER 4 mg (n=812)	Total (n=2444)
Sex (n, %)				
Male	210 (25.9%)	212 (25.9%)	212 (26.1%)	634 (25.9%)
Female	602 (74.1%)	608 (74.1%)	600 (73.9%)	1810 (74.1%)
Age (years)				
Mean (SD)	59.2 (12.56)	60.1 (11.92)	59.6 (12.47)	59.6 (12.32)
Age (years) (n, %)				
< 65	523 (64.4%)	504 (61.5%)	509 (62.7%)	1536 (62.8%)
≥ 65	289 (35.6%)	316 (38.5%)	303 (37.3%)	908 (37.2%)
< 75	737 (90.8%)	739 (90.1%)	729 (89.8%)	2205 (90.2%)
≥ 75	75 (9.2%)	81 (9.9%)	83 (10.2%)	239 (9.8%)
Race (n, %)				
White	778 (95.8%)	774 (94.4%)	780 (96.1%)	2332 (95.4%)
Black or African American	22 (2.7%)	30 (3.7%)	20 (2.5%)	72 (2.9%)
Asian	8 (1.0%)	8 (1.0%)	5 (0.6%)	21 (0.9%)
Other †	4 (0.5%)	8 (1.0%)	7 (0.9%)	19 (0.8%)
Ethnicity (n, %)				
Hispanic/Latino	23 (2.8%)	20 (2.4%)	32 (4.0%)	75 (3.1%)
Non-Hispanic/Non-Latino	789 (97.2%)	800 (97.6%)	778 (96.0%)	2367 (96.9%)
BMI (kg/m2)				
n	811	819	809	2439
Mean (SD)	29.0 (6.29)	28.8 (5.99)	28.5 (5.69)	28.8 (5.99)
BMI category (kg/m2)				
< 25	229 (28.2%)	231 (28.2%)	224 (27.7%)	684 (28.0%)
25 to < 30	294 (36.3%)	319 (38.9%)	328 (40.5%)	941 (38.6%)
≥ 30	288 (35.5%)	269 (32.8%)	257 (31.8%)	814 (33.4%)
Geographical region (n, %)				
Eastern Europe	260 (32.0%)	270 (32.9%)	258 (31.8%)	788 (32.2%)
Western Europe	257 (31.7%)	242 (29.5%)	262 (32.3%)	761 (31.1%)
Southern Hemisphere	34 (4.2%)	39 (4.8%)	37 (4.6%)	110 (4.5%)
Canada	44 (5.4%)	47 (5.7%)	45 (5.5%)	136 (5.6%)
Northeastern US	55 (6.8%)	56 (6.8%)	53 (6.5%)	164 (6.7%)
Midwestern US	29 (3.6%)	33 (4.0%)	33 (4.1%)	95 (3.9%)
Southern US	67 (8.3%)	68 (8.3%)	57 (7.0%)	192 (7.9%)
Western US	66 (8.1%)	65 (7.9%)	67 (8.3%)	198 (8.1%)

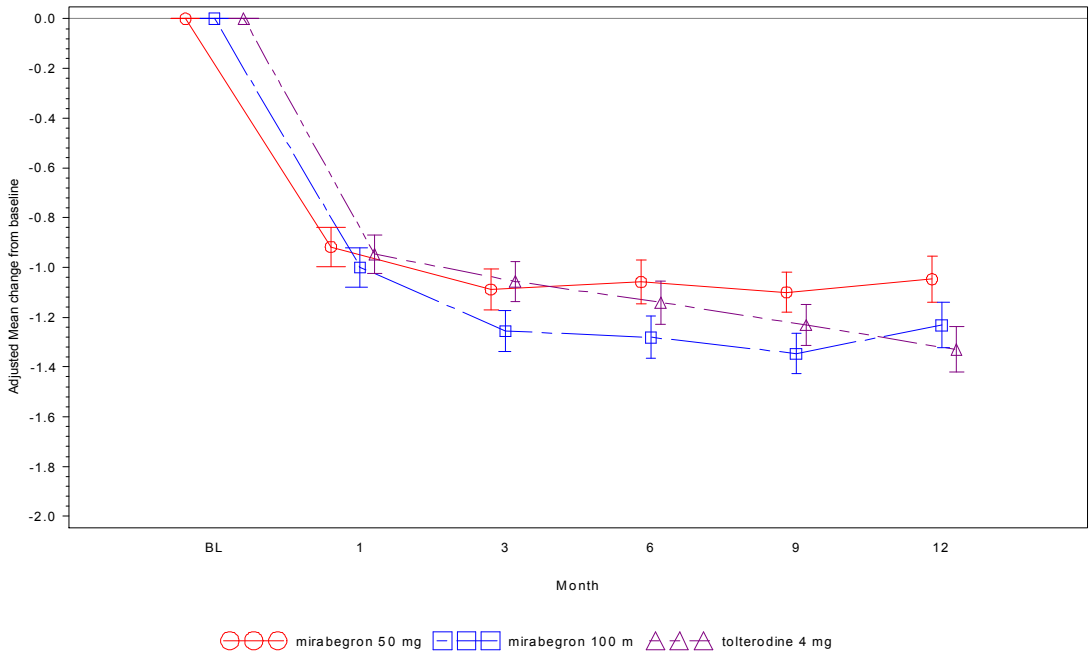
All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). The denominators for the percentage calculations of categorical variables were the number of patients with nonmissing values. BMI = weight (kg)/height (m^2).

BMI: body mass index; ER: extended release; US: United States.

† Other race: mirabegron 50 mg: American Indian or Alaska native (n=2), Indian (n=1) and White and Black/African American (n=1); mirabegron 100 mg: Mixed (n=3), American Indian or Alaska native (n=2), Native Hawaiian or Other Pacific Islander (n=2) and Guyana (n=1); tolterodine ER 4 mg: American Indian or Alaska native (n=4), Colored (n=1), Mixed (n=1) and Indian (n=1).

Source: Table 12.1.2.1.1 and Appendix 13.2.4.1

Figure 2 Adjusted Mean Change from Baseline at Each Visit in Mean Number of Incontinence Episodes per 24 Hours based on Repeated Measures, FAS-I

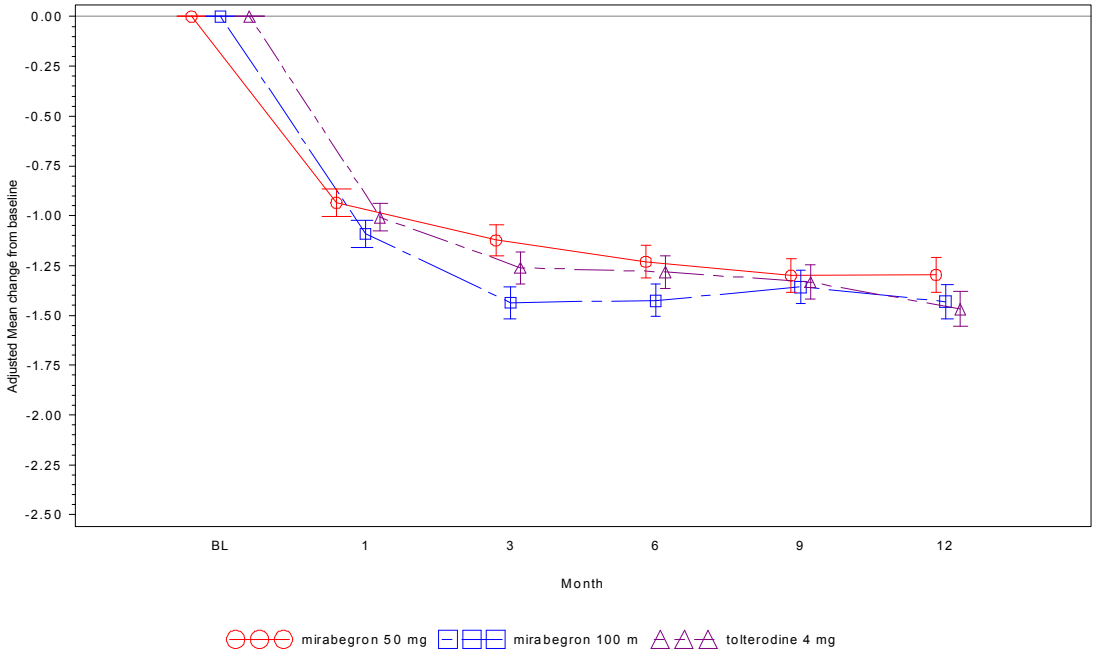


All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and who had at least 1 incontinence episode and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set Incontinence [FAS-I]). Adjusted mean changes are based on the repeated measures model. SE bars are 1 x SE.

BL: Baseline.

Source: Figure 12.3.1.3

Figure 3 Adjusted Mean Change from Baseline at Each Visit in Mean Number of Micturitions per 24 hours based on Repeated Measures, FAS

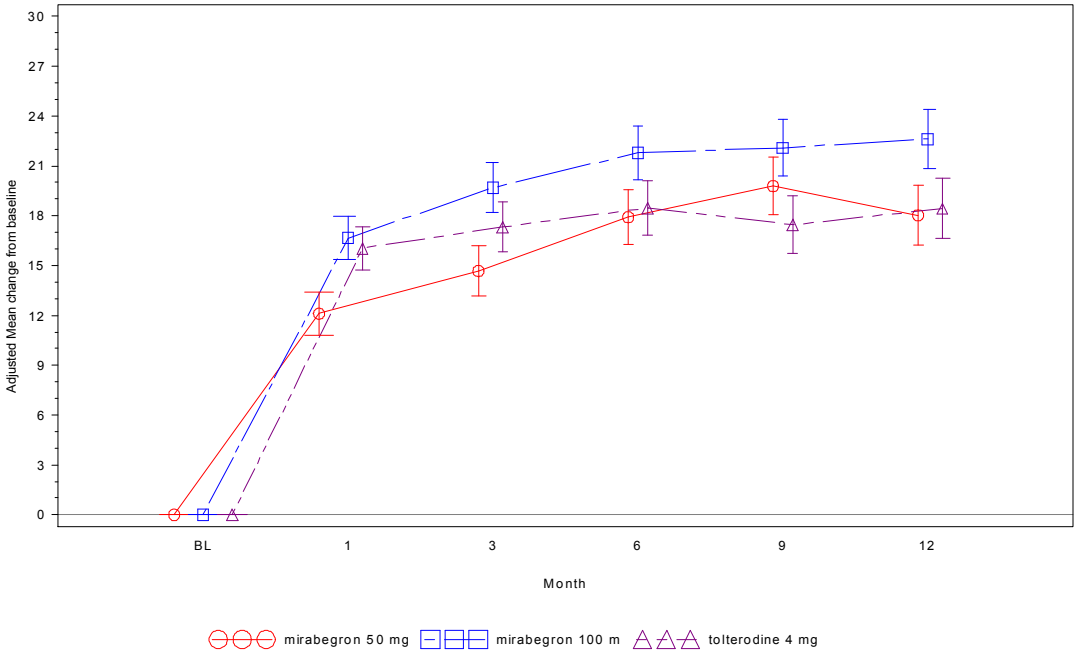


All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). Adjusted mean changes are based on the repeated measures model. SE bars are 1 x SE.

BL: Baseline.

Source: Figure 12.3.2.3

Figure 4 Adjusted Mean Change from Baseline at Each Visit in Mean Volume Voided (mL) per Micturition Based on Repeated Measures , FAS



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]). Adjusted mean changes are based on the repeated measures model. SE bars are 1 x SE.

BL: Baseline.

Source: Figure 12.3.3.3

Table 2 Overview of Incidence of Treatment-emergent Adverse Events

Parameter	Mirabegron 50 mg (n=812) n (%)	Mirabegron 100 mg (n=820) n (%)	Mirabegron Total (n=1632) n (%)	Tolterodine ER 4 mg (n=812) n (%)
Adverse events	485 (59.7%)	503 (61.3%)	988 (60.5%)	508 (62.6%)
Treatment-related adverse events	213 (26.2%)	192 (23.4%)	405 (24.8%)	224 (27.6%)
Adverse events by severity†				
Mild	222 (27.3%)	240 (29.3%)	462 (28.3%)	251 (30.9%)
Moderate	212 (26.1%)	211 (25.7%)	423 (25.9%)	218 (26.8%)
Severe	51 (6.3%)	52 (6.3%)	103 (6.3%)	39 (4.8%)
Deaths ‡	2 (0.2%)	0	2 (0.1%)	2 (0.2%)
Serious adverse events	42 (5.2%)	51 (6.2%)	93 (5.7%)	44 (5.4%)
Treatment-related serious adverse events	10 (1.2%)	4 (0.5%)	14 (0.9%)	5 (0.6%)
Adverse events leading to study drug discontinuation §	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Treatment-related adverse events leading to study drug discontinuation	35 (4.3%)	29 (3.5%)	64 (3.9%)	31 (3.8%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). Adverse events that were summarized were reported after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug. Treatment-related adverse events were adverse events with relationship to study drug assessed by the investigator as possible or probable or adverse events with a missing relationship to study drug.

AE: adverse event; ER: extended release; TEAE: treatment-emergent adverse event.

† The number of patients shows maximum severity ('missing' is handled as most severe). Patients with 1 or more adverse events within a level of the MedDRA term were counted only once in that level.

‡ An additional (non-treatment-emergent) death occurred in 1 patient in the mirabegron 50 mg group (Patient No. [redacted]).

§ Two patients in the mirabegron 50 mg group (Patient No. [redacted] and Patient No. [redacted]) and 4 patients in the tolterodine ER 4 mg group (Patient No. [redacted], Patient No. [redacted], Patient No. [redacted] and Patient No. [redacted]) discontinued the study due to a non-TEAE. Additionally, 2 patients in the mirabegron 50 mg group (Patient No. [redacted] and Patient No. [redacted]) temporarily interrupted study medication due to an AE but did not permanently discontinue study medication due to the event until several weeks later. These 8 patients are not included in this table but are included in Figure 1.

Source: Table 12.6.1.1 and Table 12.6.1.3

Table 3 Common (≥ 2% of Patients in Any Treatment Group) Treatment-emergent Adverse Events

MedDRA (v9.1) Preferred Term	Mirabegron			Tolterodine ER 4 mg (n=812) n (%)
	50 mg (n=812) n (%)	100 mg (n=820) n (%)	Total (n=1632) n (%)	
Hypertension	75 (9.2%)	80 (9.8%)	155 (9.5%)	78 (9.6%)
Urinary tract infection	48 (5.9%)	45 (5.5%)	93 (5.7%)	52 (6.4%)
Nasopharyngitis	32 (3.9%)	35 (4.3%)	67 (4.1%)	25 (3.1%)
Headache	33 (4.1%)	26 (3.2%)	59 (3.6%)	20 (2.5%)
Back pain	23 (2.8%)	29 (3.5%)	52 (3.2%)	13 (1.6%)
Constipation	23 (2.8%)	25 (3.0%)	48 (2.9%)	22 (2.7%)
Influenza	21 (2.6%)	25 (3.0%)	46 (2.8%)	28 (3.4%)
Dry mouth	23 (2.8%)	19 (2.3%)	42 (2.6%)	70 (8.6%)
Sinusitis	22 (2.7%)	18 (2.2%)	40 (2.5%)	12 (1.5%)
Diarrhoea	15 (1.8%)	24 (2.9%)	39 (2.4%)	16 (2.0%)
Arthralgia	17 (2.1%)	19 (2.3%)	36 (2.2%)	16 (2.0%)
Dizziness	22 (2.7%)	13 (1.6%)	35 (2.1%)	21 (2.6%)
Cystitis	17 (2.1%)	11 (1.3%)	28 (1.7%)	19 (2.3%)
Tachycardia	8 (1.0%)	19 (2.3%)	27 (1.7%)	25 (3.1%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). 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.

ER: extended release.

Source: Table 12.6.1.5

Table 4 Common (≥ 2% of Patients in Any Treatment Group) Treatment-related Treatment-emergent Adverse Events

MedDRA (v9.1) Preferred Term	Mirabegron 50 mg (n=812) n (%)	Mirabegron 100 mg (n=820) n (%)	Mirabegron Total (n=1632) n (%)	Tolterodine ER 4 mg (n=812) n (%)
Hypertension	43 (5.3%)	50 (6.1%)	93 (5.7%)	42 (5.2%)
Dry mouth	20 (2.5%)	18 (2.2%)	38 (2.3%)	67 (8.3%)
Constipation	18 (2.2%)	17 (2.1%)	35 (2.1%)	19 (2.3%)
Headache	18 (2.2%)	14 (1.7%)	32 (2.0%)	14 (1.7%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). 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.

ER: extended release.

Source: Table 12.6.1.11

Table 5 Serious Treatment-emergent Adverse Events That Occurred in Any SOC and Also by Preferred Terms That Occurred in at Least 2 Patients in Any Treatment Group

MedDRA (v9.1) System Organ Class Preferred Term†	Mirabegron			Tolterodine ER 4 mg (n=812) n (%)
	50 mg (n=812) n (%)	100 mg (n=820) n (%)	Total (n=1632) n (%)	
Any serious adverse event	**42 (5.2%)**	**51 (6.2%)**	**93 (5.7%)**	**44 (5.4%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.1%)**	**11 (1.3%)**	**12 (0.7%)**	**4 (0.5%)**
Breast cancer	0	2 (0.2%)	2 (0.1%)	2 (0.2%)
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Cardiac disorders	**8 (1.0%)**	**2 (0.2%)**	**10 (0.6%)**	**8 (1.0%)**
Atrial fibrillation	2 (0.2%)	0	2 (0.1%)	3 (0.4%)
Myocardial infarction	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Angina pectoris	0	0	0	2 (0.2%)
Gastrointestinal disorders	**3 (0.4%)**	**7 (0.9%)**	**10 (0.6%)**	**2 (0.2%)**
Injury, poisoning and procedural complications	**5 (0.6%)**	**5 (0.6%)**	**10 (0.6%)**	**2 (0.2%)**
Surgical and medical procedures	**2 (0.2%)**	**7 (0.9%)**	**9 (0.6%)**	**4 (0.5%)**
Infections and infestations	**5 (0.6%)**	**3 (0.4%)**	**8 (0.5%)**	**3 (0.4%)**
Musculoskeletal and connective tissue disorders	**3 (0.4%)**	**5 (0.6%)**	**8 (0.5%)**	**2 (0.2%)**
Osteoarthritis	2 (0.2%)	1 (0.1%)	3 (0.2%)	1 (0.1%)
Nervous system disorders	**5 (0.6%)**	**2 (0.2%)**	**7 (0.4%)**	**5 (0.6%)**
Cerebrovascular accident	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Reproductive system and breast disorders	**3 (0.4%)**	**4 (0.5%)**	**7 (0.4%)**	**8 (1.0%)**
Uterine prolapse	0	2 (0.2%)	2 (0.1%)	0
Renal and urinary disorders	**1 (0.1%)**	**5 (0.6%)**	**6 (0.4%)**	**3 (0.4%)**
Vascular disorders	**4 (0.5%)**	**1 (0.1%)**	**5 (0.3%)**	**2 (0.2%)**
General disorders and administration site conditions	**3 (0.4%)**	**1 (0.1%)**	**4 (0.2%)**	**2 (0.2%)**
Investigations	**1 (0.1%)**	**3 (0.4%)**	**4 (0.2%)**	**0**
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	**2 (0.2%)**	**1 (0.1%)**	**3 (0.2%)**	**1 (0.1%)**
Blood and lymphatic system disorders	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**1 (0.1%)**
Eye disorders	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**1 (0.1%)**
Hepatobiliary disorders	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**2 (0.2%)**
Cholelithiasis	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Skin and subcutaneous tissue disorders	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Ear and labyrinth disorders	**0**	**1 (0.1%)**	**1 (0.1%)**	**1 (0.1%)**
Metabolism and nutrition disorders	**1 (0.1%)**	**0**	**1 (0.1%)**	**2 (0.2%)**
Psychiatric disorders	**1 (0.1%)**	**0**	**1 (0.1%)**	**0**

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). Adverse events that were summarized were reported after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug. 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.

Footnotes continued on next page.

ER: extended release.

† The table displays the incidence of serious adverse events for all SOCs. Preferred terms are displayed for those serious adverse events that occurred in at least 2 patients in any treatment group.

Source: Table 12.6.1.7

Table 6 Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Study Drug That Occurred in Any SOC and Also by Preferred Terms That Occurred in at Least 2 Patients in Any Treatment Group

MedDRA (v9.1) System Organ Class Preferred Term†	Mirabegron			Tolterodine ER 4 mg (n=812) n (%)
	50 mg (n=812) n (%)	100 mg (n=820) n (%)	Total (n=1632) n (%)	
Any TEAE leading to discontinuation	**48 (5.9%)‡**	**50 (6.1%)**	**98 (6.0%)‡**	**46 (5.7%)‡**
Gastrointestinal disorders	**14 (1.7%)**	**9 (1.1%)**	**23 (1.4%)**	**11 (1.4%)**
Constipation	7 (0.9%)	2 (0.2%)	9 (0.6%)	0
Nausea	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
Dry mouth	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Abdominal pain	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Abdominal pain upper	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Gastritis	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nervous system disorders	**10 (1.2%)**	**8 (1.0%)**	**18 (1.1%)**	**10 (1.2%)**
Headache	5 (0.6%)	4 (0.5%)	9 (0.6%)	3 (0.4%)
Dizziness	4 (0.5%)	2 (0.2%)	6 (0.4%)	0
General disorders and administration site conditions	**4 (0.5%)**	**5 (0.6%)**	**9 (0.6%)**	**2 (0.2%)**
Fatigue	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)
Pain	2 (0.2%)	0	2 (0.1%)	0
Cardiac disorders	**4 (0.5%)**	**4 (0.5%)**	**8 (0.5%)**	**7 (0.9%)**
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Myocardial infarction	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Angina pectoris	0	0	0	2 (0.2%)
Atrial fibrillation	0	0	0	2 (0.2%)
Eye disorders	**5 (0.6%)**	**3 (0.4%)**	**8 (0.5%)**	**3 (0.4%)**
Vision blurred	3 (0.4%)	1 (0.1%)	4 (0.2%)	1 (0.1%)
Dry eye	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Infections and infestations	**6 (0.7%)**	**2 (0.2%)**	**8 (0.5%)**	**3 (0.4%)**
Urinary tract infection	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**7 (0.9%)**	**7 (0.4%)**	**1 (0.1%)**
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Skin and subcutaneous tissue disorders	**2 (0.2%)**	**5 (0.6%)**	**7 (0.4%)**	**1 (0.1%)**
Pruritus	0	2 (0.2%)	2 (0.1%)	0
Vascular disorders	**4 (0.5%)**	**3 (0.4%)**	**7 (0.4%)**	**4 (0.5%)**
Hypertension	4 (0.5%)	2 (0.2%)	6 (0.4%)	3 (0.4%)
Renal and urinary disorders	**2 (0.2%)**	**4 (0.5%)**	**6 (0.4%)**	**4 (0.5%)**
Dysuria	0	2 (0.2%)	2 (0.1%)	0
Investigations	**1 (0.1%)**	**3 (0.4%)**	**4 (0.2%)**	**4 (0.5%)**
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Injury, poisoning and procedural complications	**3 (0.4%)**	**2 (0.2%)**	**5 (0.3%)**	**1 (0.1%)**
Reproductive system and breast disorders	**2 (0.2%)**	**2 (0.2%)**	**4 (0.2%)**	**3 (0.4%)**
Psychiatric disorders	**1 (0.1%)**	**2 (0.2%)**	**3 (0.2%)**	**1 (0.1%)**

Table continued on next page

MedDRA (v9.1) System Organ Class Preferred Term†	Mirabegron			Tolterodine ER 4 mg (n=812) n (%)
	50 mg (n=812) n (%)	100 mg (n=820) n (%)	Total (n=1632) n (%)	
Blood and lymphatic system disorders	**0**	**2 (0.2%)**	**2 (0.1%)**	**1 (0.1%)**
Ear and labyrinth disorders	**0**	**2 (0.2%)**	**2 (0.1%)**	**2 (0.2%)**
Vertigo	0	2 (0.2%)	2 (0.1%)	1 (0.1%)
Metabolism and nutrition disorders	**2 (0.2%)**	**0**	**2 (0.1%)**	**3 (0.4%)**
Musculoskeletal and connective tissue disorders	**0**	**2 (0.2%)**	**2 (0.1%)**	**1 (0.1%)**
Respiratory, thoracic and mediastinal disorders	**2 (0.2%)**	**0**	**2 (0.1%)**	**2 (0.2%)**
Hepatobiliary disorders	**0**	**1 (0.1%)**	**1 (0.1%)**	**0**
Immune system disorders	**1 (0.1%)**	**0**	**1 (0.1%)**	**1 (0.1%)**
Pregnancy, puerperium and perinatal conditions	**1 (0.1%)**	**0**	**1 (0.1%)**	**0**
Surgical and medical procedures	**0**	**1 (0.1%)**	**1 (0.1%)**	**1 (0.1%)**

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). Adverse events that were summarized were reported after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug. 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.

AE: adverse event; ER: extended release; TEAE: treatment-emergent adverse event.

† The table displays the incidence of TEAEs leading to permanent discontinuation of study drug for all SOCs; preferred terms are displayed for those TEAEs leading to discontinuation that occurred in at least 2 patients in any treatment group.

‡ Two patients in the mirabegron 50 mg group (Patient No. [redacted] and Patient No. [redacted]) and 4 patients in the tolterodine ER 4 mg group (Patient No. [redacted], Patient No. [redacted], Patient No. [redacted] and Patient No. [redacted]) discontinued the study due to a non-TEAE. Additionally, 2 patients in the mirabegron 50 mg group (Patient No. [redacted] and Patient No. [redacted]) temporarily interrupted study medication due to an AE but did not permanently discontinue study medication due to the event until several weeks later. These patients are not included in this table.

Source: Table 12.6.1.13

Table 7 Summary of Treatment-emergent Adverse Events of Interest, SAF

Category	Mirabegron 50 mg (n=812) n (%)	Mirabegron 100 mg (n=820) n (%)	Mirabegron Total (n=1632) n (%)	Tolterodine ER 4 mg (n=812) n (%)
QTc prolongation type	3 (0.4%)	2 (0.2%)	5 (0.3%)	3 (0.4%)
Hypertension type	89 (11.0%)	83 (10.1%)	172 (10.5%)	86 (10.6%)
Cardiac arrhythmia	32 (3.9%)	34 (4.1%)	66 (4.0%)	49 (6.0%)
Urinary retention	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Acute urinary retention	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Hypersensitivity	45 (5.5%)	44 (5.4%)	89 (5.5%)	42 (5.2%)
Syncope/seizure	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Hepatotoxicity	17 (2.1%)	19 (2.3%)	36 (2.2%)	15 (1.8%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]).

ER: extended release; QTc: corrected QT interval.

Source: Table 12.6.1.15, Table 12.6.1.16, Table 12.6.1.17, Table 12.6.1.18, Table 12.6.1.19, Table 12.6.1.20, Table 12.6.1.21 and Table 12.6.1.22

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

	Mirabegron				Tolterodine ER 4 mg (n=812)	
	50 mg (n=812)		100 mg (n=820)			
Pulse Rate (bpm)						
AM						
n	791		802		792	
Baseline mean (SE)	71.0 (0.36)		70.2 (0.37)		70.1 (0.35)	
Adjusted mean change from baseline (SE)	0.9 (0.23)		1.6 (0.22)		1.5 (0.22)	
95% two-sided CI	(0.5, 1.4)		(1.2, 2.1)		(1.1, 2.0)	
PM						
n	789		802		792	
Baseline mean (SE)	74.2 (0.36)		74.1 (0.37)		73.8 (0.36)	
Adjusted mean change from baseline (SE)	0.4 (0.24)		1.3 (0.24)		1.9 (0.24)	
95% two-sided CI	(-0.1, 0.8)		(0.8, 1.7)		(1.4, 2.4)	
Blood Pressure (mm Hg)	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
AM						
n	791	791	802	802	793	793
Baseline mean (SE)	126.7 (0.58)	77.6 (0.31)	125.9 (0.56)	77.2 (0.29)	126.8 (0.55)	77.6 (0.30)
Adjusted mean change from baseline (SE)	0.2 (0.33)	-0.3 (0.21)	0.4 (0.33)	0.4 (0.20)	-0.5 (0.33)	0.1 (0.21)
95% two-sided CI	(-0.4, 0.9)	(-0.7, 0.1)	(-0.2, 1.1)	(-0.0, 0.8)	(-1.1, 0.2)	(-0.3, 0.5)
PM						
n	789	789	802	802	793	793
Baseline mean (SE)	126.4 (0.50)	76.2 (0.30)	125.7 (0.50)	75.9 (0.29)	126.3 (0.49)	76.1 (0.29)
Adjusted mean change from baseline (SE)	-0.3 (0.33)	-0.0 (0.21)	0.1 (0.32)	0.1 (0.21)	-0.0 (0.33)	0.6 (0.21)
95% two-sided CI	(-0.9, 0.3)	(-0.4, 0.4)	(-0.5, 0.8)	(-0.3, 0.5)	(-0.7, 0.6)	(0.2, 1.0)

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

ANCOVA: analysis of covariance; bpm: beats per minute; DBP: diastolic blood pressure; ER: extended release; SBP: systolic blood pressure.

Source: Table 12.6.3.8.1