Advisory Committee Briefing Document

Mirabegron (YM178)
For the Treatment of Overactive Bladder

April 5, 2012

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Advisory Committee Briefing Materials: Available for Public Release Without Redaction

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List of Abbreviations and Definitions of Terms

^{14}C-mirabegron	^{14}C-labeled mirabegron
AE	Adverse event
ANCOVA	Analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
AR	Adrenoceptor
AUR	Acute urinary rentention
BCS	Biopharmaceutical Classification System
BMI	Body mass index
BOO	Bladder outlet obstruction
bpm	Beats per minute
BPH	Benign prostatic hyperplasia
cAMP	Cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CIOMS	The Council for International Organizations of Medical Sciences
CL	Total body clearance
CL_{cr}	Creatinine clearance
CL_R	Renal clearance
CNS	Central nervous system
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DDI	Drug-drug interaction
EC_{50}	Concentration of mirabegron that resulted in a 50% maximum response
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EM	Extensive metabolizer
ER	Extended release
FAS	Full analysis set
FAS-I	Full analysis set - incontinence
HIRD	HealthCore Integrated Research Database
HRQL	Health-related quality of life
HLT	Higher level term
IA	Intrinsic activity
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IOP	Intraocular pressure
IR	Immediate release
ITT	Intent-to-Treat
IVIVC	In vitro-in vivo correlation
LUTS	Lower urinary tract symptoms
MACE	Major adverse cardiac events
MRHD	Maximum recommended human dose
NDA	New Drug Application
NEC	Not elsewhere classified
NSA	National Scientific Advice
OAB	Overactive bladder
OAB-q	Overactive bladder questionaire
OCAS	Oral controlled absorption system
OCT	Organic cation transporters
PCS	Potentially clinically significant
PD	Pharmacodynamic
P-gp	P-glycoprotein

PIP	Pediatric Investigational Plan
PK/PD	Pharmacokinetic/pharmacodynamic
PM	Poor metabolizer
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PPS	Per protocol set
PT	Preferred term
PVR	Postvoid residual volume
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected using Bazett's correction formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcI	Individually corrected QT interval
RR	Relative risk
SAE	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SJS	Stevens-Johnson syndrome
SMQ	Standardized MedDRA Query
SOC	System organ class
SPA	Special Protocol Assessment
TdP	Torsade de Pointes
TEAE	Treatment-emergent adverse event(s)
TQT	Thorough QT
TS-VAS	Treatment Satisfaction-Visual Analog Scale
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection

1 EXECUTIVE SUMMARY

Astellas Pharma Global Development, Inc (APGD) submitted a New Drug Application (NDA) for mirabegron extended release tablets in August 2011. Mirabegron is a selective human beta 3-adrenoceptor (AR) agonist, for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. On April 5, 2012 an Advisory Committee will be held at the request of the FDA Division of Reproductive and Urologic Drug Products.

Development Objective

OAB is a disturbance of filling/storage and has been defined by the International Continence Society as a "symptom syndrome consisting of urgency with or without urge urinary incontinence, often associated with urinary frequency and nocturia" [Wein & Rovner, 2002]. Its etiology is not completely clear, but involves detrusor overactivity in a subset of subjects [Birder et al, 2010]. The prevalence of OAB is estimated to be 34 million in the United States (US) and 22 million in Europe [Irwin et al, 2008; Kim et al, 2006; Stewart et al, 2003; Milsom et al, 2001]. OAB has a significant impact on health-related quality of life (HRQL), particularly emotional symptoms, sexual health and overall well-being [Rogers et al, 2009; Resnick & Yalla, 1992]. The problematic and unpredictable symptoms of OAB can have damaging effects on an individual's daily routine [Milsom et al, 2001]. Antimuscarinics are the current standard therapeutic agents for the treatment of OAB. Antimuscarinics are associated with adverse event(s) (AE) such as dry mouth, constipation, and blurred vision at therapeutic doses, which may limit patient adherence to the therapy [Chapple et al, 2008; Hegde, 2006].

Mirabegron, by its effects at the beta-3 AR, represents a novel mechanism of action for the treatment of OAB compared with the standard pharmacological intervention, antimuscarinic agents. The proposed therapeutic dose of mirabegron is 50 mg orally once daily with or without food.

Mirabegron received marketing authorization in Japan in July 2011. A Marketing Application Authorization was filed with the European Medicines Agency in August 2011. Marketing applications were also filed in Brazil (December 2011), Canada (February 2012) and Switzerland (March 2012).

Nonclinical Program

A total of 153 nonclinical studies have been conducted to date. Mirabegron was a selective agonist of beta 3-AR in all species tested. Mirabegron showed very low intrinsic activity (IA), and much reduced binding affinity, for cloned human beta 1-AR and beta 2-AR. For in vitro studies, mirabegron relaxed the detrusor smooth muscle during the urinary bladder fill-void cycle by activation of beta 3-AR without interfering with the voiding contraction. Studies in animal models have shown that mirabegron increased bladder capacity. Unlike antimuscarinics, mirabegron did not impair bladder contraction during voiding.

Nonclinical safety of mirabegron was evaluated in single dose toxicity studies in rats, dogs and cynomolgus monkeys; repeated dose toxicity studies in rats (up to 26 weeks), dogs (up to 2 weeks), and cynomolgus monkeys (up to 52 weeks); in vitro and in vivo genotoxicity studies; carcinogenicity studies in mice and rats; reproductive and developmental toxicity studies in rats and rabbits; local irritation studies in rabbits; and other toxicity studies (skin sensitization, impurities, hemolysis, and combination with solifenacin). Nonclinical findings in the heart and liver were observed at systemic exposures well in excess of those achievable at the maximum recommended human dose (MRHD) based on exposure (i.e., area under the curve). Central nervous system (CNS) findings (decreased activity) were observed in multiple species at systemic exposures near that of the clinical exposures, however, these findings were transient (absent after multiple dosing), reversible, and not associated with histopathologic findings. Mirabegron demonstrated no discernible genotoxicity or

carcinogenicity. The 8 mirabegron metabolites identified in human plasma do not contribute to the pharmacological activity.

In safety pharmacology studies, mirabegron increased the heart rate of dogs and, to a lesser extent, monkeys. The mechanism for the increase in heart rate observed in monkeys at supratherapeutic doses 11.5-fold MRHD is via beta 1-AR stimulation. Differences in cross sensitivity to mirabegron for beta 1-AR activation in humans and animals suggest that the heart rate effects of mirabegron in humans would be less than that of animals at any given systemic exposure level. In vitro ion channel studies showed that neither mirabegron nor its 5 most abundant metabolites inhibited sodium, potassium or calcium ion channel conductance at clinically relevant concentrations. Furthermore, in vitro dog ventricular wedge studies showed no QT interval corrected for heart rate (QTc) interval prolongation, no prolongation of action potential duration and no indication of ventricular arrhythmogenic potential.

Clinical Program

The global clinical development program consisted of 41 studies conducted over approximately 10 years and included 10,552 subjects. Of these, 29 phase 1 studies including 1800 volunteers provide a thorough characterization of the clinical pharmacology of mirabegron. Twelve phase 2/3 studies characterized the efficacy and/or safety of mirabegron in patients. The efficacy of mirabegron in the treatment of symptoms of OAB is supported by 6 global, 12-week phase 2b/3 studies. The safety of mirabegron is further supported by 12 phase 2/3 studies including 8752 patients (8433 patients with OAB) of which, 5863 (5648 patients with OAB) received mirabegron. A total of 622 of the 5648 patients with OAB received mirabegron continuously for at least 52 weeks (365 days). In addition, 1572 patients had at least 6 months (182 days) of continuous exposure and 1482 patients had at least 9 months (274 days) of continuous exposure to mirabegron.

Populations in the mirabegron development program for OAB are representative of the population that would receive the product after market approval. In the Global Phase 2/3 Population, 75.0% of mirabegron-treated patients were female. Overall, 74.9% patients were White, 21.5% were Asian, and 3.1% were Black or African American; 4.6% were Hispanic or Latino. The median age was 60 years of age; 35.7% patients were ≥ 65 years of age and 9.8% patients were ≥ 75 years of age. The population included approximately 48% antimuscarinic treatment-naïve patients and approximately 52% patients previously treated with antimuscarinic therapy.

Regulatory interactions with the Division of Reproductive and Urologic Products at the FDA were held at regular intervals during the mirabegron development program including Pre-Investigational New Drug (IND), End-of-Phase 2 and Pre-NDA. The protocols for primary phase 3 studies 178-CL-046 and 178-CL-047 were submitted to the FDA for Special Protocol Assessment (SPA) review. In the SPA review, the Division agreed that the proposed phase 3 development program would support an indication of OAB with symptoms of urge incontinence, urgency and urinary frequency. Agreement on the Statistical Analysis Plans for Studies 178-CL-046 and 178-CL-047 was also received from the FDA.

The safety evaluations performed in the clinical studies conducted as part of the mirabegron clinical development program were consistent with International Conference on Harmonisation (ICH) E1A and allow for sufficient characterization and quantification of the safety profile of mirabegron. Safety data were assessed as per ICH E3, M4 and 21CFR§314.50 and associated guidance.

Clinical Pharmacology

After oral administration in healthy volunteers, mirabegron was absorbed to reach peak plasma concentrations (C_{max}) between 3 and 4 hours. Mean C_{max} and AUC increased more than dose proportionally over the dose range. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 to 200 mg mirabegron increased C_{max}

and AUC_{tau} by approximately 8.4- and 6.5-fold. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg.

Mirabegron was extensively distributed. The volume of distribution at steady state (V_{ss}) is approximately 1670 L. Mirabegron is bound (approximately 71%) to human plasma proteins and distributes to erythrocytes.

Mirabegron was metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron was the major circulating component; 2 non-pharmacologically active major metabolites were observed in human plasma and are phase 2 glucuronides representing 16% and 10% of total exposure, respectively. Although in vitro studies suggested a role for cytochrome P450 (CYP)2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicated that these isozymes play a limited role in the overall elimination.

Mirabegron was cleared by multiple mechanisms (renal and possibly biliary excretion of unchanged drug, and metabolism) and drug-metabolizing enzymes, with no single predominating clearance pathway. Renal clearance (CL_R) was independent of dose and averaged approximately 13 L/h, corresponding to nearly 25% of total clearance. Steady state concentrations were achieved within 7 days of once daily dosing with mirabegron.

Evaluation of intrinsic factors in volunteers demonstrated no dose adjustments are required on the basis of age, gender, race and genetic polymorphism for CYP2D6. Volunteers with severe renal impairment (creatinine clearance [CL_{CR}] 15 to 29 mL/min or estimated glomerular filtration rate [eGFR] 15 to 29 mL/min per 1.73 m^2) or moderate hepatic impairment (Child-Pugh Class B) had a greater than 2-fold increase in AUC_{inf} and C_{max}, respectively. A dose of mirabegron 25 mg is recommended for these special populations in order to achieve exposures similar to those produced with 50 mg in a non-impaired population.

Evaluation of extrinsic factors in healthy volunteers included an evaluation of food effect and a number of drug-drug interaction studies with compounds affecting CYP3A and P-glycoprotein (P-gp), with substrates for CYP3A, CYP2D6 and P-gp and with other urologic products. Drugs evaluated included ketoconazole, rifampin, oral contraceptive, metformin, metoprolol, warfarin, desipramine, digoxin, solifenacin and tamsulosin. While changes in mirabegron plasma exposure were seen in several of these studies, these changes are less than 2-fold and no dosage adjustment or precaution is necessary. Drugs that are CYP2D6 substrates are not expected to require dose adjustment, except for drugs with narrow therapeutic indices that are significantly metabolized by CYP2D6; caution is advised if mirabegron is coadministered with CYP2D6 substrates with narrow therapeutic indices.

Coadministration of mirabegron 50 mg with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered with or without food with no discernable difference in safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose.

Efficacy

Primary evidence for the efficacy of mirabegron in the treatment of patients with OAB comes from 3 randomized, 12-week placebo-controlled studies (Studies 178-CL-046, 178- CL-047 and 178-CL-074) conducted primarily in Europe and North America. Studies conducted in Japan were considered supportive for efficacy and have been included in summaries of safety. Further, evidence for the durability of effect comes from the long-term (1-year) Study 178-CL-049. These studies included patients representative of the target patient population. The population included both treatment naive patients and patients who had been previously treated with OAB antimuscarinic therapy. In each of the primary studies, each treatment arm contained approximately 450 patients. In 2 studies, patients were randomized to an oral dose of mirabegron 50 mg, 100 mg or placebo once daily. In one of these studies, an additional treatment arm received an oral antimuscarinic agent (tolterodine 4 mg extended

release [ER]) as an active control which provides an informative reference from an efficacy, toleration and safety perspective. In a third study, patients were randomized to an oral dose of 25 mg, 50 mg or placebo once daily. For the combined primary studies 1380 patients received placebo, 432 patients received mirabegron 25 mg, 1375 patients received mirabegron 50 mg and 929 patients received mirabegron 100 mg.

The primary efficacy studies consistently demonstrated the efficacy of mirabegron 25, 50 and 100 mg compared with placebo for the coprimary endpoints of change from baseline to final visit in mean number of incontinence episodes and mean number of micturitions per 24 hours. Mirabegron 50 mg, the recommended therapeutic dose, demonstrated superiority compared with placebo for key secondary endpoints as defined in the phase 3 program, including change from baseline to final visit in mean volume voided per micturition, change from baseline to week 4 in mean number of incontinence episodes and micturitions per 24 hours, and change from baseline to final visit in measurements of urgency. The effect of mirabegron 25, 50 and 100 mg on the coprimary efficacy endpoints was generally comparable, and a clear incremental efficacy benefit for mirabegron 100 mg compared with mirabegron 50 mg was not demonstrated. The magnitude of effect for the key secondary efficacy endpoints was comparable for mirabegron 50 mg and 100 mg, and notably lower for mirabegron 25 mg. The odds ratio for responders with a ≥ 50% reduction from baseline to final visit in incontinence episodes was 1.54 (95% CI: 1.26, 1.89) for the mirabegron 50 mg group.

Standard and clinically established instruments to assess quality of life measures were utilized in these studies to assess the impact of mirabegron on the patient's experience of symptoms and changes in HRQL. Patient-reported outcome measures included the Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC) and Treatment Satisfaction-Visual Analog Scale (TS-VAS). Mirabegron 50 mg led to significant changes in HRQL measures in parallel with the improvements in objective measures of OAB while mirabegron 25 mg offered little benefit to patients based on HRQL measures.

The directional parallelism between the subjective and objective measures for mirabegron 50 mg substantially supports the clinical significance of the effect of mirabegron.

Pooled analyses of the coprimary efficacy endpoints were conducted for multiple subgroup parameters. These analyses supported the efficacy of mirabegron regardless of demographic characteristics, OAB characteristics, intrinsic/extrinsic factors including comorbid conditions or selected concomitant medications or when administered with or without food. Efficacy with mirabegron was demonstrated in patients who were antimuscarinic treatment naive and in patients who failed previous OAB antimuscarinic therapy.

The durability of effect was demonstrated in the 52-week clinical safety study.

Safety

The safety of mirabegron has been investigated in 1462 volunteers in the phase 1 studies and 5863 patients in the phase 2/3 studies, of which 622 patients with OAB received mirabegron continuously for at least 52 weeks (365 days).

In the Global OAB 12-week Phase 2/3 Population, serious adverse event(s) (SAE), treatment-emergent adverse event(s) (TEAE) and TEAE leading to permanent discontinuation of study drug were reported by 1.7%, 53.4% and 3.6% for mirabegron, 1.8%, 55.2% and 2.9% for placebo, and 1.7%, 60.2% and 3.8% for tolterodine patients, respectively. There was no apparent dose response across mirabegron groups. The greatest proportion of TEAE (36.1%) were classified as mild in severity. The proportion of patients reporting at least 1 severe TEAE was low (3.1% to 3.3%) and similar across treatment groups. In the EU/NA Long-term Controlled Population SAE, TEAE and TEAE leading to permanent discontinuation of study drug were reported by 5.7%, 60.5% and 6.0% for mirabegron and 5.4%, 62.6% and 5.7% for tolterodine patients, respectively. Antimuscarinic side effects, specifically dry mouth, were reported less frequently in mirabegron-

treated patients (2.0%) compared with tolterodine-treated patients (11.1%) in the Global OAB 12-week Phase 2/3 Population and in the EU/NA Long-term Controlled Population (2.6% versus 8.6%, respectively); dry mouth was reported with a similar frequency in mirabegron-treated and placebo-treated patients in the 12-week studies. In the EU/NA OAB 12-week phase 3 Population, across all treatment groups, including placebo, patients on alpha-1 antagonists had a higher SAE rate (3.7% placebo, 3.3% mirabegron 50 mg and 2.9% tolterodine) than patients not on alpha-1 antagonists (2.0% placebo, 2.0% mirabegron 50 mg and 2.2% tolterodine); similar results were observed in the EU/NA Long-term Controlled Population.

Cardiovascular: Mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute (bpm) compared with placebo in patients with OAB. In EU/NA OAB 12-week Phase 3 Population, a low proportion of mirabegron 50 mg-treated patients reported any occurrence of tachycardia (57/1375, 4.1%) at a frequency greater than placebo-treated patients (48/1380, 3.5%) and tolterodine-treated patients (16/495, 3.2%). In these same studies, tachycardia and palpitations were reported as an AE in the mirabegron 50 mg group (1.2%; 0.4%) at a higher frequency than placebo (0.6%; 0.1%). In the EU/NA Long-term Controlled Population, the occurrence of any tachycardia was 28/812 (3.4%) for patients who received mirabegron 50 mg and 55/812 (6.8%) for tolterodine-treated patients. The change from baseline pulse rate following mirabegron at doses of 50 mg was similar to or less than the change from baseline pulse rate described with several antimuscarinics used in the treatment of OAB, including fesoterodine and trospium, and measured with tolterodine as a comparator in the mirabegron database [Toviaz package insert, 2011; Sanctura XL package insert, 2011]. Consistent with this finding, rates of categorical changes in pulse and adverse event(s) (AE) related to rapid pulse or tachyarrhythmias were comparable between 50 mg of mirabegron and tolterodine; a dose response was not observed for the occurrence of tachyarrhythmias.

Mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with a mean 0.4 to 0.6 mm Hg change from baseline systolic blood pressure (SBP)/diastolic blood pressure (DBP) compared with placebo in the EU/NA OAB 12-week Phase 3 Population. Unlike the change in pulse rate, the 95% CIs for the change from baseline in blood pressure compared with placebo consistently included zero. Graphical exposure-effect analysis of SBP/DBP in patients with OAB indicated that there was no overall trend for change from baseline in either parameter with increasing mirabegron AUC. Categorical increases from baseline in SBP/DBP for the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations were generally comparable across all treatment groups and there was not an increase in AE rates of hypertension.

There was no evidence of an increase in cardiovascular outcomes of death, SAE, ventricular arrhythmias or Antiplatelet Trialists' Collaboration (APTC)/Major Adverse Cardiac Events (MACE) events associated with mirabegron treatment compared to either placebo or tolterodine.

The 10-year CVD risk estimates based on the Framingham Study were calculated using data from the EU/NA 12-week and long-term phase 3 studies. The assessment of CVD risk change associated with pharmacotherapy may be more accurately assessed using data from the 1-year double-blind study 178-CL-049, which included tolterodine ER as an active control, rather than data from the 12-week studies. In the EU/NA Long-term Controlled Population (Study 178-CL-049), median changes from baseline to final visit in CVD risk estimate using mean AM/PM SBP values were the same for mirabegron 50 mg (0.1%) and tolterodine ER 4 mg (0.1%). The percent of patients with increases from baseline to final visit in the 10-year general CVD risk estimate ≥ 5% based on mean AM/PM SBP values was 3.6% for the mirabegron 50 mg group and 4.1% for the tolterodine ER 4 mg group; 1 patient in the mirabegron 50 mg group and 0 patients in the tolterodine ER 4 mg group had a value ≥10%.

There were no AE of torsade de pointe (TdP) in the development program. In (thorough QT) TQT testing, QTc prolongation using ICH criteria (95% CI of QTc >10 msec) was seen only in females at a dose of 200 mg which was associated with 6.5-times greater exposure (AUC) than the proposed 50 mg dose.

Urinary retention: In the EU/NA OAB 12-week Phase 3 Population, few TEAE of acute urinary retention (AUR) were reported across the treatment groups with frequency in mirabegron-treated patients less than that observed for placebo- or tolterodine-treated patients. There was no difference in postvoid residual (PVR) volume mean change from baseline or shift analyses across treatment groups. No events of AUR were observed in mirabegron-treated patients in Studies 178-CL-047 and 178-CL-074, where patients at risk for AUR were not specifically excluded.

In the EU/NA Long-term Controlled Population, 2 TEAE for AUR were reported, one in mirabegron 100 mg (occurred in a 59-year-old female immediate post-op for severe lumbar spinal stenosis) and one patient in tolterodine (65-year-old man with chronic history of lower urinary tract symptoms (LUTS) discontinued study drug due to the event).

In a urodynamic safety study in 200 male patients at risk for AUR (lower urinary tract symptoms/bladder outlet obstruction [LUTS/BOO]), administration of mirabegron at doses of 50 and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate.

Urinary tract infection (UTI): UTI has been identified as an adverse drug reaction with mirabegron. The frequency of UTI was higher in mirabegron patients (2.9%) compared with placebo patients (1.8%) in the 12-week OAB studies. There was no evidence of a mirabegron dose response and the frequency was comparable to tolterodine for the Global OAB 12-week Phase 2/3 Population (mirabegron: 4.3% and tolterodine: 4.4%) and the EU/NA Long-term Populations (mirabegron: 8.8% and tolterodine: 10.0%). Very few of the cases of UTI were serious or resulted in permanent discontinuation of study drug.

Renal colic: Very few cases of renal colic were observed in the program. The frequency of urolithiasis was generally < 0.5%, comparable across the mirabegron, placebo and tolterodine treatment groups, and few events were serious or resulted in permanent discontinuation of study drug.

Neoplasm: In the pooled Global OAB 12-week Phase 2/3 Population, there was an imbalance of adjudicated new malignancies in one of 6 studies (Study 178-CL-047: 4/442, 0.90% mirabegron 50 mg, 2/433, 0.46% mirabegron 100 mg, 0/453, 0% placebo) and in the EU/NA long-term study (Study 178-CL-049: 9/820, 1.10% , mirabegron 100 mg, 3/812, 0.37% mirabegron 50 mg, 4/812, 0.49% tolterodine 4 mg). Overall, there was (1) no evidence of a dose response in the occurrence of adjudicated malignancies; (2) no consistent signal in tumor types; and (3) no increase in the frequency of malignancy events with longer-term mirabegron exposure. An observed numerical imbalance of new malignant events was reported early after starting study medication (< 6 months) with eventual convergence of the probability for new malignancies over time. Given the natural history of cancer development, coupled with negative genotoxicity and 2-year rodent carcinogenicity studies, it is biologically implausible that mirabegron can result in the development of wide array of tumors during short-term exposure.

The observed number of adjudicated cases of the most frequent malignancies reported in mirabegron-treated patients was similar or less than expected numbers in an age-adjusted population.

Hepatic: Across the entire mirabegron clinical development program, 1.0% of mirabegron-treated patients reported a 3-fold or more transaminase elevation. No patient had a 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation in the absence of another underlying cause.

Hypersensitivity: Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura and lip and eyelid edema, occurred in mirabegron-treated subjects during the clinical development program including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses > 100 mg, with nonimmediate, primarily cutaneous reactions cannot be ruled out. These cutaneous reactions were generally reversible with discontinuation of mirabegron and symptomatic treatment as clinically indicated.

Pregnancy: There have been 9 pregnancies during the clinical development program (7 in mirabegron-treated patients, 1 in a placebo-treated volunteer and 1 in a patient whose treatment assignment remains blinded). Of the 7 mirabegron-treated cases, 3 pregnancies were completed with outcome of full-term live born males with no congenital anomalies, 1 pregnancy resulted in spontaneous abortion, 2 pregnancies resulted in elective abortions, and there was 1 completed suicide in which pregnancy was discovered on autopsy. A spontaneous complete abortion of 1 of 2 gestational sacs was reported in the placebo-treated healthy volunteer; no additional information is available. A spontaneous abortion was reported for a patient whose treatment remains blinded.

Benefit-Risk

Mirabegron is a new chemical entity with a mechanism of action (beta 3-AR agonist) distinct from the current standard therapeutic agents, primarily antimuscarinics, for the treatment of symptoms of OAB.

The clinical efficacy of mirabegron 50 mg was established in 3 placebo-controlled primary studies. The effect of mirabegron 50 mg has been consistently shown to be superior to placebo. Results from quality of life endpoints provide strong evidence that the patients not only obtained objective evidence of improvement but also clinically meaningful benefits from mirabegron in the treatment of their disease. Mirabegron has demonstrated efficacy in patients who are antimuscarinic treatment naive as well as patients who failed previous OAB antimuscarinic treatment. The durability of effect was demonstrated in the 52-week clinical safety study. The range of responses for mirabegron 50 mg in the mean difference from placebo for incontinence episodes and micturition frequency is within the range of values observed with approved OAB treatments [Chapple et al, 2008]. These results are also consistent with the range observed in individual studies reported in approved US product labels for other OAB agents [Detrol LA, 2011; Ditropan XL, 2011; Enablex, 2012; Sanctura XR, 2011; Toviaz, 2012; Vesicare, 2012].

Mirabegron at the proposed dose of 50 mg once daily was well tolerated in the OAB treatment population as a whole and in the various subpopulations with multiple comorbidities and concomitant medications. Adverse event rates were generally low and comparable between the mirabegron and placebo groups, and were generally not treatment limiting. Common adverse drug reactions (AE reported in the mirabegron 50 mg group at a frequency >1%, higher than placebo and with plausible causative link to mirabegron) in the EU/NA OAB 12-week phase 3 studies included tachycardia (1.2% mirabegron, 0.6% placebo) and UTI (2.9% mirabegron, 1.8% placebo). Mirabegron was associated with a low frequency of nonimmediate cutaneous hypersensitivity which was generally mild/moderate in severity.

Antimuscarinics are the current standard pharmacotherapeutic agents for the treatment of OAB. Typical antimuscarinic side effects limit their use. Adverse effects associated with antimuscarinic therapy, such as dry mouth, were observed with mirabegron at a frequency similar to or lower than placebo and lower than antimuscarinics in both the mirabegron clinical studies and in the OAB literature. Consistent with its distinct mechanism, mirabegron offers an additional pharmacologic treatment option for patients with OAB. Mirabegron addresses an unmet medical need for patients

with OAB who are not candidates for antimuscarinic therapy, who are intolerant to antimuscarinic therapy or those who have an inadequate response to prior antimuscarinic therapy.

In conclusion, mirabegron at a proposed therapeutic dose of 50 mg once daily with or without food represents a new approach for the treatment of OAB which is safe, well tolerated and effective for the treatment of patients with OAB under the conditions in the proposed labeling. The benefits of treatment exceed any risk associated with the use of the product.

2 PRODUCT DEVELOPMENT RATIONALE

2.1 Pharmacologic Class

Mirabegron is a selective agonist for human beta 3-AR that is indicated for the treatment of OAB. Mirabegron is a compound with a distinct mechanism of action compared with the current standard of care, primarily antimuscarinics, as pharmacotherapy for the treatment of symptoms associated with OAB.

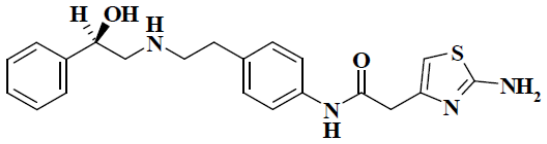
Mirabegron decreases resting intravesical pressure in rats, and decreases the frequency but not the force of rhythmic bladder contractions. Mirabegron decreases carbachol-induced intravesical pressure in dogs and increases the bladder capacity and decreases the voiding frequency in water-loaded monkeys. Antimuscarinic agents such as oxybutynin show a limited effect on resting bladder pressure and notably reduce the contractile force of the bladder at higher doses in rats.

In a rat model of bladder hyperactivity, mirabegron increased bladder capacity. In addition, in a rat model of partial BOO, mirabegron showed a decreased frequency of nonvoiding contractions without affecting voided volume per micturition, voiding pressure or residual urine volume. In this same model, antimuscarinic agents decreased voided volume per micturition and increased residual urine volume, without reducing nonvoiding contractions.

These observations are in agreement with effects for other beta 3-AR agonists in bladder function models [Woods et al, 2001].

The structural formula of mirabegron is shown in Figure 1.

Figure 1 Chemical Structure of Mirabegron



2.2 Problem Statement

2.2.1 OAB Background Information

OAB has been defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia [Wein & Rovner, 2002]. Its etiology is not completely clear, but involves detrusor overactivity, a status of increased sensitivity of the bladder to contraction-mediating transmitters and mediators originating from the urothelium [Birder et al, 2010]. Detrusor overactivation involves afferent signaling which convey as bladder sensations that are felt as urgency in patients diagnosed with OAB [Gillespie, 2004]. Prevalence estimates for OAB in the literature vary; the prevalence of OAB is estimated to be 34 million in the US and 22 million in Europe [Irwin et al, 2008; Kim et al, 2006; Stewart et al, 2003; Milsom et al, 2001]. A 2006 population-based study in men and women 18 years of age and older in Canada and 4 European countries estimated an overall prevalence of OAB of 11.8%.

In the US, the mean age of OAB patients ranges from 50.7 to 69 years of age [Asche et al, 2011; Coyne et al, 2011; Andersson et al 2009; Darkow et al, 2005]. The mean age of OAB patients in

clinical trial databases for OAB drugs ranges from 58 to 61 years of age, reflecting the demographics of OAB with a significant proportion of OAB patients ≥ 65 years of age (ranging from 33% - 42%) [Detrol LA package insert 2011; Ditropan package insert, 2011; Enablex package insert, 2012; Vesicare package insert, 2012]. OAB comorbid diseases include obesity, frequent falls and fractures, stroke, diabetes mellitus, skin infections, bladder cancer, prostate cancer, depression, hypertension and cardiovascular disease, frequent UTIs [Coyne, Sexton et al, 2008; McGrother et al, 2006; Darkow et al, 2005; Stewart et al, 2003]. The prevalence of OAB increases with age, affecting 30% to 40% of the population older than 75 years of age [Wein & Rovner, 1999].

The burden of disease for OAB is often noted to be underestimated due to reluctance of OAB patients to seek medical attention. Costs include the cost of diagnosis, treatment, routine care, as well as lost wages and productivity, and burdens include suffering, decreased quality of life and decreased functionality.

2.2.2 Medical Need for Treatment

OAB has a profound influence on a person's physical, social and emotional well-being [Resnick & Yalla, 1992]. The condition has a significant impact on HRQL, particularly emotional symptoms, sexual health and overall well-being [Rogers et al, 2009]. The problematic and unpredictable symptoms of OAB can have damaging effects on an individual's daily routine [Milsom et al, 2001]. Individuals with OAB are constantly worried about when leakage or urgency will occur and have developed elaborate mechanism to cope with daily obstacles caused by OAB. Some of these include reduction in fluid intake, frequent voids to avoid leakage, using incontinence pads or navigating to the closest toilet location [Milsom et al, 2001].

Study results using patient reported outcome measures such as the OAB-q and PPBC showed that OAB had a negative impact on quality of life, work productivity, sexuality and the emotional well-being in both men and women in Sweden, Italy, Canada, Germany and the United Kingdom [Coyne, Sexton et al, 2008]. Other studies have also demonstrated the association between OAB prevalence and lower levels of work productivity among both men and women in the US, and with sleep apnea and erectile dysfunction in men [Kemmer, 2009; Sexton et al, 2009; Irwin et al 2008]. OAB patients have been found to suffer a higher prevalence of sleep disturbance due to nocturia [Brown et al, 2000], and the prevalence of depression and skin infections in this population may be directly attributable to OAB [Klotz et al, 2007]. Overall, patients with OAB generally exhibit poor health, impaired quality of life, social isolation and depression [Holroyd-Leduc et al, 2004].

OAB can be managed by various treatment modalities, including bladder and behavioral training, biofeedback, electrical stimulation or pharmacotherapy. The pharmacotherapeutic treatment options indicated for OAB are muscarinic receptor antagonists, such as darifenacin, fesoterodine, oxybutynin solifenacin, trospium and tolterodine. The efficacy of these agents is measured by their ability to change the number of micturitions per day and their ability to reduce incontinence episodes for those who have incontinence due to OAB at baseline, although these changes vary from drug to drug and study to study depending on the specific OAB populations being studied and the attributes of their disease at baseline. The results of a meta-analysis of 73 clinical studies on the efficacy of antimuscarinic drugs showed the mean decrease from baseline in the number of incontinence episodes per day ranged from 0.2 to 1.1 and the mean decrease from baseline in the number of micturitions per day ranged from 0.5 to 1.3 episodes per day [Chapple et al, 2008]. Agents producing this degree of change have resulted in a meaningful improvement in symptoms and significant improvements in the HRQL for patients with OAB.

Correlations between baseline symptoms of OAB (incontinence, urgency and micturition frequency) and the degree of impairment in quality of life (QoL) measures have been observed [Coyne, Matza et al, 2007]. Further, in several large scale clinical trials significant correlations have been found between reductions in incontinence episodes and micturition frequency and improvements in QoL

scores by various instruments [Coyne et al, 2005; Coyne, Matza et al, 2007; Abrams et al, 2008; Van Kerrebroeck et al, 2009].

One of the challenges in the treatment of OAB is low adherence to prescribed medication. Antimuscarinic therapy is often prescribed following insufficient results with behavior modification alone; however, rates of treatment discontinuation are consistently high. Rates of discontinuation found in medical claims studies are especially high, with 43% to 83% of patients discontinuing medication within the first 30 days and rates continuing to rise over time [Sexton et al, 2011]. Additionally, findings from medical claims studies also suggest that over half of patients never refill their initial prescription and adherence levels tend to be low [Sexton et al, 2011]. For most antimuscarinics, continuation rates are less than 50% at 6 months [Brostrom & Hallas, 2009]. The low levels of persistence and adherence raise concern about the balance between the efficacy and tolerability of antimuscarinic agents. Efficacy and tolerability are key influencers of adherence levels [Basra et al, 2008; Haab & Castro-Diaz, 2005]. Furthermore, there is a strong association between decreased antimuscarinic medication adherence and increased health care service use in older adults with OAB in a managed care setting [Balkrishnan et al, 2006]. A drawback of antimuscarinic agents is that they also affect the salivary gland, intestine and eye, resulting in side effects such as dry mouth, constipation and blurred vision, which limits their chronic use [Gomelsky & Dmochowski, 2011; Chapple et al, 2008; Garely & Burrows, 2002; Chapple, 2000]. This highlights the societal, as well as the individual, consequences of the limitations of current pharmacotherapeutic agents for the treatment of OAB. An effective agent with improved toleration would assist patients and prescribers in dealing with the challenge of low adherence to OAB medication.

2.2.3 Role of Mirabegron in OAB Treatment

OAB remains a condition for which medical therapy can provide benefit, but for which there are limited treatment options. Pharmacological treatment is currently limited to antimuscarinics. Mirabegron is a compound with a distinct pharmacologic approach for the oral treatment of OAB. As shown in this briefing document, mirabegron is a safe and effective therapeutic agent for the treatment of patients with OAB with an improved toleration profile compared to antimuscarinic agents.

2.3 Scientific Rationale and Product Development

Early studies identified human beta 3-ARs on the surface of white and brown adipocytes [Krief et al, 1993], while more recent studies have noted beta 3-AR expression in human heart, gall bladder, gastrointestinal tract, prostate, urinary bladder detrusor, ureter, skeletal muscle, brain, near-term myometrium, coronary resistance arteries and penis cavernous bodies [Coman et al, 2009; Ursino et al, 2009; Dessy et al, 2004].

Whereas antimuscarinic agents reduce urine voiding by inhibiting the contraction of the detrusor muscles, activation of beta 3-AR in the bladder trigone facilitates urine storage through flattening and lengthening of the bladder base [Yamanishi et al, 2003]. The beta 3-AR subtype is dominant in the human detrusor muscle, and a role for beta 3-ARs in promoting urine storage in the bladder has been identified [Kumar et al, 2003; Yamaguchi, 2002].

Animal models demonstrated that beta 3-AR agonists FK175 and CL-316243 were effective in increasing bladder capacity in rats providing rationale for developing beta 3-Ar agonists as a treatment for overactive bladder syndrome [Fujimura et al, 1999; Woods et al, 2001; Takeda et al, 2002; Yamaguchi, 2002; Leon et al, 2008].

In the receptor binding study using membrane fractions from Chinese hamster ovary (CHO) cells expressing human beta AR subtypes, mirabegron showed high affinity for the human beta 3-AR (105-fold higher affinity for beta 3-AR compared with beta 1-AR and 33-fold higher affinity for beta 3-AR compared with beta 2-AR) [Table 1].

Table 1 Affinity of Mirabegron for Human Beta-Adrenoceptor Subtypes

Test Article	K_i (nmol/L)		
	Beta 1	Beta 2	Beta 3
Mirabegron	4,200 ± 900	1,300 ± 300	40 ± 20.2

K_i values are expressed as the mean ± SE of 3 runs.
K_i: binding affinity.

Table 2 shows a comparison of the beta 3-AR agonist activity of mirabegron in different species as well as an overview of data of the cross activation of beta 1- and beta 2-AR. The low IA values of mirabegron for rat, dog, monkey and human beta 1-AR and beta 2-AR in these experiments, even at concentrations up to 10,000 nmol/L, did not allow potency values (concentration of mirabegron that resulted in a 50% maximum response [EC_{50}]) to be calculated, with the exception of rat beta 1-AR, in which the mirabegron EC_{50} was 610 nmol/L.

Table 2 Species Differences of Mirabegron Agonist Activity for Beta AR Subtypes

Test Article	Beta 1		Beta 2		Beta 3	
	EC_{50} (nmol/L)	IA	EC_{50} (nmol/L)	IA	EC_{50} (nmol/L)	IA
Human						
Mirabegron	–	0.1	–	0.2	1.5 (0.89 - 3.2)	0.8
Isoproterenol	34 (23 - 50)	1.0	21 (10 - 42)	1.0	49 (39 - 61)	1.0
Rat						
Mirabegron	610 (360 - 2300)	0.6	–	0.1	19 (8.1 - 37)	1.0
Isoproterenol	31 (18 - 53)	1.0	110 (90 - 150)	1.0	60 (41 - 88)	1.0
Dog						
Mirabegron	–	0.3	–	0.1	7.9 (2.4 - 120)	0.8
Isoproterenol	80 (40 - 160)	1.0	39 (19 - 74)	1.0	180 (94 - 370)	1.0
Monkey						
Mirabegron	–	0.2	–	0.1	32 (20-55)	0.8
Isoproterenol	84 (67 - 110)	1.0	77 (57 - 100)	1.0	170 (150 - 200)	1.0

EC_{50} (concentration that induces 50% of the maximum response by isoproterenol) is expressed as the mean (95% CI) of 3 or 4 runs (a run represents the mean of 2 assays).
IA value is relative to the maximum response (1.0) of the full agonist isoproterenol.
-: EC_{50} not calculated when IA was < 0.5.
AR: adrenoceptor; EC_{50}: concentration of mirabegron that resulted in a 50% maximum response; IA: intrinsic activity.

Mirabegron showed full-agonist activity (IA ≥ 0.8) in mammalian cells transfected with human, rat, dog or monkey beta 3-ARs. Weak agonist activity was observed for mirabegron in mammalian cells transfected with either beta 1- (IA: 0.1 – 0.6) or beta 2-ARs (IA: 0.1 – 0.2). Mirabegron showed little or no off-target affinity for a wide panel of receptors, ion channels or transporters. These data indicate that mirabegron is a selective beta 3-AR agonist.

In vitro, mirabegron induced an increase in cyclic adenosine monophoshate (cAMP) levels in rat bladder strips and was associated with a concentration-related relaxation of precontracted human and rat detrusor muscle strips. In vivo, mirabegron decreased the frequency of premicturition contractions, micturition frequency and intravesicular pressure, as well as increased functional bladder capacity in rat OAB models and in volume-loaded monkeys. Unlike antimuscarinics, mirabegron did not impair bladder contraction during voiding. These nonclinical results provided a rationale for studying mirabegron in patients with OAB.

2.4 Nonclinical Development Program

A total of 153 nonclinical studies have been completed to date. Pivotal safety pharmacology studies and pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (standards for nonclinical studies on drug safety), in accordance with the Guidelines for Toxicity

Studies on Drugs and ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines.

As described in Section 2.3, mirabegron is a selective beta 3-AR agonist and nonclinical data provide proof of principle that stimulation of beta 3-AR in the bladder with mirabegron enhances urine storage without affecting voiding contractions.

The nonclinical pharmacokinetics of mirabegron, including its absorption, distribution, metabolism and excretion were evaluated in a series of in vitro and in vivo studies.

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation and amide hydrolysis. Structural analysis of in vivo metabolites demonstrated that the 8 most abundant human plasma metabolites were detected in either rats or cynomolgus monkeys at systemic exposures that were equal to or greater than that observed in humans at the MRHD. The steady state systemic exposures to the major metabolites, M11 and M12, in both rats and cynomolgus monkeys were greater than that observed at steady state in humans at the MRHD.

Nonclinical safety of mirabegron was evaluated in single dose toxicity studies in rats, dogs and cynomolgus monkeys; repeated dose toxicity studies in rats (up to 26 weeks), dogs (up to 2 weeks), and cynomolgus monkeys (up to 52 weeks); in vitro and in vivo genotoxicity studies; carcinogenicity studies in mice and rats; reproductive and developmental toxicity studies in rats and rabbits; local irritation studies in rabbits; and other toxicity studies (skin sensitization, impurities, hemolysis, and combination with solifenacin). Based on these studies, the heart, liver, CNS and fetal development have been identified as the target organs or processes. With respect to the heart and liver, nonclinical findings were observed at systemic exposures in excess of those achievable at the MRHD. CNS findings (decreased activity) were observed in multiple species at systemic exposures near that of the clinical exposures, however, these findings were transient (absent after multiple dosing), reversible and not associated with histopathologic findings.

A summary of observations from the pivotal repeated dose rodent and nonrodent studies is presented in Table 3.

The safety pharmacology studies assessing cardiovascular safety showed that mirabegron could increase heart rate when orally administered to conscious dogs or monkeys, but that there was a clear species difference in this response. The magnitude of differences in heart rate changes can be explained by the differences in cross activation of beta 1-AR in dogs and monkeys. This difference may account for the observed species difference. Nonclinical studies assessing cardiovascular safety are further discussed in Sections 5.6.1.2 and 5.6.1.8.

Fetal findings of dilated aorta and cardiomegaly are limited to rabbits, are not beta 3-AR mediated and are not a teratogenic effect of mirabegron. The cardiomegaly and dilated aorta seen at high systemic exposures (35.7-fold the human systemic exposure at MRHD), were a functional change mediated by a beta 1-AR induced increase in heart rate, both of which were attenuated by coadministration of metoprolol.

Mirabegron did not show any discernable evidence of genotoxicity or carcinogenic potential and was negative in 2-year rat and mouse carcinogenicity studies. Nonclinical studies assessing genotoxicity and carcinogenicity are discussed further in Section 5.6.3.1.

Table 3 Summary of Nonclinical Observations from Pivotal Repeated Dose Rodent and Non Rodent Studies and Embryo-Fetal Studies in Rats and in Rabbits

	26-week repeated dose (rats)		52-week repeated dose (monkey)	
Repeated Dose Studies	**NOEL (mg/kg/day)**	**Rat:Human AUC Ratio†**	**NOEL (mg/kg/day)**	**Monkey:Human AUC Ratio**
Heart Rate	ND	ND	> 30‡	7.9-12.6
QTc Prolongation	ND	ND	> 30‡	7.9-12.6
Increased transaminases	10	1.7-3.2	> 30	7.9-12.6
Increased creatinine	> 100	58.7-83.2	> 30	7.9-12.6
Altered glucose	> 100	58.7-83.2	> 30	7.9-12.6
CNS clinical observations (decreased activity)	< 3	0.2-0.3	10	2.1-3.7
	Rat		**Rabbit**	
Embryo-Fetal Studies	**NOEL (mg/kg/day)**	**Rat:Human AUC Ratio**	**NOEL (mg/kg/day)**	**Rabbit:Human AUC Ratio**
Maternal toxicity	30	6.2	3	0.7
Fetal body weight	30	6.2	3	0.7
Delayed ossification	30	6.2	3	0.7
Cardiomegaly or dilated aorta	Not observed in rats	–	10	14.1

--: not applicable; CNS: central nervous system; MRHD: maximum recommended human dose; ND: not determined; NOEL: no observed effect level; QTc: QT interval corrected for heart rate.
† Comparison of animal data with values at the MRHD (50 mg).
‡ QTc intervals and heart rate changes were not significantly different from pretreatment baseline values.

In conclusion, mirabegron, a selective beta 3-AR agonist, showed a primary pharmacology of induced bladder relaxation during the filling phase and inhibition of the frequency of non-voiding activity, without impairing voiding efficiency. Data from the nonclinical program supported that mirabegron has a safety profile acceptable for the treatment of patients with OAB at the proposed therapeutic dose of 50 mg.

2.5 Clinical Development Program

The global clinical development program consisted of 41 studies conducted over approximately 10 years in 10,552 subjects [Appendix 1, Table 1]. The initial clinical development program examined an indication of type 2 diabetes mellitus and was discontinued due to the absence of efficacy demonstrated in this population. A total of 29 phase 1 studies and 12 phase 2/3 studies (9 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally in Europe, Japan, the US, Canada, Australia/New Zealand and South Africa. These studies were conducted in accordance with Good Clinical Practice, ICH guidelines and applicable laws and regulations.

An overview of the clinical program is shown in Figure 2.

Additionally, 3 studies are currently ongoing:

- A phase 3 12-week study to evaluate mirabegron in patients with OAB in Korea, China, Taiwan and India, 178-CL-090;
- A phase 1 study in volunteers in Taiwan, Study 178-CL-092; and
- A phase 2 12-week study to evaluate the combination of mirabegron and solifenacin in patients with OAB in Europe, Study 178-CL-100.

2.5.1 Clinical Pharmacology Program

The mirabegron clinical pharmacology program consisted of 29 studies in 1800 volunteers and provides a thorough characterization of the clinical pharmacology of mirabegron. The majority of the studies were performed in healthy male and female volunteers 18 to 55 years of age and also included

healthy elderly male and female volunteers ≥ 65 years of age. The relevance of studies in the young was demonstrated by appropriate comparisons of pharmacokinetics between young and elderly volunteers. Population/pharmacokinetic (PK) analysis methods were used to characterize the clinical pharmacokinetics of mirabegron in patients with OAB.

The results of the clinical pharmacology program are discussed in Section 3.2.

2.5.2 Phase 2/3 Clinical Development Program

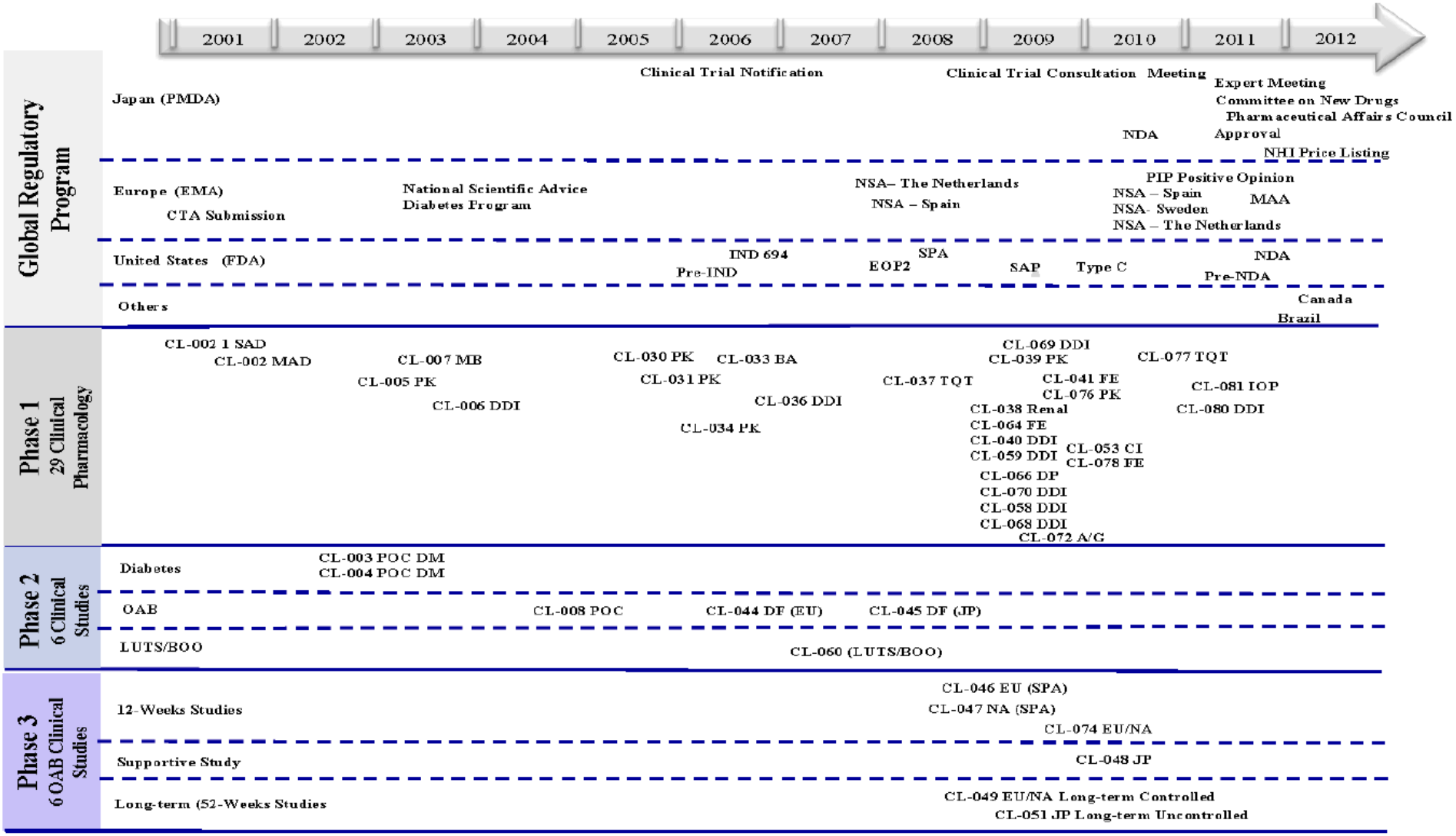
The efficacy of mirabegron in the treatment of patients with symptoms of OAB was evaluated in 9 studies [Table 4], including:

- 3 primary phase 3 studies (178-CL-046, 178-CL-047 and 178-CL-074),
- 1 supportive phase 3 study (178-CL-048),
- 2 supportive phase 2b studies (178-CL-044 and 178-CL-045),
- 1 phase 2a proof-of-concept study (178-CL-008),
- 1 phase 3 long-term (52 weeks) safety study (178-CL-049), and
- 1 phase 3 open label, long-term (52 weeks) safety study (178-CL-051).

Primary evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from 3 randomized, 12-week placebo-controlled studies (Studies 178-CL-046, 178- CL-047 and 178-CL-074) conducted primarily in Europe and North America. Phase 2b studies and studies conducted in Japan are considered supportive for efficacy and have been included in summaries of safety.

The phase 3 clinical development program for mirabegron was conducted in accordance with the agreements made at the End of Phase 2 Meeting with the Agency and is consistent with the SPA reviews of the pivotal studies 178-CL-046 and 178-CL-047.

Figure 2 Clinical Development Program



BOO: bladder outlet obstruction; DDI: drug-drug interaction; DF: dose finding; EOP: end of phase; FE: food effect; IND: investigational new drug; IR: immediate release; LTS: long-term study; LUTS: lower urinary tract symptoms; MR: modified release; NDA: new drug application; OAB: overactive bladder; POC: proof of concept; SPA: special protocol assessment; TQT; through QT.

Table 4 Description of Clinical Studies Providing Information Relevant to Efficacy

Study No. /Location of Sites that Enrolled Patients	Study Dates (First Screening to Last Visit)†	Design/Control & Study Objective	Duration of Treatment	Treatment Groups		
				Treatment	n FAS‡	n FAS-I§
Primary Studies						
178-CL-046 189 sites in Australia, Austria, Belgium, Belarus, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland, UK	Apr 2008 – Mar 2009	**Phase 3**, randomized, double-blind, placebo-controlled and active-controlled study to evaluate the efficacy and safety of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 50 mg Mirabegron 100 mg Tolterodine ER 4 mg¶	480 473 478 475	291 293 281 300
178-CL-047 132 sites in Canada and US	Mar 2008 – Apr 2009	**Phase 3**, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 50 mg Mirabegron 100 mg	433 425 412	325 312 296
178-CL-074 151 sites in Canada, US, Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden	Apr 2009 – Apr 2010	**Phase 3**, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 25 mg Mirabegron 50 mg	415 410 426	262 254 257
Supportive Studies						
178-CL-048 93 sites in Japan	Jul 2009 – Feb 2010	**Phase 3**, randomized, double-blind, placebo-controlled and active-controlled study to evaluate the efficacy and safety of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 50 mg Tolterodine ER 4 mg¶	368 369 368	264 266 240
178-CL-044 97 sites in Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, and UK	Apr 2006 – Mar 2007	**Phase 2b**, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging study to evaluate dose-response efficacy, safety, tolerability, and population/PK of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 25 mg Mirabegron 50 mg Mirabegron 100 mg Mirabegron 200 mg Tolterodine ER 4 mg¶	166 167 167 168 166 85	106 99 108 111 110 53
178-CL-045 60 sites in Japan	Sep 2007 – Apr 2008	**Phase 2b**, randomized, double-blind, placebo-controlled, parallel group study to evaluate dose-response efficacy, safety, and PK of mirabegron	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Placebo Mirabegron 25 mg Mirabegron 50 mg Mirabegron 100 mg	211 209 208 207	140 134 144 150

Table continued on next page.

Study No. /Location of Sites that Enrolled Patients	Study Dates (First Screening to Last Visit)†	Design/Control & Study Objective	Duration of Treatment	Treatment Groups		
				Treatment	n FAS‡	n FAS-I§
178-CL-049†† 306 sites in Australia, Canada, New Zealand, South Africa, US, Austria, Belarus, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovakia, Ukraine, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and UK	Apr 2008 – May 2010	**Phase 3**, randomized, double-blind, active-controlled study to evaluate the long-term safety and tolerability of mirabegron	2-week single-blind placebo run-in followed by 12-month double-blind treatment period	Mirabegron 50 mg Mirabegron 100 mg Tolterodine ER 4 mg¶	789 802 791	479 483 488
178-CL-051†† ‡‡ 26 sites in Japan	Dec 2008 – Mar 2010	**Phase 3**, open-label study to evaluate the long term safety of mirabegron 50 mg with an optional dose increase to 100 mg at week 8.	1-week single-blind placebo run-in followed by 52-week open-label treatment period	Mirabegron 50 mg to 100 mg (*all subjects*) Subjects maintained at mirabegron 50 mg Subjects increased to mirabegron 100 mg	196 146 50	149 104 45
178-CL-008 30 sites in Belgium, Czech Republic, Germany, Spain, Sweden, and UK	Apr 2004 – Jan 2005	**Phase 2a**, randomized, double-blind, parallel group, placebo-controlled and active-controlled proof-of-concept study to evaluate efficacy, safety, population PK, and tolerability of mirabegron	2-week single-blind placebo run-in followed by 4-week double-blind treatment period	Placebo Mirabegron IR 100 mg bid Mirabegron IR 150 mg bid Tolterodine ER 4 mg¶	64 65 63 63	41 37 41 41

Mirabegron OCAS formulation used unless noted.
ER: Extended release; FAS: full analysis set; FAS-I: full analysis set incontinence; IR: immediate release; PK: pharmacokinetics; UK: United Kingdom; US: United States.
†For studies with no screening assessment, date of informed consent or first enrollment is presented.
‡ In all studies except Study 178-CL-051, the FAS was comprised of all randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement. In Study 178-CL-051, an open-label study, the FAS was comprised of all patients with at least one dose of open-label study drug who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement.
§ The FAS-Incontinence (FAS-I) included all patients in the FAS who had at least one incontinence episode recorded in the baseline 3-day micturition diary diary (FAS Incontinence [FAS-I]).
¶The active comparator is designated tolterodine ER which represents the modified release formulation evaluated within individual studies, including Detrusitol SR (slow release) and Detrol LA (long-acting).
†† All efficacy analyses were secondary in Studies 178-CL-049 and 178-CL-051 since neither are placebo-controlled.
‡‡ In Study 178-CL-051, patients were allowed to titrate from a dose of 50 mg to a dose of mirabegron 100 mg (2 tablets of mirabegron 50 mg taken once daily) at week 8 if the following criteria were met: the therapeutic effect of the investigational dosage was found to be insufficient at the week 8 visit; safety of the patient was considered, in the judgment of investigator or subinvestigator, not at risk; and the patient requested a higher dose. Fifty patients titrated to a dose of 100 mg at week 8. Of these, 2 patients then down-titrated back to a dose of 50 mg due to safety reasons.

2.5.3 Clinical Development Safety Database

The safety of mirabegron has been investigated in 5863 patients (5648 patients with OAB) in the phase 2/3 studies [Table 5] and 1462 volunteers in phase 1 studies. In addition to the 5863 mirabegron-treated patients, the phase 2/3 program included 2312 patients treated with placebo and 1834 patients treated with an active comparator. A total of 622 of the 5648 patients with OAB treated with mirabegron received mirabegron for at least 1 year (continuous exposure).

Mirabegron exposure of patients in the phase 2/3 clinical development program is shown in Table 6.

Table 5 Source and Number of Patients Treated in the Global Phase 2/3 Clinical Population

Study	Treatments							
Global OAB 12-week Phase 2/3 Population								
		Total Daily Dose of Mirabegron						
	Placebo	25 mg	50 mg	100 mg	200 mg		Total Mirabegron	Tolterodine ER 4 mg
178-CL-046	494		493	496			989	495
178-CL-047	453		442	433			875	
178-CL-074	433	432	440				872	
Subtotal of EU/NA OAB 12-week Phase 3 population	*1380*	*432*	*1375*	*929*			*2736*	*495*
178-CL-044	169	169	169	168	167		673	85
178-CL-045	213	210	208	208			626	
178-CL-048	380		379				379	378
Totals	2142	811	2131	1305	167		**4414**	958
Other phase 2 studies included in the Global Phase 2/3 Population								
		Total Daily Dose of Mirabegron						
	Placebo	25 mg	50 mg	100 mg	200 mg	300 mg	Total Mirabegron	Tolterodine ER 4 mg
DM 178-CL-003 †	19				40		40	
178-CL-004 †‡	20				40		40	
OAB 178-CL-008	66				65	65	130	64
BOO/LUTS 178-CL-060	65		70	65			135	
Totals	170		70	65	145	65	**345**	64
EU/NA Long-term Controlled Population								
	Mirabegron mg/day		Mirabegron New Exposure §		Mirabegron Re-exposure ¶		Total Mirabegron	Tolterodine ER 4 mg
	50 mg	100 mg						
178-CL-049	812	820	**901**		731		1632	812 ††
Japan Long-term Uncontrolled Population								
	Mirabegron mg/day						Total Mirabegron	
	50 mg (only)	100 mg (used)						
178-CL-051 ‡‡	153	50					**203**	
Total Number of Unique Mirabegron Patients in the Global Phase 2/3 Population §§	4414 + 345 + 901 + 203 = **5863 (5648 OAB Patients)**							

All randomized patients who took at least one dose of study drug (Safety Analysis Set).
BOO: bladder outlet obstruction; DM: diabetes mellitus; ER: extended release; LUTS: Lower urinary tract symptoms; OAB: overactive bladder.
† Patients randomized to mirabegron in Studies 178-CL-003 and 178-CL-004 received a daily dose of 60 mg (1 week), 130 mg (1 week), and 200 mg (10 weeks); they are included in the 200 mg column.
Footnotes continued on next page.

‡ Patients in Study 178-CL-004 received either placebo or mirabegron in combination with metformin.
§ Mirabegron new exposure indicates patients on mirabegron in Study 178-CL-049 who did not receive mirabegron in Studies 178-CL-046 or 178-CL-047.
¶ Mirabegron re-exposure indicates patients on mirabegron in Study 178-CL-049 who also took mirabegron in Studies 178-CL-046 or 178-CL-047.
†† Includes 108 tolterodine new exposures and 704 tolterodine re-exposures for patients who had previously received tolterodine in Study 178-CL-046 or 178-CL-047.
‡‡ Patients in Study 178-CL-051 received a starting dose of 50 mg mirabegron and could potentially increase to 100 mg mirabegron. Patients in the mirabegron 50 mg (only) column only received mirabegron 50 mg; patients in the mirabegron 100 mg (used) column had their dose increased from 50 mg to 100 mg.
§§ Total number of patients treated with mirabegron in phase 2/3 clinical trials: total mirabegron from placebo-controlled 12-week OAB phase 2/3 population + total mirabegron from other phase 2 studies + mirabegron new exposures from the EU/NA Long-term controlled phase 3 population + total mirabegron from the Japan Long-term uncontrolled phase 3 population.

Table 6 Summary of Study Drug Exposure, Global Phase 2/3 Population

Characteristic		Cumulative Exposure of Total Mirabegron † (n = 5863)	Continuous Exposure of Total Mirabegron ‡ (n = 5863)
Duration of Exposure (days) n (%)	≥ 84	4203 (71.7)	4191 (71.5)
	≥ 182	1596 (27.2)	1572 (26.8)
	≥ 274	1508 (25.7)	1482 (25.3)
	≥ 365	964 (16.4)	622 (10.6)
Duration (days)	Mean (SD)	162.2 (142.66)	152.0 (125.78)
	Median	85.0	85.0
	Min, Max	1,490	1,396
Patient-years of exposure	Total	2603.55	2439.44

Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060 and 178-CL-074.
† For patients who received mirabegron in more than one study, duration is summed across studies.
‡ For patients who received mirabegron in more than one study, only the study with the longest exposure across all doses is included.

2.6 Regulatory History

US

Regulatory interactions with the Division of Reproductive and Urologic Products at the FDA have been held at regular intervals during the mirabegron development program, including Pre-IND and End-of-Phase 2 and Pre-NDA. In addition, the protocols for primary phase 3 studies 178-CL-046 and 178-CL-047 were submitted to the FDA for SPA review in December 2007. In accordance with a written response from FDA received in February 2008, both protocols were amended to incorporate the SPA recommendations prior to enrollment of patients. Key Agency recommendations, which were implemented as a result of the SPA and the End-of-Phase 2 discussion, were to include coprimary endpoints of incontinence episode frequency and micturition frequency, to define severe hypertension and exclude patients with severe hypertension at screening and baseline, and to define criteria for recording hypertension as an AE. In the SPA review, the Division agreed that the proposed phase 3 development program would support an indication of OAB with symptoms of urge incontinence, urgency and urinary frequency. In addition, agreement on the statistical analysis plans (SAP) for Studies 178-CL-046 and 178-CL-047 was received from the FDA in May 2009.

As part of the comments from the Division during the SPA of the phase 3 primary trial, Study 178-CL-047, the Division requested that the Sponsor consider adding a 25 mg arm to the study design. Study 178-CL-074 was designed to further evaluate mirabegron 25 and 50 mg once daily versus placebo. The protocol and statistical analyses for Study 178-CL-074 were similar to that of Studies 178- CL-046 and 178-CL-047. Also as part of the SPA comments received from the Division, FDA indicated that data from the phase 3 program were not sufficient to allow removal of precautionary

statements included in the current anti-muscarinic OAB labeling regarding the possibility of bladder outflow obstruction and urinary retention in the labeling for mirabegron. Further dialog ensued with the Division on this topic at a Type C meeting in December 2009. The current program was not designed to address removal of this standard precaution in the US labeling of OAB drugs.

Europe

The primary studies to support efficacy of mirabegron were designed to be consistent with Committee for Medicinal Products for Human Use (CHMP) guidance for the clinical investigation of medicinal products for urinary incontinence and included measures of both absolute and relative effect on the patient perception of treatment effect. Regulatory interactions with the Competent Authorities in Europe have been held at regular intervals during the mirabegron development program. National Scientific Advice (NSA) meetings have been conducted with the Competent Authorities in The Netherlands (March 2010), Sweden (March 2010) and Spain (March 2010) for the OAB development program. The phase 3 protocols were shared with the Competent Authorities at NSA meetings with The Netherlands (October 2007) and Spain (December 2007) prior to conduct and the protocols were adapted accordingly. In addition, a Pediatric Investigation Plan (PIP) for mirabegron has been submitted to the EMA Pediatric Committee, with a positive opinion communicated in August 2010; the measures of the agreed PIP were deferred until after submission of the MAA for the adult indication. An Eligibility Request for utilization of the Centralised Procedure for the mirabegron MAA was submitted to EMA in July 2010; EMA confirmed that mirabegron is eligible for the Centralised Procedure. Introductory meetings were held with the Rapporteur and Co-Rapporteur prior to submission of the MAA in August 2011.

Japan

An NDA was submitted to the Japanese Ministry of Health, Labor and Welfare in June 2010. The application was supported primarily by the clinical development program conducted in Japan. The Japan NDA was approved in July 2011 and the product was launched in September 2011.

Other

An NDA was submitted in Brazil in December 2011, an NDS was submitted in Canada in Feburary 2012 and an MAA was submitted in Switzerland in March 2012.

3 OVERVIEW OF BIOPHARMACEUTICS AND CLINICAL PHARMACOLOGY

This section provides an overview of data relevant to the pharmacokinetics and pharmacodynamics of mirabegron.

The following completed clinical pharmacology and biopharmaceutical studies support dosing and other claims for mirabegron [Table 7]:

- 18 clinical pharmacology studies which used the Oral Controlled Absorption System (OCAS) formulation (a modified release formulation),
- 5 clinical pharmacology studies which used the immediate release (IR) formulations (solution and IR tablet), and
- 6 bioavailability, food effect and in vitro-in vivo correlation (IVIVC) studies which used OCAS formulations with varying release rates.

Healthy volunteers were enrolled in these studies with the exception of the renal and hepatic impairment studies.

Table 7 Overview of Mirabegron Phase 1 Clinical Studies

Study No.	Type of Study	Dose (mg)	No. E/C
Biopharmaceutic Studies			
178-CL-030	OCAS Selection	200 qd OCAS-F, S and -M 100 bid IR tablet	36/34
178-CL-033	Absolute BA	50, 150 sd OCAS; 15, 50 sd iv over 2 hrs	12/12
178-CL-076	IVIVC, Absolute BA	25, 50, 100 sd OCAS-H,L,M; OCAS-M other batch; 7.5 15, 30 sd iv over 2 hrs	91/75
178-CL-041	Effect of Food; Pivotal	50, 100 sd	76/64
178-CL-064	Effect of Food	50 sd	24/23
178-CL-078	Effect of Food;Pivotal	50, 100 sd	72/70
Healthy Subject PK and Initial Tolerability Studies			
178-CL-001	Single-dose PK and Food Effect	0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, 340 sd IR capsule	85/85
		160 sd IR capsule	12/12
178-CL-002	Multiple-dose PK and Food Effect	40, 80, 160, 240 qd for 7 days IR capsule	40/38
178-CL-007	Mass Balance	^{14}C-mirabegron 160 sd drinking IR solution	4/4
178-CL-031	Single- and Multiple-dose PK in Young and Elderly	50, 100, 200, 300 sd followed by 50, 100, 200, 300 qd for 10 days	96/96
178-CL-066	Dose Proportionality	25, 50, 100 sd	12/12
178-CL-034	Single- and Multiple-dose PK in Japanese Subjects	0, 50, 100, 200, 300, 400 sd 0, 100, 200 qd	40/40 24/24
Studies in Special Populations (Intrinsic Factors)			
178-CL-072	Age and Sex	25, 50, 100 qd	75/67
178-CL-038	Renal Impairment	100 sd	33/32
178-CL-039	Hepatic Impairment	100 sd	32/32
Studies of Drug-Drug Interaction (Extrinsic Factors)			
178-CL-005	CYP2D6 Genotype, Metoprolol PK Interaction	160 sd IR capsule	16/16
		160 qd IR capsule; metoprolol 100 sd	12/12
178-CL-006	Metformin PK Interaction	160 qd IR tablet; metformin 500 bid	32/31
178-CL-036	Ketoconazole PK Interaction	100 sd; ketoconazole 400 qd	24/23
178-CL-040	Warfarin PK and PD Interaction	100 qd; warfarin 25 sd	24/24
178-CL-058	Desipramine PK Interaction	100 qd; desipramine 50 sd	28/27
178-CL-068	COC PK Interaction	100 or placebo qd; COC (EE 30 mcg + LNG 150 mcg) qd	30/23
178-CL-059	Digoxin PK Interaction	100 qd; digoxin 0.250 sd	25/23
178-CL-069	Solifenacin PK Interaction	100 sd; solifenacin 10 qd; 100 qd; solifenacin 10 sd	41/40
178-CL-070	Rifampin PK Interaction	100 sd; rifampin 600 qd	24/24
178-CL-080	Tamsulosin Cardiovascular PD Interaction	100 qd; tamsulosin 0.4 sd (PR)100 sd; tamsulosin 0.4 qd (PR)	48/46
Pharmacodynamic Studies			
178-CL-053	Mechanism of Cardiovascular Responses	200 sd; bisoprolol 10 sd; propranolol 160 sd (PR)	12/12
178-CL-037	Thorough QT	100, 200 qd for 7 days; moxifloxacin 400 sd	49/43
178-CL-077	Thorough QT	50, 100, 200 qd for 10 days; moxifloxacin 400 sd	352/319
178-CL-081	Intraocular Pressure	100 qd	321/305

Unless noted studies used OCAS formulation.
^{14}C-mirabegron: ^{14}C-labeled mirabegron; CYP: cytochrome P450; E/C: enrolled/completed; sd: single dose; OCAS: oral-controlled absorption system (-F [fast], -M [medium], -S [slow], -H [high], -L [low]); IR: immediate release; PK: pharmacokinetic(s); BA: bioavailability; IVIVC: in vitro-in vivo correlation; COC: combined oral contraceptive (containing ethinyl estradiol and levonorgestrel); EE: ethinyl estradiol; LNG: levonorgestrel; PR: prolonged release.

3.1 Overview of Formulation Development Process

The attributes of mirabegron are consistent with parameters set out in regulatory guidelines to be considered a Class 3 compound (high solubility and low permeability) in the Biopharmaceutical Classification System (BCS) (FDA guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, 2000). The BCS was developed to aid in predicting the in vivo behavior of

drugs based on in vitro assessments of solubility and permeability and classification is based on these factors [Amidon et al, 1995]. Compounds in this BCS class often are affected by food consumption and absorption can be dependent on activity of gut influx and efflux transporters.

The early clinical studies were conducted with IR capsules and tablets. An aqueous solution was used for the human mass balance study. Since the IR formulations showed a considerable decrease in plasma exposure with food and high peak-to-trough fluctuations in plasma concentrations with once daily dosing, a modified release (OCAS) tablet was developed; OCAS is a hydrophilic gel-forming matrix tablet.

Tablets used in the primary phase 3 efficacy and safety studies and the majority of the clinical pharmacology studies are identical to the commercial tablets, except that the commercial product will be debossed.

3.2 Pharmacokinetics

Mirabegron has a chiral center, but has been developed as the R-configured enantiomer. Mirabegron did not demonstrate chiral inversion after oral administration of radiolabeled mirabegron in healthy volunteers. The pharmacokinetic parameters in healthy volunteers are presented in Figure 38 and [Appendix 1, Table 2].

3.2.1 Absorption

After oral administration of mirabegron in healthy volunteers, mean peak plasma concentrations were reached between 3.0 and 4.3 hours. Mirabegron is a substrate for the efflux transporter P-gp and the influx organic cation transporters (OCT) OCT1, OCT2 and OCT3 in vitro. The absorption of mirabegron is dose-dependent, likely attributed to saturated efflux transporters in the intestine. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg.

3.2.2 Distribution

Mirabegron has a large volume of distribution at steady state of approximately 1670 L, indicating extensive distribution. Mirabegron is moderately bound (approximately 71%) to human plasma proteins, including albumin and alpha-1 acid glycoprotein. Small variations in the unbound fraction had minimal impact on the overall variability in mirabegron pharmacokinetics. In-vitro erythrocyte concentrations of ^{14}C-labeled mirabegron (^{14}C-mirabegron) were about 2-fold higher than in plasma, indicating that mirabegron distributes to erythrocytes.

3.2.3 Elimination

Total body clearance (CL) from plasma is approximately 57 L/h. Blood clearance is estimated to be approximately 41 L/h, which is about half the liver blood flow. Following an initial more rapid distribution phase, the elimination of mirabegron is multi-phasic with a terminal $t_{1/2}$ of approximately 50 hours. The $t_{1/2}$ was independent of dose, route of administration and formulation, indicating no absorption-rate limitation in the pharmacokinetics of the OCAS tablet. The effective half-life is estimated to be about 19 hours (based on population PK analysis). Steady state concentrations were achieved within 7 days of once daily dosing with mirabegron. Mirabegron is cleared by multiple mechanisms (renal and possibly biliary excretion of unchanged drug and metabolism) and drug-metabolizing enzymes, with no single predominating clearance pathway.

3.2.3.1 Metabolism

The metabolism of mirabegron was evaluated in vitro in plasma and human liver microsomes in 6 studies. In addition, plasma, urine and/or feces samples from clinical pharmacology studies were evaluated for mirabegron metabolites in 8 clinical studies. The postulated metabolic pathways of mirabegron in humans are shown in Figure 3.

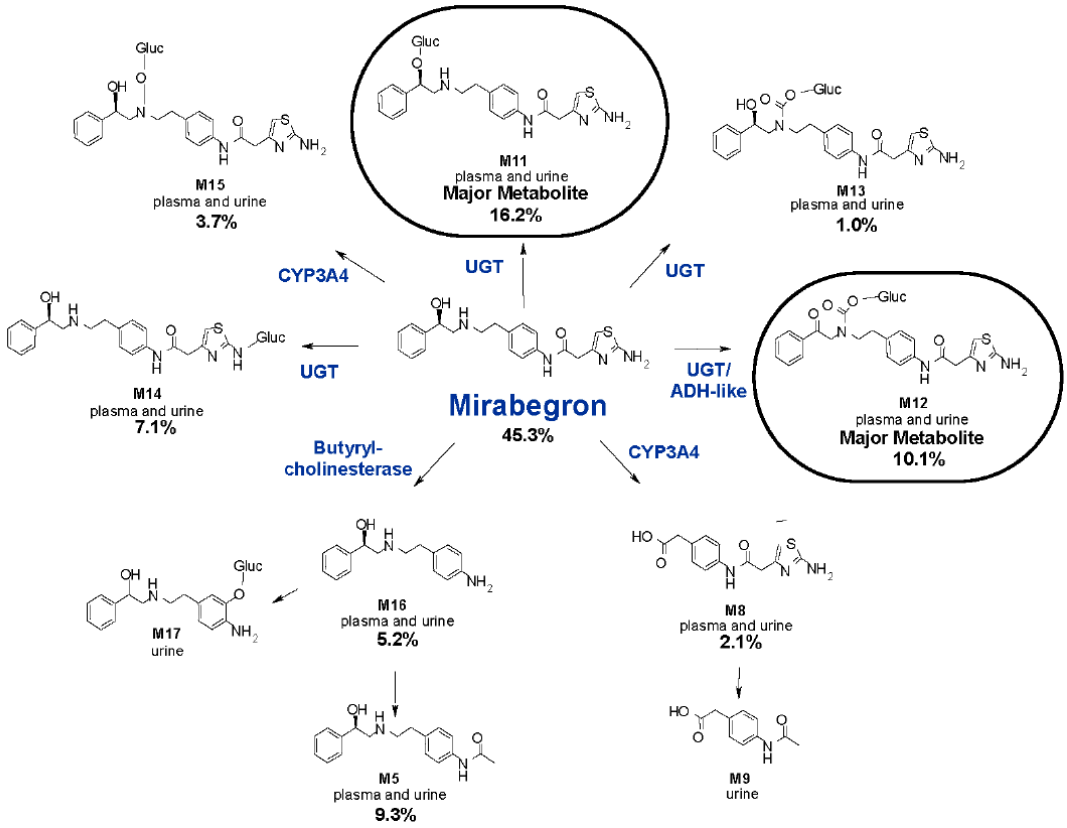
Mirabegron was metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation and amide hydrolysis. Urinary excretion data suggest that butyrylcholinesterase is the most important enzyme involved in the metabolism of mirabegron, in addition to contributions from uridine diphospho-glucuronosyltransferase, CYP3A4 and CYP2D6 enzymes and possibly alcohol dehydrogenase. CYP3A4 is the primary responsible isoenzyme for in vitro hepatic oxidative metabolism of mirabegron, with a minor role of CYP2D6.

Mirabegron was the major circulating component following a single radioactive dose of mirabegron. A total of 10 metabolites (M5, M8, M9, M11, M12, M13, M14, M15, M16 and M17) were identified in human urine. Eight of these (M5, M8, M11, M12, M13, M14, M15 and M16) were also observed in human plasma after oral administration.

The time course of the metabolite plasma concentration profiles was generally delayed by about 0.5 to 1.5 hours compared with the parent profile, with mean t_{max} values ranging between 3.6 and 6.3 hours. Metabolite-to-parent AUC ratios were relatively constant across multiple oral doses of 25 to 200 mg qd, indicating that the metabolism of mirabegron is not saturable over this dose range. M11 and M12 were considered to be major metabolites according to the ICH M3 (R2) guidance; both are phase 2 glucuronides representing 16% and 10% of total exposure in plasma.

In vitro studies revealed that none of the metabolites observed in plasma were pharmacologically active. Agonist activities of the above metabolites on beta 3-AR were less than 1/400-fold that of mirabegron and activities on other beta ARs were negligible. In addition, no other relevant affinities at biological targets were observed. Unchanged mirabegron is proposed to be the drug moiety mainly responsible for the pharmacological effects of the drug.

Figure 3 Postulated Metabolic Pathways of Mirabegron in Humans



Mirabegron or metabolite-to-total AUC_{tau} ratios (%) at a mirabegron dose of 50 mg qd in healthy male and female volunteers. ADH: alcohol dehydrongenase; CYP: cytochrome P450; UGT: uridine diphosphate-glucuronosyltransferase.

3.2.3.2 Excretion

CL_R averages approximately 13 L/h, which corresponds to nearly 25% of CL. The CL_R estimates are consistent across doses and study days and were similar after oral and intravenous administration, indicating that the excretion process is independent of dose or administration route and is not altered with repeated dosing. Renal elimination of mirabegron is likely to occur primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and is approximately 6% after a daily dose of 25 mg and 9% after a daily dose of 50 mg.

Following the administration of 160 mg ^{14}C-mirabegron to healthy volunteers, approximately 55% of ^{14}C-mirabegron was recovered in the urine and 34% in the feces. Unchanged mirabegron accounted for 45% of the urinary radioactivity and the majority of the fecal radioactivity.

These results indicate that the elimination of mirabegron is likely to be through both biliary and renal excretion of unchanged drug and metabolism.

3.2.4 Dose Proportionality

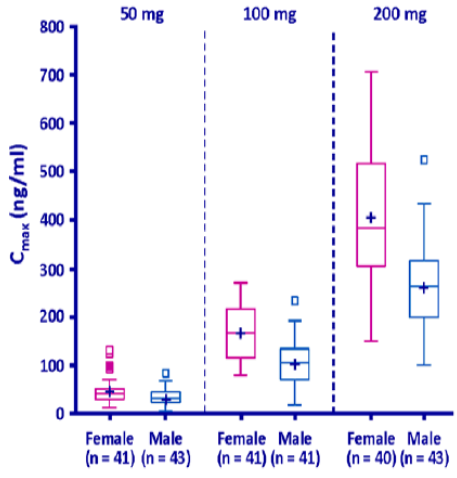
No deviations from dose proportionality in mirabegron pharmacokinetics parameters were observed after single-dose intravenous administration of mirabegron. After oral administration, a greater than dose-proportional increase in mirabegron C_{max} and AUC was observed, due to an increase in absolute bioavailability with increasing dose [Figure 4]. In the overall population of males and females, a 2-fold increase in dose of mirabegron (from the proposed therapeutic dose of 50 mg to the supratherapeutic dose of 100 mg) increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a supratherapeutic dose of mirabegron 200 mg increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the proposed therapeutic dose of 50 mg. Similar fold increases were obtained for males and females separately.

Mirabegron metabolites also demonstrated a more than dose proportional increase in C_{max} and AUC_{tau} after multiple mirabegron doses (25 to 200 mg qd), similar to that observed with the parent compound, indicating that the greater than dose-proportional increase in mirabegron exposure is not caused by saturable first-pass metabolism.

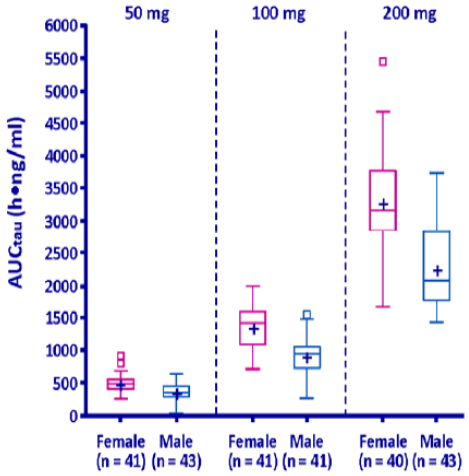
The non-proportionality after oral administration may be attributed to a relative decrease of efflux transport caused by saturation of efflux transporters (predominantly P-gp) by mirabegron.

Figure 4 Mirabegron C_{max} and AUC_{tau} after Multiple Doses of Mirabegron in Healthy Male and Female Volunteers

(A) C_{max}



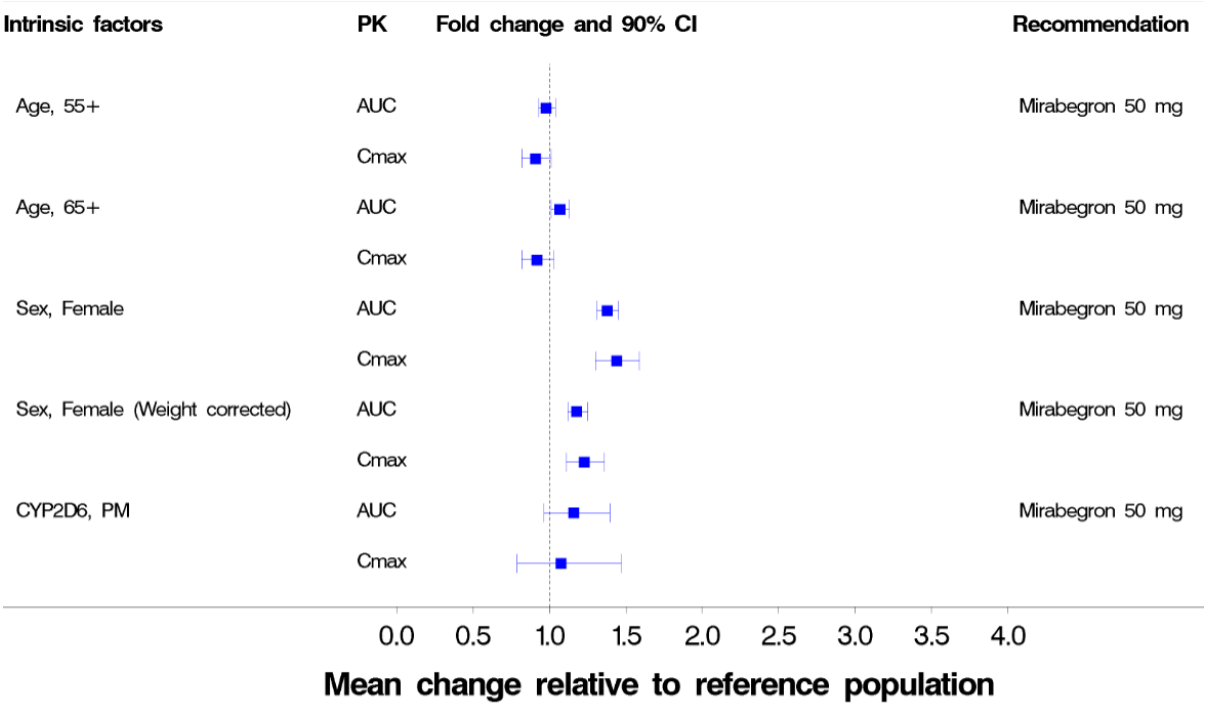
(B) AUC_{tau}



3.2.5 Effect of Intrinsic Factors

The effect of age, sex, CYP2D6 genotype, renal and hepatic impairment on the pharmacokinetics of mirabegron was studied in several single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of these effects are presented in Figure 5 and Figure 6, as well as dosage adjustments to be recommended in the package insert, as a result of the effect. While changes in mirabegron plasma exposure were seen in several of these studies, these changes do not reach the level, > 2-fold mean change relative to reference population, where dosage adjustment or precautions would be necessary.

Figure 5 Effect of Intrinsic Factors on the Pharmacokinetics of Mirabegron



CYP: cytochrome P450; PM; poor metabolizers.

Age

Age has no clinically relevant impact on mirabegron exposure. There were no statistically significant differences in mirabegron C_{max} and AUC_{tau} between older volunteers aged 55 years and above and younger volunteers (18-45 years). Similar results were obtained for the elderly subpopulation aged 65 years and above. Population PK analysis of phase 2/3 data indicated that age had a minimal effect on mirabegron exposure. The typical AUC was predicted to be 11% higher in a subject aged 90 years compared to a typical OAB subject aged 60 years. Dose adjustment based on age is therefore not necessary.

Gender

Mirabegron C_{max} and AUC_{tau} were approximately 40% to 50% higher, respectively, in females compared with males. The magnitude of the gender differences is attenuated with correction for body weight; however, weight-normalized values for C_{max} and AUC_{tau} were approximately 20% to 30% higher in females compared to those in males. This remaining increased exposure is attributed to a higher absolute bioavailability of mirabegron in females compared to males. No dose adjustment based on sex is recommended; the efficacy and safety of mirabegron at the proposed therapeutic dose have been demonstrated in both male and female OAB patients.

Race

Race has no clinically relevant impact on mirabegron exposure. There were no apparent differences in pharmacokinetic parameters among subjects of White, Black, Asian or other racial origin [Table 8]. In addition, race was not found to influence any of the pharmacokinetic parameters in the population PK analysis of phase 2/3 data. Plasma exposure in Japanese healthy volunteers was higher than in Western volunteers, which was largely related to differences in body weight. Dose adjustment based on race is not necessary.

Table 8 Influence of Race on Pharmacokinetic Parameters of Mirabegron, Study 178-CL-077

Dose	Parameter mean (CV%)	White	Black	Asian	Other
50 mg qd	n	33	44	4	3
	AUC_{tau} (ng·h/mL)	435 (35)	431 (37)	455 (14)	345 (21)
	C_{max} (ng/mL)	41.6 (58)	41.4 (54)	53.0 (44)	39.5 (30)
100 mg qd	n	39	39	3	1
	AUC_{tau} (ng·h/mL)	1160 (37)	1150 (33)	1170 (37)	1100 (-)
	C_{max} (ng/mL)	145 (45)	131 (42)	157 (45)	154 (-)
200 mg qd	n	41	36	2	4
	AUC_{tau} (ng·h/mL)	2640 (33)	2720 (30)	4210 (42)	3140 (21)
	C_{max} (ng/mL)	318 (46)	339 (38)	539 (27)	381 (14)

(-) : not evaluable.

Body Weight

The magnitude of the observed mirabegron exposure differences between male and female volunteers and between Japanese and Western volunteers was attenuated with correction for body weight. Population PK analysis of phase 2/3 data confirmed that body weight affected mirabegron exposure. Relative to a subject with a body weight of 70 kg, AUC_{tau} was about 53% higher in a volunteer with a body weight of 30 kg and approximately 17% lower in a volunteer with a body weight of 100 kg. The increase in exposure with lower body weight is less than would be achieved if the dose were doubled (resulting in a 190% and 160% increase in C_{max} and AUC, respectively). Dose adjustment based on body weight is not necessary.

Genetic Polymorphism

Genetic polymorphism for the CYP2D6 isozyme has no clinically relevant impact on mirabegron exposure. The absence of substantial differences in exposure between poor metabolizers (PM) and extensive metabolizers (EM) of CYP2D6 is consistent with the multiple elimination pathways for mirabegron. No dose adjustment is needed in patients who are poor metabolizers for CYP2D6.

PM of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition) exhibited similar or only slightly higher mirabegron plasma exposure compared with EM [Figure 5 and Table 12]. Following a single 160 mg dose of mirabegron IR, mean mirabegron C_{max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 PM compared to EM. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC_{tau} was 8% and 12% higher, respectively, in CYP2D6 PM compared to EM and mean C_{max} values were similar between the 2 phenotypes.

No dose adjustment is needed for mirabegron when coadministered with CYP2D6 inhibitors or in patients who are CYP2D6 PM [Figure 5].

Renal Impairment

Following single dose administration of mirabegron 100 mg in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated using the Modification of Diet in Renal Disease equation), mean mirabegron C_{max} and AUC_{inf} were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59

mL/min/1.73 m^2) C_{max} and AUC_{inf} were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) C_{max} and AUC_{inf} were increased by 92% and 118% relative to volunteers with normal renal function [Figure 6 and Table 9].

No dose adjustment is required in patients with mild to moderate renal impairment; a reduction of the dose to 25 mg once daily in patients with severe renal impairment is recommended. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1.73 m^2 or CL_{cr} < 15 mL/min or patients requiring hemodialysis) and, therefore, is not recommended for use in this patient population.

Hepatic Impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC_{inf} were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC_{inf} values were 175% and 65% higher [Figure 6 and Table 9].

No dose adjustment is required in patients with mild hepatic impairment; a reduction of the dose to 25 mg is recommended for patients with moderate hepatic impairment. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, is not recommended for use in this patient population.

Figure 6 Effect of Intrinsic Factors on the Pharmacokinetics of Mirabegron

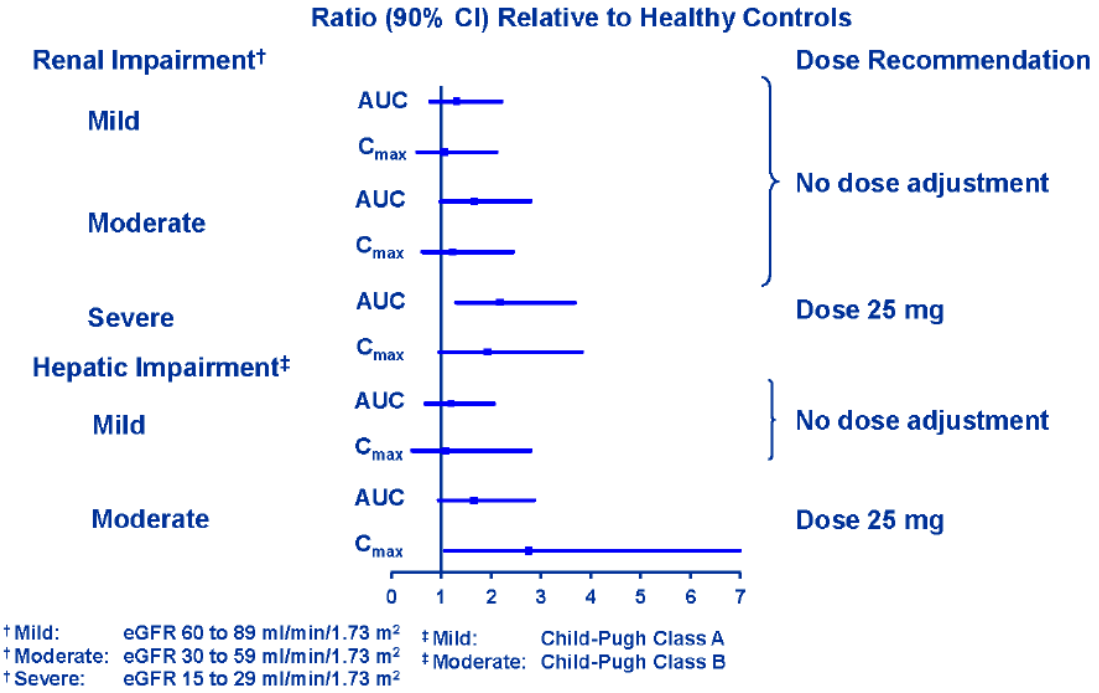


Table 9 Effect of Renal or Hepatic Impairment on the Pharmacokinetic Parameters of Mirabegron

Renal or Hepatic Function Group	Parameter	n	Ratio (%) Impaired/Healthy Volunteers	90% CI (%)
Mild renal impairment	AUC_{inf}	8	131	(78, 220)
	C_{max}	8	106	(53, 210)
Moderate renal impairment	AUC_{inf}	8	166	(99, 280)
	C_{max}	8	123	(62, 244)
Severe renal impairment	AUC_{inf}	8	218	(130, 367)
	C_{max}	8	192	(97, 381)
Mild hepatic impairment	AUC_{inf}	8	119	(69, 205)
	C_{max}	8	109	(42, 280)
Moderate hepatic impairment	AUC_{inf}	8	165	(95, 285)
	C_{max}	8	275	(108, 698)

Patients with OAB

Mean AUC_{tau} estimates in patients with OAB were approximately 20% to 50% lower compared with fasted AUC_{tau} values in healthy volunteers [Table 10]. As mirabegron administration in the phase 2b/3 studies occurred either with food or irrespective of food, the lower mean plasma exposure in patients with OAB may be due to an effect of food reducing the absorption of mirabegron. The lower exposure may also be due to the sparse sampling scheme used in the patient studies, which may have missed the absorption phase and peak concentrations and underestimated the true exposure.

In patients with OAB without significant renal or hepatic impairment a significant difference in pharmacokinetic characteristics of mirabegron between patients and healthy volunteers is not expected.

Table 10 Comparison of Mean Mirabegron Exposures in Patients with OAB and Healthy Volunteers as a Function of Study and Dose

AUC_{tau} (ng·hr/mL)		Dose (mg)			
Study	**Statistic**	**25 qd**	**50 qd**	**100 qd**	**200 qd**
Patients with OAB					
178-CL-044	Mean (%CV)	83 (51)	213 (47)	607 (58)	1760 (42)
	n	154	154	163	155
178-CL-045	Mean (%CV)	82 (44)	216 (56)	616 (55)	-
	n	198	194	194	-
178-CL-046	Mean (%CV)	-	224 (57)	611 (59)	-
	n	-	459	466	-
178-CL-047	Mean (%CV)	-	211 (59)	662 (60)	-
	n	-	392	386	-
178-CL-048	Mean (%CV)	-	252 (49)	-	-
	n	-	358	-	-
178-CL-074	Mean (%CV)	77 (63)	204 (57)	-	-
	n	397	411	-	-
Healthy Volunteers†					
178-CL-037	Mean (%CV)	-	-	870 (44)	2200 (31)
	n	-	-	46	45
178-CL-072	Mean (%CV)	154 (36)	435 (32)	1220 (32)	-
	n	47	46	48	-
178-CL-077	Mean (%CV)	-	431 (35)	1150 (34)	2740 (32)
	n	-	84	82	83

OAB: overactive bladder.
† Data are presented for overall population of healthy male and female volunteers.

3.2.6 Effect of Extrinsic Factors

The effect of food or coadministered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of coadministered drugs were studied in several single and

multiple dose studies. Pharmacokinetic measures indicating the magnitude of the effect of coadministered drugs on mirabegron pharmacokinetics are presented in Figure 7.

Effect of Food and Alcohol

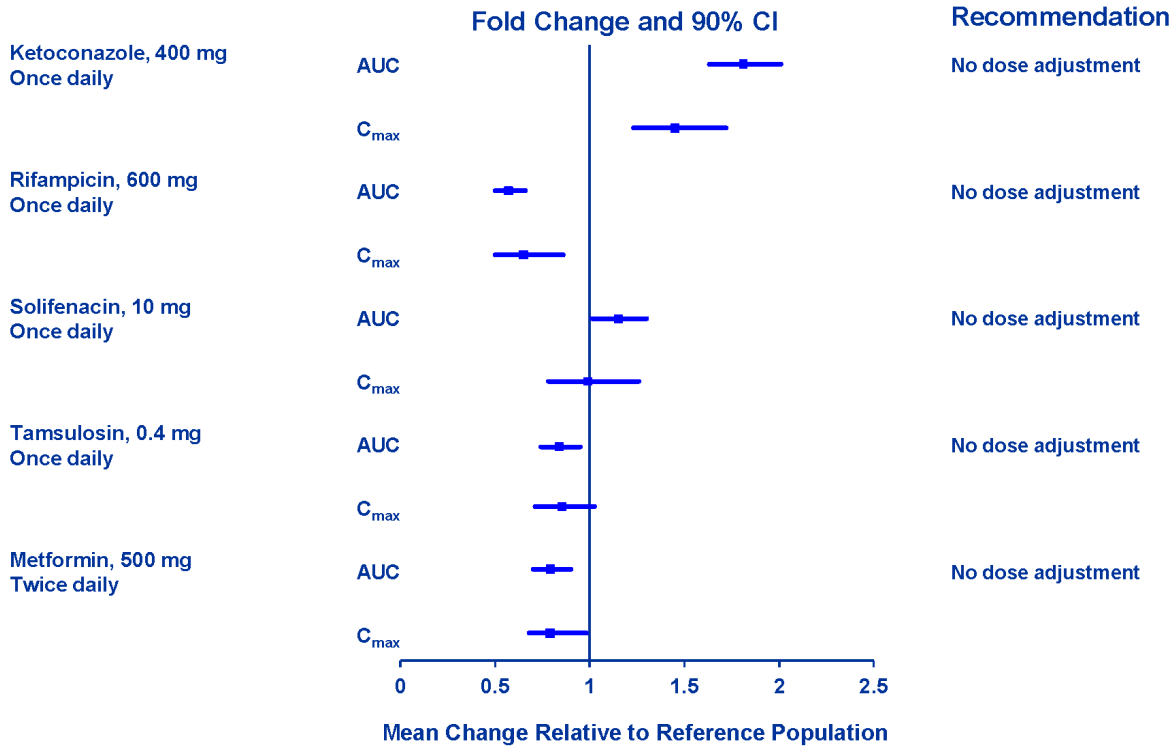
Mirabegron OCAS tablets exhibited a decrease in plasma exposure with food that was dependent on meal composition (low-fat versus high-fat). Mirabegron can be taken with or without food at the proposed therapeutic dose. The effect of food on mirabegron efficacy and safety is further discussed in Section 3.2.8.

Alcohol is unlikely to accelerate mirabegron dissolution and release from the OCAS formulation. Addition of 4% ethanol to the dissolution medium showed similar dissolution profiles for mirabegron OCAS tablets compared to buffer, whereas the addition of 40% ethanol showed delayed dissolution profiles.

Effect of Coadministered Drugs on the Pharmacokinetics Mirabegron

Mirabegron is cleared by multiple mechanisms (metabolism, renal and possibly biliary excretion) and drug-metabolizing enzymes, with no single predominating clearance pathway [Section 3.2.3]. Therefore, coadministered drugs were expected to have a low propensity to affect the pharmacokinetics of mirabegron. These expectations have been confirmed in the drug-drug interaction (DDI) studies. A number of interaction studies with compounds affecting CYP3A, P-gp, as well as renal secretion and with other urologic products were performed in healthy volunteers. While changes in mirabegron plasma exposure were seen in several of these studies, these changes do not reach the level where dosage adjustment or precautions would be necessary [Figure 7].

Figure 7 Effect of Coadministered Drugs on the Pharmacokinetics of Mirabegron



The largest changes in mirabegron plasma exposure were observed during coadministration with potent modulators of CYP3A and P-gp [Table 11]. The potent CYP3A and P-gp inhibitor ketoconazole (400 mg qd) caused a 45% increase in C_{max} and an 81% increase in AUC_{inf} of mirabegron (100 mg sd). Coadministration of rifampin (600 mg qd), a potent CYP3A and P-gp inducer, resulted in a 35% decrease in C_{max} and a 44% decrease in AUC_{inf} of mirabegron (100 mg sd). These results indicate that mirabegron is not a sensitive substrate for CYP3A4 in vivo. No dose adjustment is needed for mirabegron when coadministered with ketoconazole, rifampin or other modulators of CYP3A or P-gp.

Mirabegron pharmacokinetics was not affected to a clinically significant extent by metformin, solifenacin or tamsulosin [Table 11]. In addition, there was no clinically relevant pharmacodynamic (PD) interaction between tamsulosin and mirabegron. No dose adjustment for mirabegron is necessary when combined with metformin, solifenacin or tamsulosin.

Table 11 Effect of Coadministered Drugs on the Pharmacokinetic Parameters of Mirabegron

Coadministered Drug and Dose	n	Mirabegron Dose	Ratio (%) with/without Coadministered Drug (90% CI)	
			C_{max}	AUC
CYP3A and/or P-gp Inhibitors				
Ketoconazole 400 mg qd	23	100 mg sd	145 (123, 172)	181 (163, 201)
CYP3A and/or P-gp Inducers				
Rifampin 600 mg qd	24	100 mg sd	65 (50, 86)	56 (49, 65)
Other				
Metformin 500 mg bid	12	160 mg IR qd	79 (68, 93)	79 (70, 90)
Solifenacin 10 mg qd	20	100 mg sd	99 (78, 126)	115 (101, 130)
Tamsulosin 0.4 mg qd	24	100 mg sd	85 (71, 103)	84 (74, 95)

CYP: cytochrome 450; IR: immediate release; P-gp: P-glycoprotein; sd: single dose.

As an interaction of mirabegron with an inhibitor of CYP2D6 was not expected, the effect of a potent CYP2D6 inhibitor on mirabegron PK was not studied. Poor metabolizers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition) exhibited similar or only slightly higher mirabegron plasma exposure compared with extensive metabolizers [Section 3.2.5]. No dose adjustment is needed for mirabegron when coadministered with CYP2D6 inhibitors or in patients who are CYP2D6 PM [Figure 5].

Table 12 Influence of CYP2D6 Predicted Phenotype on Single and Multiple Dose Pharmacokinetic Parameters of Mirabegron

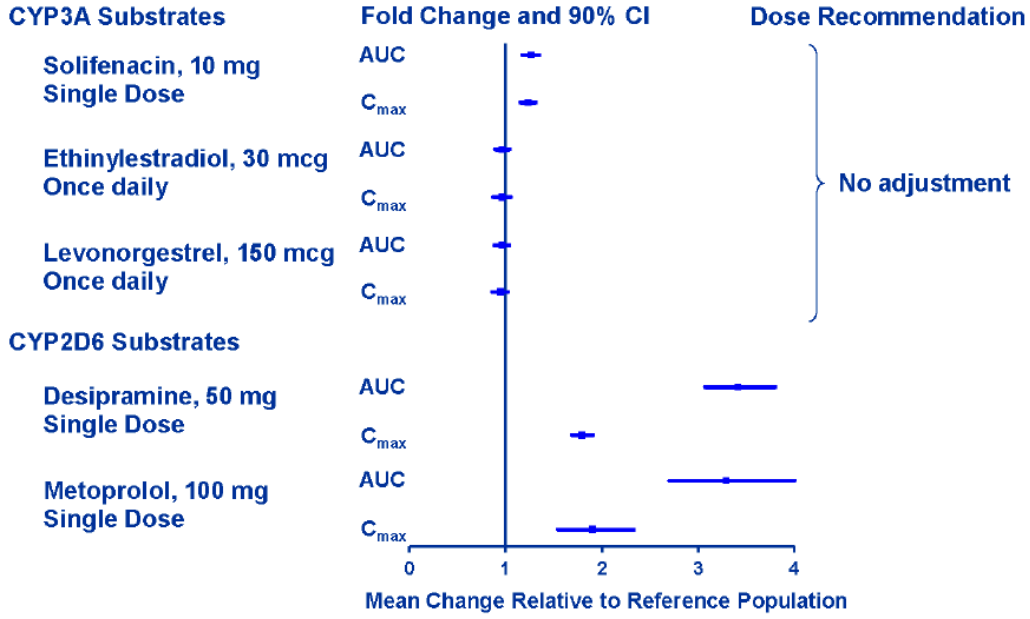
Dose	Parameter mean (CV%)	CYP2D6 EM	CYP2D6 PM
160 mg IR	n	8	8
	AUC_{inf} (ng·h/mL)	1250 (12)	1490 (26)
	C_{max} (ng/mL)	230 (23)	263 (43)
50 mg qd	n	56	3
	AUC_{tau} (ng·h/mL)	438 (38)	475 (18)
	C_{max} (ng/mL)	43.0 (61)	43.8 (46)
100 mg qd	n	43	10
	AUC_{tau} (ng·h/mL)	1170 (32)	1310 (27)
	C_{max} (ng/mL)	141 (42)	147 (43)

CYP: cytochrome P450; EM: extensive metabolizer; IR: immediate release; PM: poor metabolizer.

Effect of Mirabegron on the Pharmacokinetics of Coadministered Drugs

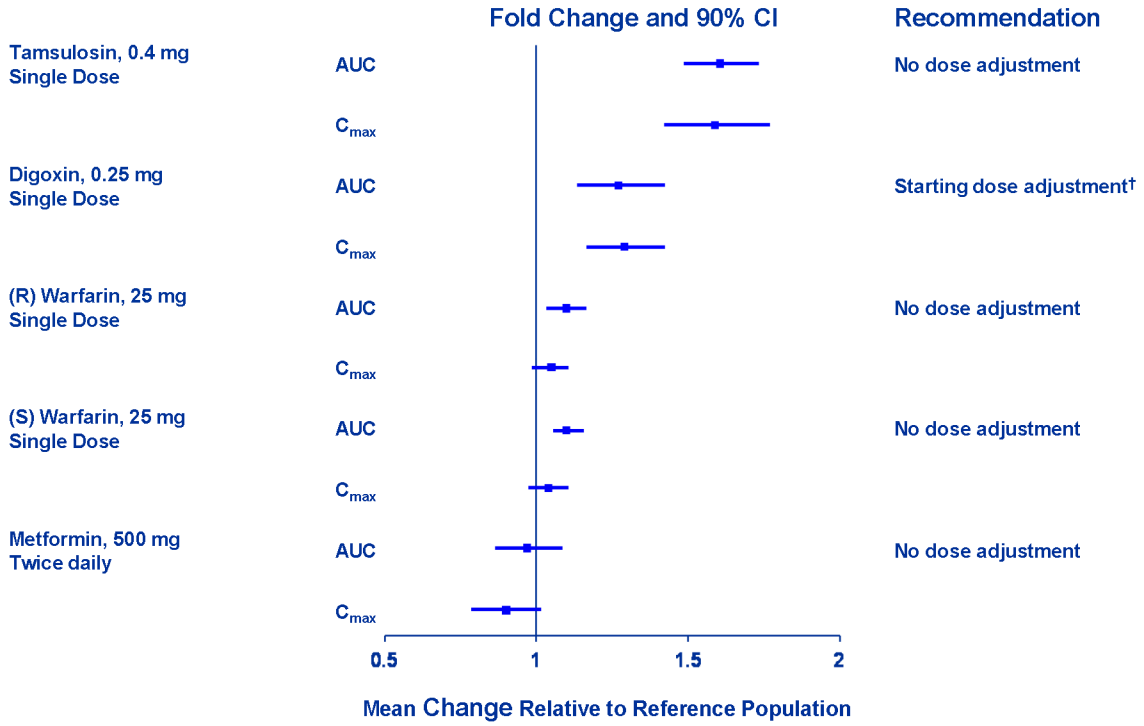
Pharmacokinetic measures indicating the magnitude of the effect of mirabegron on the pharmacokinetics of coadministered drugs are presented in Figure 8 and Figure 9.

Figure 8 Effect of Mirabegron on the Pharmacokinetics of Coadministered Drugs, CYP3A or CYP2D6 Substrates



CYP: cytochrome 450.
Caution is advised if mirabegron is coadministered with narrow therapeutic index medications significantly metabolized by CYP2D6.

Figure 9 Effect of Mirabegron on the Pharmacokinetics of Other Coadministered Drugs



† For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

In vitro studies have demonstrated that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of coadministered drugs metabolized by the following CYP enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit activity of those enzymes at clinically relevant concentrations in vitro. Mirabegron did not affect the metabolism of glibenclamide (a CYP3A4 substrate) or tolbutamide (a CYP2C9 substrate) in vitro. Mirabegron did not induce CYP1A2 or CYP3A in vitro. Mirabegron inhibited P-gp, OCT1- and OCT2-mediated drug transport at high concentrations.

DDI studies were performed with substrates for CYP2D6, CYP3A4 and/or P-gp, with other urologic products, with the narrow therapeutic index drug warfarin and with metformin, which, like mirabegron, is a renally secreted organic cation.

Multiple qd dosing of 160 mg mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC_{inf} of a single 100 mg dose of the CYP2D6 substrate metoprolol [Table 13]. Multiple once daily dosing of mirabegron 100 mg resulted in a 79% increase in C_{max} and a 241% increase in AUC_{inf} of a single 50 mg dose of the CYP2D6 substrate desipramine. At 15 days after the last mirabegron dose no relevant effect on the pharmacokinetics of desipramine was measured. Caution is advised if mirabegron is coadministered with narrow therapeutic index medications significantly metabolized by CYP2D6.

Mirabegron (100 mg qd) did not affect the pharmacokinetics of ethinyl estradiol and levonorgestrel (both CYP3A4 substrates; combined oral contraceptive) or solifenacin (a CYP3A4 substrate) to a clinically significant extent. Mirabegron (100 mg qd) increased plasma exposure of the CYP2D6 and CYP3A4 substrate tamsulosin (0.4 mg sd) by approximately 60%. Coadministration of mirabegron 100 mg and tamsulosin 0.4 mg in healthy middle-aged men caused no statistically significant changes in the pulse rate or SBP response compared with either drug administered alone. DBP was statistically significantly lower on combination treatment compared with either drug administered alone; the effect was small and not accompanied by orthostatic symptoms or an increase in positive orthostatic stress tests.

No effects of mirabegron on the pharmacokinetics of R-warfarin or S-warfarin (probe substrate for CYP2C9) or on prothrombin time were observed when mirabegron (100 mg qd) was coadministered with warfarin (25 mg sd). Plasma exposure of metformin (500 mg bid) was not changed to a clinically relevant extent by mirabegron co-administration (160 mg IR qd).

With multiple dosing of 100 mg mirabegron qd, the C_{max} of the probe P-gp substrate digoxin (0.25 mg sd) increased 29%, while AUC_{last} increased 27% [Table 13]. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Table 13 Influence of Mirabegron on the Pharmacokinetics of Coadministered Drugs

Coadministered drug and dose	n	Mirabegron Dose	Ratio (%) with/without mirabegron (90% CI)	
			C_{max}	AUC
CYP2D6 Substrates				
Metoprolol 100 mg sd	12	160 mg IR qd	190 (154, 233)	329 (270, 400)
Desipramine 50 mg sd	27	100 mg qd	179 (169, 190)	341 (307, 380)
CYP34A Substrates				
Solifenacin 10 mg sd	20	100 mg qd	123 (115, 131)	126 (117, 135)
COC (EE 30 mcg + LNG 150 mcg)	24	100 mg qd	EE: 96 (87,105) LNG: 94 (86,102)	EE: 96 (89,104) LNG: 96 (88, 103)
P-gp Substrates				
Digoxin 0.250 mg sd	23	100 mg qd	129 (117, 142)	127 (114, 142)
Other				
Metformin 500 mg bid	32	160 mg IR qd	90 (79, 101)	97 (87, 108)
Warfarin 25 mg sd	24	100 mg qd	S-warfarin: 104 (98, 110) R-warfarin: 105 (99, 110)	S-warfarin: 110 (106, 115) R-warfarin: 110 (104, 116)
Tamsulosin 0.4 mg sd	24	100 mg qd	159 (143, 177)	161 (149, 173)

COC: combined oral contraceptives; CYP: cytochrome P450; EE: ethinyl estradiol; IR: immediate release; LNG: levonorgestrel; sd: single dose.

3.2.7 Reproducibility/Variability

Mirabegron pharmacokinetics show variability, expressed by intersubject variability estimates for C_{max} and AUC_{inf} of approximately 40% to 52% and 39% to 45%, respectively, following oral administration. Corresponding estimates for the intrasubject variability ranged from approximately 33% to 45% for C_{max} and 19% to 31% for AUC_{inf}. The majority of the variability was related to absorption. Intersubject variability after intravenous administration was noticeably lower than that after oral administration, with intersubject %CVs for C_{max} and AUC_{inf} of approximately 20%. Part of the variability in mirabegron disposition was related to body weight.

3.2.8 Mirabegron and Food Effect

The effect of food on the pharmacokinetics of mirabegron was evaluated in the clinical pharmacology studies, including 2 pivotal food effect studies and 4 exploratory studies. Analyses were also conducted examining the effect of food in relationship to efficacy and safety parameters in the 12-week phase 3 studies in patients with OAB conducted in Europe, Australia and North America.

3.2.8.1 Effect of Food on Mirabegron Pharmacokinetics

Study 178-CL-041, conducted in the US, and Study 178-CL-078, conducted in Japan, were conducted in healthy male and female volunteers. Studies 178-CL-041 and 178-CL-078 had the same study design and included evaluations of high fat and low fat meals compared with fasting conditions. The nutritional content of the high fat meals was consistent with the requirements set out in the US and EU guidances (EMA Guideline on the Investigation of Bioequivalence, 2010; Food-Effect Bioavailability and Fed Bioequivalence Studies, Guidance for Industry, Food and Drug Administration, 2002) and was similar in Studies 178-CL-041 and 178-CL-078, although the specific components of the high fat meals differed in the US and Japan. The low fat meals were identical in both studies.

Together, these studies demonstrated that a food effect was observed with mirabegron OCAS and was dependent on meal composition (low versus high fat) [Table 14]. There were no apparent differences in the magnitude of the food effect between Western and Japanese healthy volunteers or between males and females. The magnitude of the food effect was independent of the doses of mirabegron tested (50 and 100 mg).

Table 14 Analysis of the Effect of Food on Mirabegron Pharmacokinetic Parameters: Mirabegron 50 mg, Studies 178-CL-041 and 178-CL-078

Parameter (unit)	n	Meal type/Fasted	Ratio of C_{max} (%) (90% CI)	Ratio of AUC_{inf} (%) (90% CI)
Overall: Mirabegron 50 mg				
Study 178-CL-041	36	With high fat meal	54.8 (43.7, 68.7)	83.2 (74.2, 93.4)
	36	With low fat meal	25.0 (19.9, 31.3)	48.7 (43.3, 54.7)
Study 178-CL-078	35	With high fat meal	47.4 (36.6, 61.5)	71.2 (63.4, 80.0)
	35	With low fat (normal) meal	34.2 (26.3, 44.3)	49.4 (44.0, 55.5)

The observed difference in the effect of a low fat meal versus a high fat meal on the pharmacokinetics of mirabegron most likely results from adsorption of mirabegron to food components. The results of an adsorption study indicated that mirabegron had a higher adsorption rate to contents of a low fat breakfast compared with a high fat breakfast. In addition, as is demonstrated for other BCS Class 3 drugs, absorption of mirabegron is likely rate limited by intestinal membrane permeation, indicating that intestinal influx and efflux transporters are important for absorption. The efflux and influx transporters can be saturated and meal constituents can compete for drug uptake and efflux.

3.2.8.2 Analysis by Food Intake Status in the Phase 3 Studies

In the primary EU/NA 12-week, double-blind, phase 3 studies conducted in patients with OAB (Studies 178-CL-046, 178-CL-047 and 178-CL-074), patients were instructed to take study medication in the morning with a glass of water, with or without food. The clinical impact of the food effect was therefore assessed in an exploratopry analysis evaluating different food statuses (fed, fasted or mixed) on efficacy and safety in the primary phase 3 studies.

Evaluation of the coprimary efficacy endpoints for the change from baseline to final visit in mean number of incontinence episodes and mean number of micturitions per 24 hours in the food status analyses indicates that there was no impact on efficacy when mirabegron 50 or 100 mg was taken with food (defined as medication intake within 30 minutes before or after food intake) or without food [See Section 4.5.3].

Overall safety findings for TEAE, vital signs, electrocardiograms (ECG) and PVR volume provide evidence that mirabegron is safe with or without food [See Section 5.7.2.4].

Similar plasma concentrations of mirabegron were observed in fed and fasted conditions for predose pharmacokinetic samples (approximately 20 to 30 hours after dose) and postdose pharmacokinetic samples (approximately 6 to 10 hours after dose) for the mirabegron 50 and 100 mg doses in Study 178-CL-046 and Study 178-CL-047 [Appendix 2, Figure 4 and Appendix 2, Figure 5].

3.3 Pharmacodynamics

3.3.1 Effect on Cardiovascular Parameters

Dose-dependent increases in heart rate were observed with mirabegron. Mirabegron showed variable effects on SBP/DBP.

The effect of mirabegron on cardiovascular parameters is further discussed in Section 5.6.1.

3.3.2 Effect on QT Intervals of the Electrocardiogram

A dedicated TQT study, Study 178-CL-077, showed that, according to ICH E14 (2005) criteria, mirabegron did not cause individually corrected QT interval (QTcI) prolongation at the proposed therapeutic dose of 50 mg or the supratherapeutic dose of 100 mg, a dose which increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6 fold relative to the proposed therapeutic dose of 50 mg. According to ICH E14 criteria, mirabegron prolonged the QTc interval in females at the

supratherapeutic dose of 200 mg, a dose which increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the proposed therapeutic dose of 50 mg.

Further discussion of the effect of mirabegron on pulse rate and QTc are presented in Section 5.6.1.6.

3.3.3 Effect on Intraocular Pressure

Data do not support an association between mirabegron and glaucoma. Mirabegron at a supratherapeutic dose of 100 mg did not increase intraocular pressure (IOP) in healthy subjects after 56 days of treatment in Study 178-CL-081. The effect of mirabegron on IOP is further discussed in Section 5.6.5.

3.4 Clinical Pharmacology Summary

- Mirabegron T_{max} was reached between 3 and 4.3 hours. Thereafter elimination was multiphasic with an effective half life of approximately 19 hours.
- The $t_{1/2}$ was independent of dose, route of administration and formulation, indicating no absorption-rate limitation in the pharmacokinetics of the OCAS tablet.
- A 2-fold increase in dose of mirabegron (from 50 mg to 100 mg) increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a supratherapeutic dose of mirabegron 200 mg increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the proposed therapeutic dose of 50 mg.
- Multiple intrinsic and extrinsic factors examined had less than a 2-fold effect on the mean pharmacokinetic parameters (C_{max} and AUC) of mirabegron, with the exception of patients with severe renal impairment and those with moderate hepatic impairment, for whom a dose adjustment is recommended.
- Mirabegron was not studied in volunteers with severe hepatic impairment nor in volunteers with end stage renal disease.
- Mirabegron is cleared by multiple mechanisms (renal and possibly biliary excretion of unchanged drug and metabolism) and drug-metabolizing enzymes, with no single predominant clearance pathway. When administered in the presence of a strong CYP3A4 and P-gp inhibitor (ketoconazole) there was a 45% increase in C_{max} and a 81% increase in AUC_{inf}.
- Mirabegron is a moderate CYP2D6 inhibitor and caution is advised if mirabegron is coadministered with drugs that have a narrow therapeutic index and are significantly metabolized by CYP2D6.
- For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

4 OVERVIEW OF EFFICACY

Primary evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from 3 randomized, placebo-controlled primary phase 3 studies (Studies 178-CL-046, 178-CL-047 and 178-CL-074) conducted primarily in Europe and North America. Phase 2b studies and phase 3 studies conducted in Japan are considered supportive for efficacy and have been included in summaries of safety.

These studies are adequate, well-controlled trials and provide substantial evidence to support the claim of effectiveness, as defined in the Code of Federal Regulations (CFR) 21 CFR§314.126 (US), and are consistent with the ICH Harmonized Tripartite Efficacy Guidelines, in particular E8, E9 and E10. The primary studies were also designed consistent with Committee for Proprietary Medicinal Products guidance (Note on Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence) and included measures of both absolute and relative effect on the patient perception of treatment effect.

Efficacy data from the primary phase 3 studies will be presented individually and pooled. In addition, efficacy data from the supportive studies will be presented individually. Evidence for the durability of effect comes from the long-term (1-year) Study 178-CL-049.

4.1 Description of the Clinical Program

The initial clinical development program examined an indication of type 2 diabetes mellitus and was discontinued due to the absence of efficacy demonstrated in this population (Studies 178-CL-003 and 178-CL-004).

As described in Section 2.3, beta 3-AR agonists have been proposed as bladder relaxant drugs and therapeutic drugs for treatment of OAB [Yamaguchi, 2002]. Mirabegron demonstrated statistically and clinically significant improvements in the symptoms of OAB relative to placebo in a proof-of-concept study (Study 178-CL-008).

The efficacy of mirabegron in the treatment of symptoms of OAB, including urinary frequency, urge urinary incontinence and urgency has been demonstrated across 6 global, 12-week phase 2b/3 studies [Table 4]. The primary phase 3 studies (Studies 178-CL-046, 178-CL-047 and 178-CL-074) evaluated doses of 25, 50 or 100 mg mirabegron orally once daily; two studies evaluated mirabegron 50 and 100 mg and the third study evaluated mirabegrion 25 and 50 mg. These doses were selected upon completion of a phase 2 program which examined 200 mg in addition to the above doses. Supportive efficacy data is demonstrated in two phase 2b dose-finding studies (Study 178-CL-044 and 178-CL-045) and one phase 3 study (Study 178-CL-048) across the dose range of 25 mg to 200 mg mirabegron once daily.

The design of the mirabegron primary phase 3 studies was consistent with designs utilized in the evaluation of compounds approved for the use in the treatment of OAB. A summary of study design across OAB trials included in the approval dossiers for mirabegron and other approved OAB drugs is presented in Table 15. The majority of studies were randomized, double-blind, placebo-controlled, parallel-group, fixed-dose studies with a treatment duration of 12 weeks. Most OAB drugs included at least one pivotal trial with an active comparator arm.

Table 15 Summary of Study Design for Trials Included in Approval Dossiers

	Study Number	Randomized, double blind	Placebo controlled	Active controlled	Study size	Duration of Treatment
Mirabegron	178-CL-046	●	●	Tolterodine	1987	12 weeks
	178-CL-047	●	●		1329	12 weeks
	178-CL-074	●	●		1306	12 weeks
Fesoterodine	SP-583	●	●	Tolterodine	1103	12 weeks
	SP-584	●	●		800	12 weeks
Solifenacin	905-CL-013	●	●		672	12 weeks
	905-CL-014	●	●		634	12 weeks
	905-CL-015	●	●	Tolterodine	1081	12 weeks
	905-CL-018	●	●		911	12 weeks
Trospium	IP631-003	●	●		523	12 weeks
	IP631-005	●	●		658	12 weeks
Trospium XR	IP631-018	●	●		601	12 weeks
	IP631-022	●	●		564	12 weeks
Darifenacin	1001	●	●	Tolterodine	680	12 weeks
	1002	●	●		439	12 weeks
	1041	●	●		561	12 weeks
Tolterodine	CTN 94-OATA-008	●	●		293	12 weeks
	CTN 94-OATA-009	●	●		316	12 weeks
	CTN 94-OATA-010	●	●		274	12 weeks
Tolterodine ER	98-TOCR-007	●	●		1529	12 weeks

ER: extended release; XR: extended release.
Source FDA Documents: Summary Review Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Statistical Review(s) Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Medical Review(s) Application Number 21-518 (VESIcare, Solifenacin Succinate) 2004, Medical Review Application Number 21-595 (Sanctura, Trospium Chloride). Medical Review(s) (Parts 1, 2 and 3) 2004, Medical Review Application Number 22-103 (Sanctura XR, Trospium Chloride) 2007, Medical and Statistical Review(s)Application Number 21-513 (Enablex, Darifenacin Hydrobromide) 2004, Medical Review(s) (Parts 1 and 2) Application Number 20-771 (Detrol, Tolterodine L-tartrate) 1998, Medical Review(s) (Parts 1 and 2) Application Number 21-228 (Detrol LA, Tolterodine) 2000.

4.1.1 Relevant Features of the Patient Population

Participants in the mirabegron development program for OAB are representative of the population that would receive the product after market approval.

The primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074) consisted of female and male adults with symptoms of OAB (urinary frequency and urgency with or without incontinence) for at least 3 months **with** frequency of micturition 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 preceding the baseline visit.

Inclusion and exclusion criteria in the primary phase 3 studies allowed entry of patients who were antimuscarinic treatment naive and patients who had been previously treated with OAB antimuscarinic therapy. Male patients with a history of benign prostatic hyperplasia (BPH) were not excluded, provided that their BPH medications had been taken on a long-term basis at the same dose, the dose had not changed in the month prior to entry into the study, and no new drug of the same class had been added to the regimen in the month prior to the study.

The demographic characteristics of the patient populations included in OAB studies from regulatory filings and from the mirabegron development program are presented in Table 16. The demographic characteristics of OAB patients, including OAB patients with incontinence episodes, in the mirabegron program are fully concordant with other studies from development programs for approved OAB products.

Table 16 Demographic Characteristics of Patients Included in Clinical Trials

Drug	Study Number	Treatment	Mean Age (years)	Age Groups		Gender		Race	
				≥ 65 years (%)	≥ 75 years (%)	Male (%)	Female (%)	White (%)	Black (%)
Mirabegron	Pooled Primary Studies	Placebo	59.2	38.0	11.6	27.3	72.7	92.4	6.0
		Mirabegron 50 mg	59.7	37.7	11.3	28.9	71.1	93.3	4.6
		Mirabegron 100 mg	59.8	38.2	12.4	27.1	72.9	94.2	4.0
	Pooled Primary Studies - Incontinence Subset	Placebo	59.9	39.3	12.8	17.5	82.5	91.8	6.6
		Mirabegron 50 mg	60.7	41.2	12.9	19.5	80.5	93.3	4.8
		Mirabegron 100 mg	60.8	40.7	14.6	16.3	83.7	93.8	4.9
Fesoterodine	SP-583	Overall study population†	57	33	11	19	81	--	--
	SP-584	Overall study population†	59			24	76	--	--
Solifenacin	905-CL-013	Overall study population†	58	~33	11	18.3	81.7	82	--
	905-CL-014	Overall study population†	60	40	14	18.0	82.0	90	--
	905-CL-015	Overall study population†	58	--	--	24.9	75.1	98	--
	905-CL-018	Overall study population†	56	~30	7.4	18.0	82.0	>96	--
Trospium	IP631-003	Overall study population†	--	--	--	25	75	--	--
	IP631-005	Overall study population†	61	--	--	19	81	--	--
Trospium XR	IP631-018	Placebo	59.3	36.3	9.9	15.5	84.5	85.5	9.9
		Trospium XR	60.4	38.3	14.1	14.8	85.2	86.6	8.7
	IP631-022	Placebo	54.4	32.4	9.9	12.3	87.7	82.4	9.9
		Trospium XR	61.2	40.0	15.4	17.9	82.1	87.5	6.4
Darifenacin	1001	Placebo	59	Placebo: 28 D7.5 mg: 29 D15 mg: 33	--	21	79	93	--
		Darifenacin 15 mg	60			10	90	88	--
	1002	Placebo	54			17	83	100	0
		Darifenacin 7.5 mg	56			13	87	100	0
		Darifenacin 15 mg	55			14	86	99	--
	1041	Placebo	57			16	84	95	--
		Darifenacin 7.5 mg	58			15	85	94	--
		Darifenacin 15 mg	57			13	87	96	--
Tolterodine	CTN 94-OATA-008	Placebo	58.2	--	--	24.6	75.4	98.2	--
		Tolterodine 2 mg	55.3	--	--	22.9	77.1	99.2	--
		Oxybutynin	57.6	--	--	25.4	74.6	99.2	--
	CTN 94-OATA-009	Placebo	60.5	--	--	34.4	65.6	92.2	--
		Tolterodine 1 mg	60.1	--	--	22.0	78.0	95.1	--
		Tolterodine 2 mg	60.2	--	--	23.3	76.7	97.7	--
Tolterodine	CTN 94-OATA-010	Placebo	62.1	--	--	19.6	80.4	92.9	--
		Tolterodine 1 mg	63.0	--	--	19.3	80.7	87.2	--
		Oxybutynin	66.3	--	--	27.7	72.3	93.8	--
Tolterodine ER	98-TOCR-007	Overall study population†	60	--	--	19	81	95	3.6
Oxybutynin XL	C-95-031	Placebo	56.8	--	--	0	100‡	~90	~5
		Oxybutynin XL	59.6	--	--	0	100‡		
		Oxybutynin IR	56.0	--	--	0	100‡		
	C-95-049-05	Oxybutynin XL	59.2	--	--	8	92	75	13
		Oxybutynin IR	59.6	--	--			90	4

--: not applicable or no data provided; ~: approximately; ER: extended release; IR: immediate release; XL: extended release; XR: extended release.

Footnotes continued on next page.

†For treatment noted as 'overall study population', available results in the FDA reviews did not include demographic information by treatment group, but only for the overall study population.
‡ Study C-95-031 for oxybutynin XL was conducted only in women.
Source FDA Documents: Medical Review(s) Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Medical Review(s) Application Number 21-518 (VESIcare, Solifenacin Succinate) 2004, Medical Review Application Number 21-595 (Sanctura, Trospium Chloride). Medical Review(s) (Parts 1, 2 and 3) 2004, Medical Review Application Number 22-103 (Sanctura XR, Trospium Chloride) 2007, Medical Review(s) Application Number 21-513 (Enablex, Darifenacin Hydrobromide) 2004, Statistical Review(s) (Parts 1 and 2) Application Number 20-771 (Detrol, Tolterodine L-tartrate) 1998, Medical Review(s) (Parts 1 and 2) Application Number 21-228 (Detrol LA, Tolterodine) 2000 and Medical Review(s) Application Number 20-897 (Ditropan XL, Oxybutynin Chloride) 1998. EMA Documents: European Public Assessment Report (EPAR), Toviaz, October 2007.

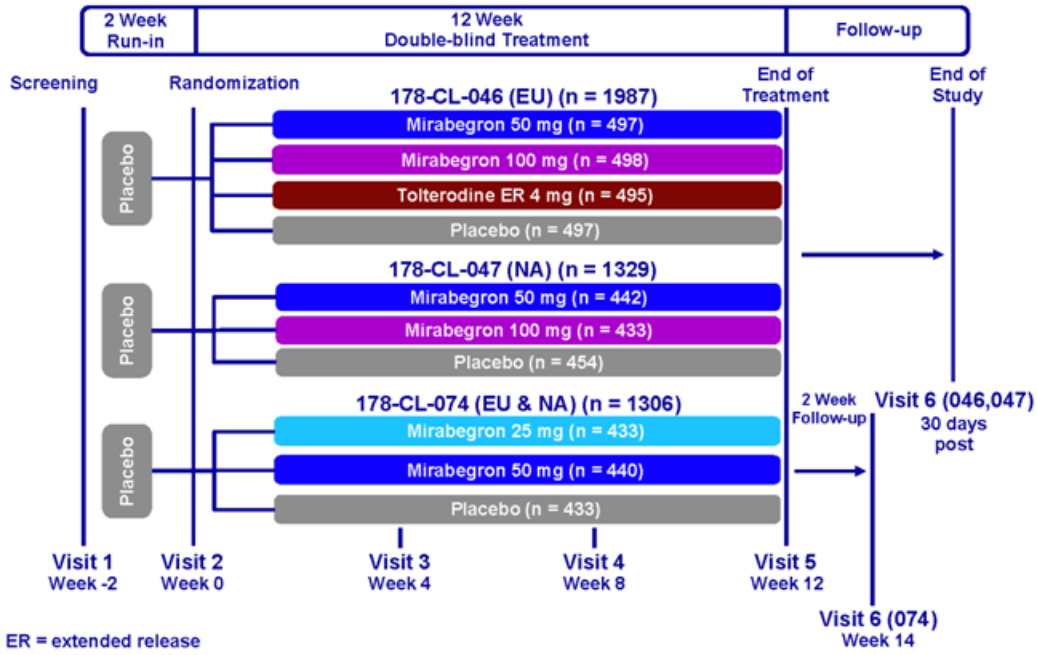
4.1.2 Study Design

The primary phase 3 studies, as well as the supportive studies, had the following design features in common [Figure 10]:

- Patients participated in a 2-week single-blind placebo run-in period followed by a 12-week double-blind, placebo-controlled treatment period.
- Patients completed a 3-day micturition diary during the 3 days prior to each study visit.
- Eligible patients were female and male adults who had symptoms of OAB (urinary frequency and urgency with or without incontinence) based on the following criteria:
  - experienced symptoms of OAB for at least 3 months (Study 178-CL-044, 178-CL-046, 178-CL-047 and 178-CL-074) or for at least 24 weeks (Study 178-CL-045 and 178-CL-048), AND
  - experienced frequency of micturition on average ≥ 8 times per 24-hour period during the 3-day micturition diary period collected during the run-in period, AND
  - experienced at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period (Study 178-CL-044, 178-CL-046, 178-CL-047 and 178-CL-074) or at least one episode of urgency per 24 hours and/or at least one urge incontinence episode per 24 hours on average during the 3-day micturition diary period (Study178-CL-045 and 178-CL-048).
- Study 178-CL-046 also included an active control, tolterodine ER 4 mg. The design allowed tolterodine to serve as informative reference for the safety, tolerability and efficacy of mirabegron . No statistical comparisons were made between mirabegron and tolterodine.

Study 178-CL-049 had a 2-week single-blind placebo run-in period and a 12-month, double-blind, tolterodine-controlled treatment period with patients randomized to tolterodine ER 4 mg, mirabegron 50 mg or mirabegron 100 mg. Patients in primary phase 3 Studies 178-CL-046 and 178-CL-047 who had completed all visits in those studies were allowed to enroll in the long-term safety study. In addition, patients who had not participated in any previous mirabegron study were allowed to enroll in Study 178-CL-049.

Figure 10 Phase 3 Study Design of the OAB Clinical Studies (12-Week)



4.1.3 Study Drug Administration

Mirabegron tablets were provided in the dose strengths of 25 mg, 50 mg and 100 mg. The dose of mirabegron examined in the primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074) and 3 supportive phase 2b (Study 178-CL-044 and 178-CL-045) and 3 (Study 178-CL-048) studies and supportive EU/NA Long-term Controlled Population is shown in Table 5.

4.2 Efficacy Data Analysis

The primary objective of the primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074) was to assess the efficacy of mirabegron (25, 50 or 100 mg) versus placebo in the treatment of patients with symptoms of OAB.

The primary objective for the 2 supportive phase 2b studies (Studies 178-CL-044 and 178-CL-045) was to assess the dose-response relationship of mirabegron on efficacy in patients with OAB; and to compare the efficacy of mirabegron versus placebo and to assess the dose-response relationship of mirabegron 25, 50, 100 and 200 mg and placebo for 12 weeks in patients with OAB based on change in mean number of micturitions per 24 hours.

For the supportive phase 3 study (Study 178-CL-048), the primary objective was to assess the efficacy of mirabegron 50 mg versus placebo in the treatment of patients with symptoms of OAB based on mean number of micturitions per 24 hours and to assess the safety and pharmacokinetics of mirabegron 50 mg.

The primary objective of Study 178-CL-049 was to assess the safety and tolerability of long-term treatment with mirabegron 50 and 100 mg in patients with symptoms of OAB. The secondary objectives of the study were to assess the efficacy of long-term treatment with mirabegron 50 and 100 mg in patients with symptoms of OAB.

4.2.1 Endpoints

The coprimary efficacy endpoints in the primary phase 3 studies were:

- change from baseline to final visit in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary; and
- change from baseline to final visit in mean number of micturitions per 24 hours based on a 3-day micturition diary.

The key secondary efficacy endpoints in these studies included:

- change from baseline to final visit in mean volume voided per micturition;
- change from baseline to week 4 in mean number of incontinence episodes per 24 hours; and
- change from baseline to week 4 in mean number of micturitions per 24 hours.

Study 178-CL-074 had 3 additional key secondary efficacy endpoints: 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. Studies 178-CL-046 and 178-CL-047 contained the same secondary endpoints; however, they were considered additional secondary endpoints and were not included in the hierarchical testing procedure for multiple endpoints. Urgency endpoints were based upon the 5-point Patient Perception of Intensity of Urgency Scale (PPIUS where 0 = No urgency, I felt no need to empty my bladder, but did so for other reasons; 1 = Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself; 2 = Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself; 3 = Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself; 4 = Urgency Incontinence, I leaked before arriving to the toilet).

Subjective endpoints were also captured via various QoL tools/questionnaires (TS-VAS, HRQL scores as assessed by the OAB-q and PPBC).

4.2.2 Relevant Statistical Considerations

All analyses were prespecified prior to database lock unless noted as a posthoc analysis. Integrated analyses were prespecified prior to database lock of the first primary phase 3 study.

Analysis Sets

The Full Analysis Set (FAS) included all randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement. The Full Analysis Set Incontinence (FAS-I) was the subset of study patients who met all requirements of the FAS but who also had at least one incontinence episode recorded in the baseline 3-day micturition diary.

Overall, patients in the FAS-I population represented 61.1%, 73.5%, 61.8% and 60.9% of patients in the FAS population in Studies 178-CL-046, 178-CL-047, 178-CL-074 and 178-CL-049, respectively. The FAS-I was used to analyze incontinence-related endpoints in these studies (mean number of incontinence episodes per 24 hours, mean number of urgency incontinence episodes per 24 hours, responders for zero incontinence episodes and responders for 50% reduction in incontinence episodes).

In Studies 178-CL-048, 178-CL-044 and 178-CL-045, the FAS-I was not defined as a separate population; however, analyses of incontinence-related endpoints included only the subset of the FAS that had at least one incontinence episode recorded in the baseline 3-day micturition diary.

Sensitivity analyses for the primary phase 3 studies were performed on the following:

- Per protocol set (PPS), defined as FAS patients who did not commit any of a prespecified list of major protocol violations,
- PPS-incontinence, defined as all PPS patients who had at least one incontinence episode at baseline,

- The Intent-to-Treat (ITT) analysis set, defined as all randomized patients who took at least one dose of double-blind study drug and who had a baseline diary with micturition measurements and
- The ITT-Incontinence analysis set, defined as all randomized patients who took at least one dose of double-blind study drug and who had micturition measurements and at least one incontinence episode in the baseline diary.

Coprimary and Key Secondary endpoints

In the primary phase 3 studies, a stepwise parallel gate keeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary and key secondary efficacy endpoints. The order in which the coprimary and key secondary endpoints were analyzed is the same as the order of presentation of these variables in Table 17. Since 2 mirabegron treatment groups (50 and 100 mg for 178-CL-046 and 178-CL-047; 25 and 50 mg for 178-CL-074) were compared with placebo, the Hochberg procedure was used to adjust for multiplicity within each stage.

Drop-outs for continuous data were handled using both repeated measures (for mean number of incontinence episodes per 24 hours, mean number of micturitions per 24 hours and mean volume voided per micturition) and last observation carried forward methodologies.

Analysis of Patient Subpopulations

Comparisons of subgroups were made for the coprimary efficacy variables listed in Section 4.2.1; change from baseline to final visit in mean number of micturitions per 24 hours; change from baseline to final visit in mean number of incontinence episodes per 24 hours.

Subpopulations analyzed included demographics, characteristics of OAB, intrinsic/extrinsic factors and food status.

4.3 Efficacy of Mirabegron in the Treatment of Patients with OAB

4.3.1 Relevant Features of the Patient Population

4.3.1.1 Primary Phase 3 Studies

Across the primary phase 3 studies, patients (FAS) were predominantly female (approximately 68.5% - 74.8%) and White (approximately 88.2% - 99.2%) with a mean age of 59.1 to 60.2 years of age (range 18 - 95 years of age). Approximately 37.0% to 39.7% of patients were ≥ 65 years of age and approximately 8.5% to 15.1% of patients were ≥ 75 years of age across all 3 studies.

At baseline, across all 3 studies, patients had a mean range of 2.53 to 2.84 incontinence episodes per 24 hours (FAS-I) and mean range of 11.60 to 11.65 micturitions per 24 hours (FAS). All 3 types of OAB were represented, including urgency incontinence only (ranging from 29.7% - 39.7%), mixed stress/urgency incontinence with urge as predominant factor (ranging from 22.6% - 38.3%) and frequency/urgency without incontinence (ranging from 32.0% - 37.7%) (FAS). Mean duration of OAB symptoms across all 3 studies in the FAS, ranged from 79.3 to 94.1 months. The proportion of FAS patients with prior surgery for OAB was relatively consistent across treatment groups, ranging from 5.2% to 11.7%. Approximately 49.6% to 56.2% of patients received prior antimuscarinic OAB medications; of these patients, 65.0% to 67.4% of patients discontinued prior antimuscarinic OAB medication due to lack of effect and 22.1% to 26.7% of patients discontinued due to poor tolerability.

The baseline OAB characteristics of the patient populations included in OAB studies from regulatory filings and from the mirabegron development program are presented in Appendix 1, Table 4. The characteristics of OAB patients, including those with incontinence episodes, in the mirabegron program are fully concordant with other OAB drug programs.

4.3.1.2 Supportive Studies

Patients in the FAS population in the supportive studies were predominantly female (82.2% in Study 178-CL-045, 83.7% in Study 178-CL-048 and 89.3% in Study 178-CL-044). The mean age of patients in the FAS population was 55.9 years of age in Study 178-CL-045, 57.2 years of age in Study 178-CL-044 and 58.3 years of age in Study 178-CL-048. The distribution of patients in the age group ≥ 65 years of age was 37.5% and 31.9% in studies 178-CL-048 and 178-CL-045, respectively, and the distribution of patients in the age group of > 65 years of age in Study 178-CL-044 was 27.4%.

All patients in the FAS populations in studies 178-CL-048 and 178-CL-045 were Asian; 98.2% of patients in Study 178-CL-044 were White.

4.3.2 Efficacy Results – Primary Phase 3 Studies

For the primary phase 3 studies (Studies 178-CL-046, 178-CL-047 and 178-CL-074) efficacy results of the coprimary and secondary endpoints are presented in Table 17.

4.3.2.1 Change from Baseline to Final Visit in Incontinence Episodes per 24 hours

Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of incontinence episodes per 24 hours compared with placebo [Table 17 and Figure 11].

The treatment-by-study interaction P value was 0.60 for change from baseline to final visit in mean number of incontinence episodes per 24 hours, indicating there was no meaningful difference among the primary phase 3 studies with respect to treatment effects for mirabegron 50 or 100 mg.

A tolterodine arm was evaluated in one primary study in order to place the efficacy of mirabegron in context versus a current commonly administered therapy for OAB. Tolterodine in this study did not show a statistically significant reduction from baseline to final visit compared with placebo in mean number of incontinence episodes per 24 hours, although it did show a statistically significant reduction at week 4, a secondary efficacy endpoint.

In the repeated measurement analysis of the mean number of incontinence episodes per 24 hours, the adjusted mean difference versus placebo and 95% CIs for both the mirabegron 50 and 100 mg groups at week 12 were similar to those at the final visit in the primary analysis for Studies 178-CL-046, 178-CL-047 and 178-CL-074 [Appendix 2, Figure 6].

Both mirabegron 50 and 100 mg demonstrated statistically significantly superior mean reduction of incontinence episodes compared with the placebo group as early as week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

While no study required incontinence at baseline, inclusion in the FAS-I required at least one episode of incontinence in the 3-day baseline micturition diary.

Two responder analyses were performed on incontinence episodes, a zero responder analysis (requiring a patient to have zero incontinence episodes per 24 hours at final visit based on the 3-day micturition diary) and a 50% reduction analysis (requiring a patient to have a ≥ 50% decrease from baseline to final visit in mean number of incontinence episodes per 24 hours).

Statistical and clinical significance was achieved for both treatment groups for responders at final visit in mean number of incontinence episodes per 24 hours [Table 18].

Table 17 Overview of Co-Primary and Key Secondary Efficacy Results, Primary Phase 3 Studies

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolt ER 4 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Co-Primary Efficacy Results										
Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours (FAS-I)										
Adjusted Change from Baseline†										
n	291	293	281	300	325	312	296	262	254	257
Mean Baseline (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)	3.03 (0.171)	2.77 (0.150)	2.69 (0.142)	2.43 (0.145)	2.65 (0.160)	2.51 (0.146)
Mean (SE)	-1.17 (0.113)	-1.57 (0.113)	-1.46 (0.115)	-1.27 (0.112)	-1.13 (0.112)	-1.47 (0.114)	-1.63 (0.117)	-0.96 (0.122)	-1.36 (0.124)	-1.38 (0.123)
95% 2-sided CI	(-1.39, -0.95)	(-1.79, -1.35)	(-1.68, -1.23)	(-1.49, -1.05)	(-1.35, -0.91)	(-1.69, -1.25)	(-1.86, -1.40)	(-1.19, -0.72)	(-1.60, -1.11)	(-1.62, -1.14)
Adjusted Difference vs Placebo†										
Mean (SE)		-0.41 (0.160)	-0.29 (0.162)	-0.10 (0.159)		-0.34 (0.160)	-0.50 (0.162)		-0.40 (0.174)	-0.42 (0.173)
95% 2-sided CI	--	(-0.72, -0.09)	(-0.61, 0.03)	(-0.42, 0.21)	--	(-0.66, -0.03)	(-0.82, -0.18)	--	(-0.74, -0.06)	(-0.76, -0.08)
P value‡	--	0.003#	0.010#	0.11	--	0.026#	< 0.001#	--	0.005#	0.001#
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours (FAS)										
Adjusted Change from Baseline†										
n	480	473	478	475	433	425	412	415	410	426
Mean Baseline (SE)	11.71 (0.143)	11.65 (0.137)	11.51 (0.124)	11.55 (0.128)	11.51 (0.157)	11.80 (0.168)	11.66 (0.167)	11.48 (0.142)	11.68 (0.153)	11.66 (0.156)
Mean (SE)	-1.34 (0.110)	-1.93 (0.111)	-1.77 (0.110)	-1.59 (0.111)	-1.05 (0.132)	-1.66 (0.133)	-1.75 (0.135)	-1.18 (0.124)	-1.65 (0.125)	-1.60 (0.122)
95% 2-sided CI	(-1.55, -1.12)	(-2.15, -1.72)	(-1.99, -1.56)	(-1.80, -1.37)	(-1.31, -0.79)	(-1.92, -1.40)	(-2.01, -1.48)	(-1.42, -0.94)	(-1.90, -1.41)	(-1.84, -1.36)
Adjusted Difference vs Placebo†										
Mean (SE)	--	-0.60 (0.156)	-0.44 (0.156)	-0.25 (0.156)	--	-0.61 (0.188)	-0.70 (0.189)	--	-0.47 (0.176)	-0.42 (0.174)
95% 2-sided CI		(-0.90, -0.29)	(-0.74, -0.13)	(-0.55, 0.06)		(-0.98, -0.24)	(-1.07, -0.33)		(-0.82, -0.13)	(-0.76, -0.08)
P value§	--	< 0.001#	0.005#	0.11	--	0.001#	< 0.001#	--	0.007#	0.015#
Key Secondary Efficacy Results										
Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition (FAS)										
Adjusted Change from Baseline†										
n	480	472	478	475	433	424	412	415	410	426
Mean Baseline (SE)	156.7 (2.40)	161.1 (2.69)	158.2 (2.43)	158.6 (2.48)	157.5 (2.82)	156.3 (2.84)	157.6 (2.97)	164.0 (2.79)	165.2 (2.84)	159.3 (2.53)
Mean (SE)	12.3 (1.99)	24.2 (2.01)	25.6 (2.00)	25.0 (2.00)	7.0 (2.41)	18.2 (2.44)	18.0 (2.47)	8.3 (2.23)	12.8 (2.24)	20.7 (2.20)
95% 2-sided CI	(8.4, 16.3)	(20.3, 28.2)	(21.6, 29.5)	(21.1, 28.9)	(2.3, 11.7)	(13.4, 22.9)	(13.1, 22.8)	(3.9, 12.7)	(8.4, 17.2)	(16.4, 25.0)
Adjusted Difference vs Placebo†										
Mean (SE)		11.9 (2.83)	13.2 (2.82)	12.6 (2.83)		11.1 (3.43)	11.0 (3.45)	--	4.6 (3.16)	12.4 (3.13)
95% 2-sided CI	--	(6.3, 17.4)	(7.7, 18.7)	(7.1, 18.2)	--	(4.4, 17.9)	(4.2, 17.7)		(-1.6, 10.8)	(6.3, 18.6)
P value§	--	< 0.001#	< 0.001#	< 0.001*	--	0.001#	0.002#	--	0.15¶	< 0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours (FAS-I)										
Adjusted Change from Baseline†										
n	291	293	281	299	325	309	293	262	254	255
Mean Baseline (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.64 (0.148)	3.03 (0.171)	2.76 (0.149)	2.69 (0.143)	2.43 (0.145)	2.65 (0.160)	2.52 (0.147)
Mean (SE)	-0.65 (0.118)	-1.04 (0.118)	-1.03 (0.120)	-1.00 (0.117)	-0.72 (0.116)	-1.20 (0.119)	-1.18 (0.122)	-0.62 (0.120)	-0.96 (0.122)	-1.13 (0.122)
95% 2-sided CI	(-0.88, -0.42)	(-1.27, -0.81)	(-1.27, -0.79)	(-1.23, -0.77)	(-0.95, -0.50)	(-1.43, -0.97)	(-1.42, -0.94)	(-0.85, -0.38)	(-1.20, -0.72)	(-1.36, -0.89)
Adjusted Difference vs Placebo†										
Mean (SE)		-0.39 (0.167)	-0.38 (0.169)	-0.35 (0.166)		-0.48 (0.166)	-0.46 (0.168)		-0.34 (0.172)	-0.51 (0.171)
95% 2-sided CI	--	(-0.71, -0.06)	(-0.71, -0.05)	(-0.68, -0.03)	--	(-0.80, -0.15)	(-0.79, -0.13)	--	(-0.68, -0.01)	(-0.85, -0.17)

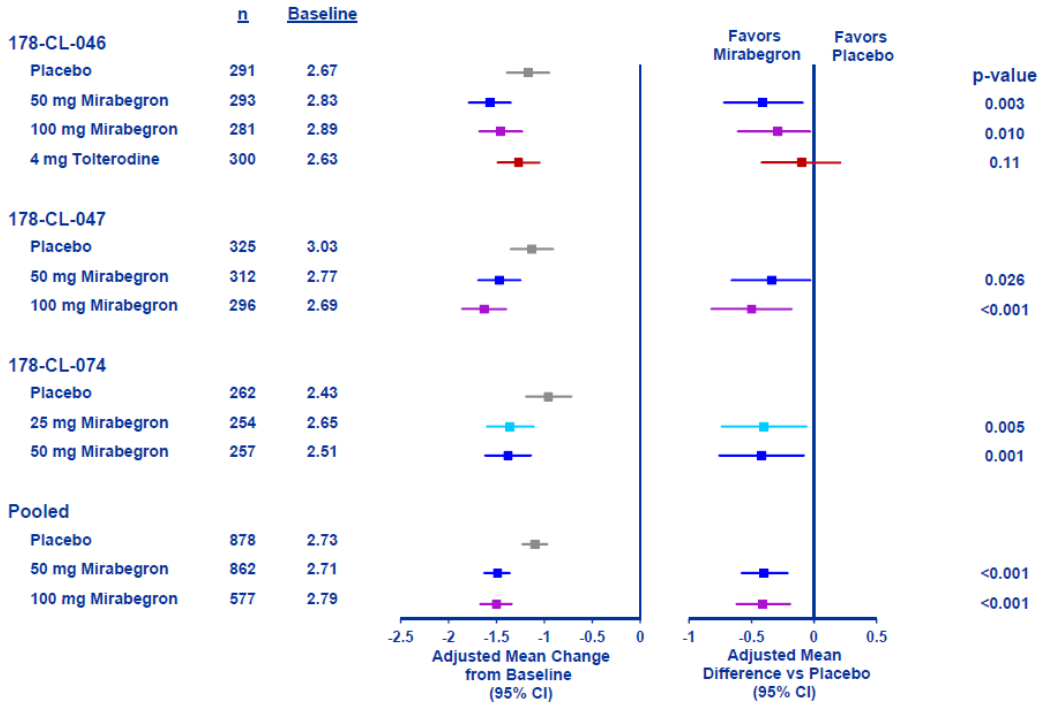
Table continued on next page.

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo	**Mirabegron 50 mg**	**Mirabegron 100 mg**	**Tolt ER 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Mirabegron 100 mg**	**Placebo**	**Mirabegron 25 mg**	**Mirabegron 50 mg**
P value‡	--	0.002#	0.002#	0.019*	--	0.003#	< 0.001#	--	0.039¶	< 0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours (FAS)										
Adjusted Change from Baseline†										
n	479	471	477	474	433	422	409	415	410	424
Mean Baseline (SE)	11.72 (0.143)	11.64 (0.137)	11.51 (0.124)	11.55 (0.128)	11.51 (0.157)	11.81 (0.169)	11.65 (0.168)	11.48 (0.142)	11.68 (0.153)	11.67 (0.157)
Mean (SE)	-0.77 (0.096)	-1.16 (0.097)	-1.29 (0.096)	-1.10 (0.096)	-0.77 (0.127)	-1.19 (0.129)	-1.37 (0.131)	-0.78 (0.124)	-0.96 (0.124)	-1.14 (0.122)
95% 2-sided CI	(-0.96, -0.58)	(-1.35, -0.97)	(-1.48, -1.10)	(-1.29, -0.91)	(-1.02, -0.52)	(-1.44, -0.93)	(-1.62, -1.11)	(-1.02, -0.53)	(-1.20, -0.71)	(-1.38, -0.90)
Adjusted Difference vs Placebo†										
Mean (SE)	--	-0.40 (0.136)	-0.52 (0.136)	-0.33 (0.136)	--	-0.42 (0.182)	-0.60 (0.183)	--	-0.18 (0.176)	-0.37 (0.174)
95% 2-sided CI		(-0.66, -0.13)	(-0.79, -0.26)	(-0.60, -0.06)		(-0.77, -0.06)	(-0.96, -0.24)		(-0.53, 0.16)	(-0.71, -0.03)
P value§	--	0.004#	< 0.001#	0.016*	--	0.022#	0.001#	--	0.30¶	0.035¶
Key Secondary Efficacy Results (Study 178-CL-074) and Pooled Primary Studies; Additional Secondary Efficacy Results Studies (178-CL-046, 178-CL-047)										
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)										
Adjusted Change from Baseline†										
n	480	472	475	473	432	425	411	413	410	426
Mean Baseline (SE)	2.37 (0.026)	2.40 (0.025)	2.45 (0.024)	2.41 (0.026)	2.45 (0.026)	2.45 (0.026)	2.46 (0.027)	2.36 (0.027)	2.37 (0.028)	2.41 (0.027)
Mean (SE)	-0.22 (0.028)	-0.31 (0.028)	-0.30 (0.028)	-0.29 (0.028)	-0.08 (0.026)	-0.19 (0.026)	-0.21 (0.027)	-0.15 (0.028)	-0.22 (0.029)	-0.29 (0.028)
95% 2-sided CI	(-0.28, -0.17)	(-0.37, -0.26)	(-0.36, -0.25)	(-0.34, -0.23)	(-0.13, -0.03)	(-0.24, -0.13)	(-0.26, -0.15)	(-0.21, -0.10)	(-0.28, -0.17)	(-0.35, -0.24)
Adjusted Difference vs Placebo†										
Mean (SE)	--	-0.09 (0.040)	-0.08 (0.040)	-0.07 (0.040)	--	-0.11 (0.037)	-0.13 (0.037)	--	-0.07 (0.040)	-0.14 (0.040)
95% 2-sided CI		(-0.17, -0.02)	(-0.16, -0.01)	(-0.15, 0.01)		(-0.18, -0.04)	(-0.20, -0.05)		(-0.15, 0.01)	(-0.22, -0.06)
P value§	--	0.018*	0.037*	0.085	--	0.004*	< 0.001*	--	0.083¶	< 0.001¶
Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 hours (FAS-I)										
Adjusted Change from Baseline†										
n	283	286	276	289	319	297	291	256	247	251
Mean Baseline (SE)	2.43 (0.129)	2.52 (0.154)	2.65 (0.138)	2.37 (0.134)	2.56 (0.138)	2.42 (0.137)	2.42 (0.130)	2.24 (0.138)	2.45 (0.137)	2.33 (0.140)
Mean (SE)	-1.11 (0.110)	-1.46 (0.109)	-1.33 (0.111)	-1.18 (0.109)	-0.89 (0.100)	-1.32 (0.104)	-1.45 (0.105)	-0.95 (0.110)	-1.31 (0.112)	-1.33 (0.111)
95% 2-sided CI	(-1.32, -0.89)	(-1.67, -1.24)	(-1.55, -1.11)	(-1.40, -0.97)	(-1.08, -0.69)	(-1.52, -1.12)	(-1.66, -1.24)	(-1.16, -0.73)	(-1.53, -1.09)	(-1.55, -1.12)
Adjusted Difference vs Placebo†										
Mean (SE)	--	-0.35 (0.155)	-0.22 (0.156)	-0.07 (0.154)	--	-0.43 (0.145)	-0.56 (0.145)	--	-0.36 (0.157)	-0.39 (0.156)
95% 2-sided CI		(-0.65, -0.05)	(-0.53, 0.09)	(-0.38, 0.23)		(-0.72, -0.15)	(-0.85, -0.28)		(-0.67, -0.05)	(-0.69, -0.08)
P value‡	--	0.003*	0.024*	0.26	--	0.005*	< 0.001*	--	0.004¶	0.002¶
Change from Baseline to Final Visit in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 hours (FAS)										
Adjusted Change from Baseline†										
n	479	470	474	472	432	424	411	413	410	426
Mean Baseline (SE)	5.78 (0.182)	5.72 (0.168)	5.97 (0.170)	5.79 (0.158)	5.61 (0.156)	5.90 (0.186)	5.96 (0.178)	5.42 (0.163)	5.57 (0.179)	5.80 (0.173)
Mean (SE)	-1.65 (0.151)	-2.25 (0.152)	-1.96 (0.151)	-2.07 (0.152)	-0.82 (0.161)	-1.57 (0.162)	-1.76 (0.165)	-1.35 (0.154)	-1.68 (0.155)	-1.94 (0.152)
95% 2-sided CI	(-1.94, -1.35)	(-2.55, -1.95)	(-2.26, -1.67)	(-2.37, -1.77)	(-1.13, -0.50)	(-1.89, -1.25)	(-2.09, 1.44)	(-1.66, -1.05)	(-1.99, -1.38)	(-2.24, -1.64)
Adjusted Difference vs Placebo†										
Mean (SE)	--	-0.60 (0.214)	-0.31 (0.214)	-0.42 (0.214)	--	-0.75 (0.228)	-0.94 (0.230)	--	-0.33 (0.219)	-0.59 (0.217)
95% 2-sided CI		(-1.02, -0.18)	(-0.73, 0.11)	(-0.84, -0.00)		(-1.20, -0.30)	(-1.40, -0.49)		(-0.76, 0.10)	(-1.01, -0.16)
P value§	--	0.005*	0.14	0.050*	--	0.001*	< 0.001*	--	0.13¶	0.007¶

Footnotes continued on next page.

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).
Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups.
ANCOVA: analysis of covariance; ER: extended release.
†Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate.
‡ Nominal P values are from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis.
§ Nominal P-values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis.
# Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
¶ Study 178-CL-074 only: Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided per micturition (P = 0.15), subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Mean volume voided per micturition and subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level. Since the mirabegron 50 mg group did not meet statistical significance with multiplicity adjustment for change from baseline to week 4 in mean number of micturitions per 24 hours (P = 0.035), subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure.

Figure 11 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours, Primary Phase 3 Studies, FAS-I



Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline and the adjusted mean difference vs placebo. Individual study results are taken from the primary analysis of the respective study from an ANCOVA with treatment group, gender and geographical region as fixed factors and baseline value as a covariate. Pooled analysis results are from the primary analysis of the pooled data set and are from an ANCOVA with treatment group, gender and study as factors and baseline value as a covariate.
ANVOCA: analysis of covariance; ER: extended release; OAB: overactive bladder.

Table 18 Responders Analysis Based on Incontinence Episodes, Primary Phase 3 Studies, FAS-I

	Placebo (n = 878)	Mirabegron 50 mg (n = 862)	Mirabegron 100 mg (n = 577)
Responders for Zero Incontinence Episodes at Final Visit †			
Responders (n [%])	332 (37.8%)	380 (44.1%)	268 (46.4%)
Difference vs Placebo (%)		6.3%	8.6%
95% 2-sided CI for Difference‡		(1.7%, 10.9%)	(3.5%, 13.8%)
Odds Ratio§		1.32	1.58
95% 2-sided CI for Odds Ratio	--	(1.08, 1.61)	(1.25, 2.00)
P value		0.008*	< 0.001*
Responders for ≥ 50% Reduction from Baseline to Final Visit in Incontinence Episodes ¶			
Responders (n [%])	523 (59.6%)	599 (69.5%)	407 (70.5%)
Difference vs Placebo (%)		9.9%	11.0%
95% 2-sided CI for Difference‡		(5.5%, 14.4%)	(6.0%, 15.9%)
Odds Ratio§		1.54	1.64
95% 2-sided CI for Odds Ratio	--	(1.26, 1.89)	(1.29, 2.07)
P value		< 0.001*	< 0.001*

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).
--: not applicable; ER: extended release; OAB: overactive bladder.
† A responder was defined as a patient with zero incontinence episodes at final visit.
‡ 95% CIs for the difference of the proportions were based on normal approximation.
§ Odds ratios of mirabegron over placebo, corresponding 95% CIs and P values were derived from a logistic regression model including treatment group, gender, study and baseline measurement.
¶ A responder was defined as a patient with a ≥ 50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment

4.3.2.2 Change from Baseline to Final Visit in Micturitions per 24 hours

Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of micturitions per 24 hours compared with placebo [Table 17 and Figure 12].

The treatment-by-study interaction P value was 0.51 for change from baseline to final visit in mean number of micturitions per 24 hours, indicating there was no difference among the primary phase 3 studies with respect to treatment effects for mirabegron 50 or 100 mg.

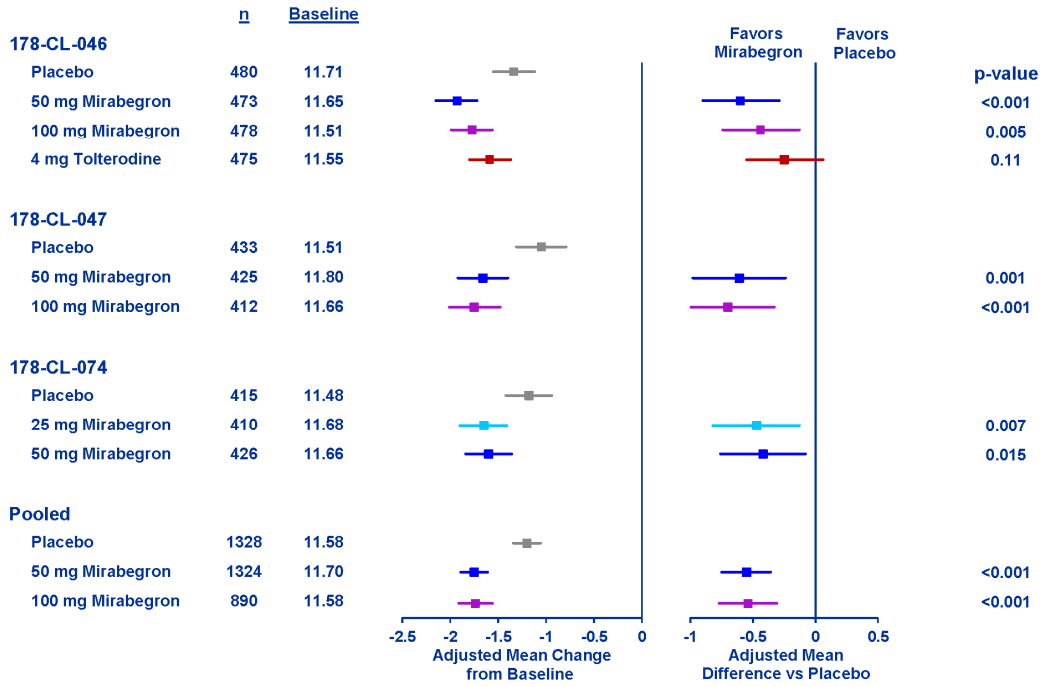
Tolterodine in Study 178-CL-046 did not show a statistically significant reduction compared with placebo in mean number of micturitions per 24 hours, although it did show a statistically significant reduction at week 4, a secondary efficacy endpoint [Table 17].

In the repeated measurement analysis of the mean number of micturitions per 24 hours, the adjusted mean difference vs placebo and 95% CIs for both the mirabegron 50 and 100 mg groups at week 12 were similar to those at the final visit in the primary analysis for Studies 178-CL-046, 178-CL-047 and 178-CL-074 [Appendix 2, Figure 7].

Both mirabegron 50 and 100 mg demonstrated statistically significantly superior mean reduction in micturitions per 24 hours compared with the placebo group as early as week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

A post-hoc responder analysis was assessed; a responder was required to have ≤ 8 micturitions per 24 hours at final visit based on the 3-day micturition diary. Statistical significance was achieved for both treatment groups for responders with ≤ 8 micturitions per 24 hours at final visit [Table 19].

Figure 12 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, Primary Phase 3 Studies, FAS



Pooled Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline and adjusted mean difference vs placebo.
Individual study results are taken from the primary analysis of the respective study from an ANCOVA with treatment group, gender and geographical region as fixed factors and baseline value as a covariate. Pooled analysis results are from the primary analysis of the pooled data set and are from an ANCOVA with treatment group, gender and study as factors and baseline value as a covariate.
ANCOVA: analysis of covariance; ER: extended release; OAB: overactive bladder.

Table 19 Responders for 8 or Fewer Micturitions per 24 Hours at Final Visit, Pooled Primary Phase 3 Studies, FAS

	Placebo (n = 1328)	Mirabegron 50 mg (n = 1324)	Mirabegron 100 mg (n = 890)
Final Visit			
Responders (n [%])	327 (24.6%)	419 (31.6%)	303 (34.0%)
Difference vs Placebo (%)		7.0%	9.4%
95% 2-sided CI for Difference†		(3.6%, 10.4%)	(5.5%, 13.3%)
Odds Ratio‡		1.57	1.69
95% 2-sided CI for Odds Ratio	--	(1.30, 1.89)	(1.37, 2.09)
P value		< 0.001*	< 0.001*

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074. All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). A responder is defined as a patient with a value ≤ 8 for mean number of micturition per 24 hours at final visit.
--: not applicable; ER: extended release; OAB: overactive bladder.
† 95% CIs for the difference of the proportions were based on normal approximation.
‡ Odds ratios of mirabegron over placebo, corresponding 95% CIs and P values were derived from a logistic regression model including treatment group, gender, study and baseline measurement.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

4.3.2.3 Change from Baseline to Final Visit in Mean Volume Voided per Micturition

Mirabegron 50 and 100 mg demonstrated a statistically significant increase from baseline to final visit in mean volume voided per micturition compared with placebo [Table 17 and Figure 13].

In Study 178-CL-074, mirabegron 25 mg did not demonstrate a statistically significant increase from baseline in mean volume voided per micturition compared with placebo. Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided per micturition, subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Mean volume voided per micturition and subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level.

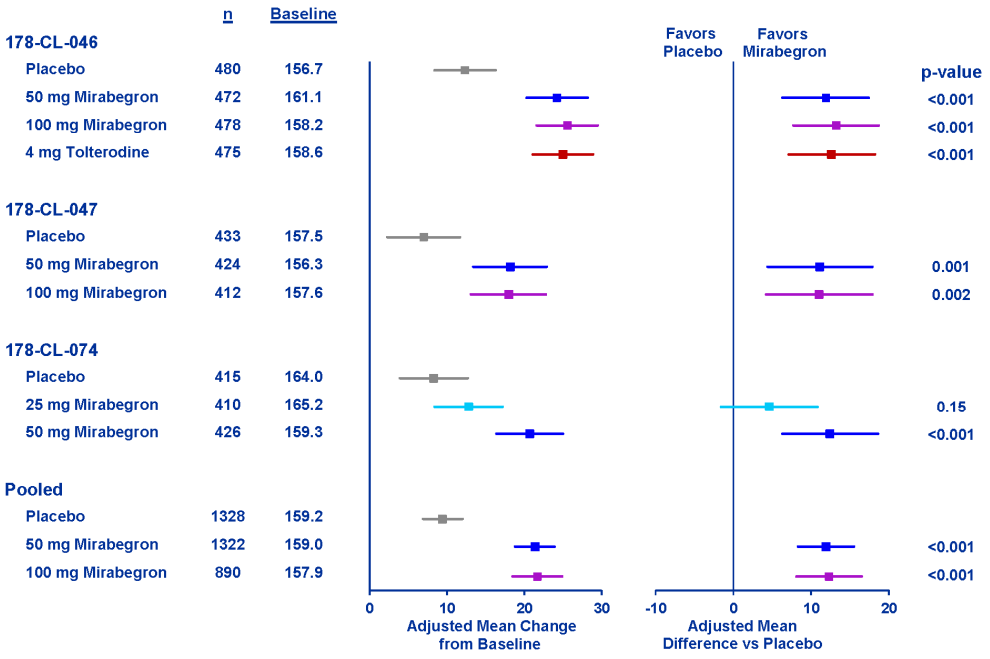
The treatment-by-study interaction P value was 0.94 for change from baseline to final visit in mean volume voided per micturition, indicating there was no difference among the primary phase 3 studies with respect to treatment effects for mirabegron 50 or 100 mg.

Tolterodine in Study 178-CL-046 demonstrated a statistically significant increase from baseline to final visit compared with placebo in mean volume voided per micturition [Table 17].

In the repeated measurement analysis of mean volume voided per micturition, the adjusted mean difference vs placebo and 95% CIs for both the mirabegron 50 and 100 mg groups at week 12 were similar to those at the final visit in the primary analysis for Studies 178-CL-046, 178-CL-047 and 178-CL-074 [Appendix 2, Figure 8].

Both mirabegron 50 and 100 mg demonstrated statistically significantly superior mean increase in mean volume voided per micturition compared with the placebo group as early as week 4 (the first measured time point), and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

Figure 13 Change from Baseline to Final Visit in Mean Volume Voided per Micturition (mL), Primary Phase 3 Studies, FAS



Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Footnotes continued on next page.

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). Horizontal bars represent 95% CIs for the adjusted mean change from baseline and the adjusted mean difference vs placebo. Individual study results are taken from the primary analysis of the respective study from an ANCOVA with treatment group, gender and geographical region as fixed factors and baseline value as a covariate. Pooled analysis results are from the primary analysis of the pooled data set and are from an ANCOVA with treatment group, gender and study as factors and baseline value as a covariate.
ANCOVA: analysis of covariance; ER: extended release; OAB: overactive bladder.

4.3.2.4 Efficacy Results for Key Secondary Endpoints

The results of the key secondary endpoints are shown in Table 17.

Change from Baseline to Week 4 in Incontinence Episodes per 24 hours

- The mirabegron 50 and 100 mg treatment groups in studies 178-CL-046 and 178-CL-047 demonstrated a statistically significant decrease in mean number of incontinence episodes per 24 hours compared with placebo from baseline to week 4, first measured time point, with multiplicity adjustment
- In Study 178-CL-074, since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided, subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure.
- Tolterodine in Study 178-CL-046 demonstrated a statistically significant reduction from baseline to week 4 compared with placebo in mean number of incontinence episodes per 24 hours.

Change from Baseline to Week 4 in Micturitions per 24 hours

- Mirabegron 50 and 100 mg in primary studies 178-CL-046 and 178-CL-047 demonstrated a statistically significant decrease in mean number of micturitions per 24 hours compared with placebo from baseline to week 4, the first measured time point, with multiplicity adjustment.
- In Study 178-CL-074, mirabegron 50 mg did not demonstrate a statistically significant difference in reduction from baseline to week 4 in mean number of micturitions per 24 hours compared with placebo with the multiplicity adjustment. Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided per micturition, subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure.
- Tolterodine in Study 178-CL-046 demonstrated a statistically significant reduction from baseline to week 4 compared with placebo.

Change from Baseline to Final Visit in Mean Level of Urgency

- All mirabegron treatment groups in the primary phase 3 studies demonstrated a reduction in mean level of urgency compared with placebo; this reduction was statistically significant for mirabegron treatment groups in Studies 178-CL-046 and 178-CL-047.
- In Study 178-CL-074, mirabegron 50 mg had a numerically improved effect compared with placebo; however due to the gatekeeping procedure there was no formal statistical significance since the prior variable (mean number of micturitions per 24 hours at week 4) failed to reach statistical significance.
- Tolterodine in Study 178-CL-046 showed a reduction from baseline to final visit compared with placebo.

Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 Hours

- The mirabegron 50 and 100 mg treatment groups in the primary phase 3 studies demonstrated a reduction in mean number of urgency incontinence episodes per 24 hours compared with placebo; this reduction was statistically significant for mirabegron treatment groups in Studies 178-CL-046 and 178-CL-047.

- In Study 178-CL-074, mirabegron 25 and 50 mg doses demonstrated a numerically improved effect compared with placebo; however, there was no formal statistical significance due to the gatekeeping procedure since prior parameters failed to reach statistical significance.
- Tolterodine in Study 178-CL-046 showed a reduction from baseline to final visit compared with placebo.

Change from Baseline to Final Visit in Mean Number of Episodes with Urgency Grade 3 or 4 per 24 Hours

- A statistically significant reduction in mean number of episodes with urgency grade 3 or 4 per 24 hours compared with placebo was demonstrated for mirabegron 50 mg in Study 178-CL-046 and mirabegron 50 and 100 mg in Study 178-CL-047.
- In Study 178-CL-074, mirabegron 50 mg demonstrated a numerically improved effect compared with placebo; however, there was no formal statistical significance due to the gatekeeping procedure since prior parameters failed to reach statistical significance.
- Tolterodine demonstrated a statistically significant reduction from baseline to final visit compared with placebo.

Change from Baseline to Final Visit Compared to Placebo in Mean Number of Pads Used per 24 hours

- Mirabegron 50 and 100 mg demonstrated statistically significant improvements from baseline to final visit compared with placebo in mean number of pads used per 24 hours in Study 178-CL-047 only.
- Mirabegron 25 mg did not demonstrate statistically significant improvement in Study 178-CL-074.
- Tolterodine did not demonstrate a statistically significant improvement from baseline to final visit compared with placebo.

4.3.2.5 Tolterodine Effects in Study 178-CL-046

In the FAS population of Study 178-CL-046, the tolterodine group demonstrated greater, but not statistically significant, reductions from baseline to final visit compared with placebo in mean number of incontinence episodes per 24 hours and in mean number of micturitions per 24 hours. In this same trial, tolterodine demonstrated:

- A stastistically significant reduction in mean number of incontinence episodes per 24 hours compared with placebo at the week 4 time point [Table 17].
- A stastistically significant reduction in mean number of micturitions per 24 hours compared with placebo at the week 4 time point [Table 17].
- A statistically significant increase in mean volume voided compared with placebo at final visit [Table 17].
- A statistically significant increase in the mean number of urgency episodes (Grade 3 or 4) per 24 hours (mean [SE]: -0.42 [0.214], 95% CI: [-0.84, -0.00] and P value=0.050) compared with placebo.
- A statistically significant greater responder analysis for 50% reduction in incontinence episodes at final visit (odds ratio versus placebo: 1.44, 95% 2-sided CI for odds ratio: [1.02, 2.03], p value=0.037).
- A statistically significant reduction compared with placebo in the adjusted mean change from baseline in number of micturitions per 24 hours at final visit for the per protocol set (PPS) subset excluding subjects with abaseline micturition frequency of less than 8 per day (mean [SE]: -0.40 [0.163], 95% 2-sided CI: [-0.72, -0.08] and P value = 0.015).

4.3.3 Summary of EU/NA OAB 12-week Phase 3 Population Results

In the primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074), mirabegron 25, 50 and 100 mg once daily demonstrated statistically significant reductions from baseline to final visit compared with placebo in both mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. A statistically significant increase in mean volume voided per micturition was demonstrated for mirabegron 50 and 100 mg across the primary phase 3 studies but not for the mirabegron 25 mg dose in Study 178-CL-074.

In the the primary phase 3 studies, mirabegron 50 and 100 mg were effective in reducing mean number of incontinence episodes and mean number of micturitions at week 4 (the first measured time point) and efficacy was maintained throughout the 12-week treatment period. Efficacy at week 4 was evident in incontinence but not in micturition frequency at the mirabegron 25 mg dose.

Mirabegron 50 and 100 mg demonstrated superiority compared with placebo for key secondary endpoints as defined in the phase 3 program, including change from baseline to final visit in mean volume voided per micturition, change from baseline to week 4 for mean number of incontinence episodes and micturitions per 24 hours and change from baseline to final visit in measurements of urgency. The magnitude of effect for the key secondary was notably higher for mirabegron 50 mg compared with mirabegron 25 mg.

Collectively, the coprimary and key secondary efficacy endpoint data support mirabegron 50 mg orally once daily for the effective treatment of patients with OAB.

4.3.4 Subjective Improvement Assessments

OAB has significant effects on HRQL, as quantified in various empirical studies [Basra & Kelleher, 2007]. Since socio-demographic, clinical, psychological and social factors are determinants of QoL, it is important to assess the perceptions of patients as is done in QoL research and also in the OAB field [Palmtag, 2004].

Several standard and clinically established instruments have been used to translate the observed changes in objective measures into patient meaningful consequences. In accordance with the recommendation of the Committee for Proprietary Medicinal Products (CPMP/EWP/18/01), the subjective outcome measures of HRQL included in the EU/NA OAB 12-week Phase 3 Population to evaluate treatment effects as perceived by the patient (i.e., OAB-q, PPBC and TS-VAS) were straightforward and reliable measures. Using these 3 different scales enabled different aspects of perceived benefit of mirabegron treatment to be examined.

Results for the following subjective outcome measures are presented in this section:

- Change from baseline to final visit in HRQL scores as assessed by the OAB-q, including Total Score; Coping, Concern, Sleep and Social Interaction Subscales; and Symptom Bother [Section 4.3.4.1];
- Change from baseline to final visit in the TS-VAS [Section 4.3.4.2];
- Change from baseline to final visit in PPBC [Section 4.3.4.3];

4.3.4.1 OAB-q

The OAB-q was developed to assess the symptom bother and HRQL impact of OAB. It has been validated in clinical and community samples and has demonstrated reliable internal consistency, test-retest reliability, construct validity and responsiveness among patients with a range of OAB symptoms [Coyne, Margolis et al, 2007; Coyne et al, 2005; Matza et al, 2005; Coyne et al, 2002]. Several language versions of the OAB-q are available and have been found to be psychometrically equivalent [Coyne, Margolis et al, 2008].

For each of the primary studies, the adjusted change from baseline and adjusted difference vs. placebo were calculated for each OAB-q subscale and total score.

Higher scores on the HRQL subscales and total score indicates a better QoL and a positive change in the HRQL subscale scores and total score indicates improvement.

Scores for the Symptom Bother scale of the OAB-q ranged from 0 to 100, with a score of 100 indicating worst severity. A negative change in Symptom Bother score indicates improvement.

In the primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074), mirabegron 50 mg demonstrated a statistically significant decrease (improvement) from baseline to final visit in the Symptom Bother Scale total score compared with placebo [Table 20].

Mirabegron 50 mg demonstrated a statistically significant increase (improvement) from baseline to final visit in the HRQL total score compared with placebo in Studies 178-CL-046 and 178-CL-047. In Study 178-CL-074, numerical improvements compared with placebo were not statistically significant for the mirabegron 50 mg dose group.

For the HRQL subscales of Coping and Concern, mirabegron 50 mg demonstrated a statistically significant increase (improvement) from baseline to final visit compared with placebo in Studies 178 CL-046 and 178-CL-047. In Study 178-CL-074, numerical improvements compared with placebo were not statistically significant for the mirabegron 50 mg dose group for these 2 subscales.

Improvements in Sleep subscale score from baseline to final visit compared with placebo were statistically significant only in Study 178-CL-047.

For the subscale of Social Interaction, numerical improvements compared with placebo were not statistically significant for the mirabegron 50 mg dose group in any of the studies. However, the Social Interaction subscale has been traditionally the least responsive of the OAB-q subscales [Coyne, Matza et al, 2007; Coyne et al, 2005].

4.3.4.2 TS-VAS

The TS-VAS is a quantitative instrument measuring subjective improvement in patients with OAB. Treatment satisfaction was assessed on a visual analogue scale with complete satisfaction indicated by a score of 10, with positive change from baseline indicating improvement.

The TS-VAS scores were analyzed for each individual primary phase 3 study; absolute values and change from baseline vs. placebo at the final visit were calculated.

Across the the primary phase 3 studies, mirabegron 25, 50 and 100 mg demonstrated statistically significant improvement relative to placebo [Table 21].

4.3.4.3 PPBC

The PPBC was developed as a global assessment of bladder condition. The PPBC scale offers a broad assessment of patient response that incorporates multiple elements of the disease in a simple question. The PPBC has demonstrated test-retest reliability, good construct validity and responsiveness to change [Coyne et al, 2006; Matza et al, 2005]. The PPBC uses a 6-point Likert scale, on which a score of 1 indicates “does not cause me any problems at all” and a score of 6 indicates “causes me many severe problems”. To assess change in the PPBC from baseline to the end of study, the baseline value was subtracted from the end of study value. Thus, score changes typically range from -2 to 2, with negative values indicating patient improvement. A 1 point change in the PPBC scale is generally considered to be clinically meaningful [Coyne et al, 2006].

The results of the PPBC scores were analyzed in the following manner: 1) across studies for adjusted change from baseline and adjusted difference vs. placebo; and 2) by a responder analysis for proportion of subjects experiencing a change of 1 or greater.

Mirabegron 50 and 100 mg demonstrated statistically significant improvement in PPBC score compared with placebo in Studies 178-CL-046 and 178-CL-047; mirabegron 25 and 50 mg did not demonstrate statistically significant improvement in PPBC score compared with placebo in Study 178-CL-074 [Table 22].

In the responder analysis, mirabegron 50 mg in Study 178-CL-046 and mirabegron 100 mg in Studies 178-CL-046 and 178-CL-047 demonstrated a statistically significant improvement in PPBC score compared with placebo; numerical improvements compared with placebo were not statistically significant for the mirabegron 50 mg in Studies 178-CL-047 and 178-CL-074 nor mirabegron 25 mg in Study 178-CL-074 [Table 23].

4.3.4.4 Summary of Subjective Improvement Assessment

Clinically meaningful improvements in OAB-q scores, as well as statistically significant change in Symptom Bother, most OAB-q subscales and the total score were observed with mirabegron 50 mg in two of the 3 primary studies. Study 178-CL-074 did not demonstrate significance over placebo for either mirabegron 25 or 50 mg for the majority of HRQL endpoints.

The directional parallelism between the subjective and objective measures substantially supports the clinical significance of the effect of mirabegron 50 mg in the treatment of symptoms of OAB.

Table 20 Change from Baseline to Final Visit in OAB-q, Primary Phase 3 Studies, FAS

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo (n = 480)	Mirabegron 50 mg (n = 473)	Mirabegron 100 mg (n = 478)	Tolterodine ER 4 mg (n = 475)	Placebo (n = 433)	Mirabegron 50 mg (n = 425)	Mirabegron 100 mg (n = 412)	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)
Symptom Bother Scale§										
Adjusted Change from Baseline†										
Mean (SE)	-14.9 (0.84)	-19.6 (0.85)	-19.9 (0.84)	-18.4 (0.85)	-10.8 (0.97)	-17.0 (0.98)	-20.2 (0.99)	-16.0 (0.90)	-17.9 (0.90)	-18.8 (0.88)
95% 2-sided CI	(-16.5, -13.2)	(-21.3, -18.0)	(-21.5, -18.2)	(-20.1, -16.8)	(-12.7, -8.9)	(-18.9, -15.1)	(-22.1, -18.2)	(-17.8, -14.3)	(-19.6, -16.1)	(-20.5, -17.1)
Adjusted Difference vs Placebo†										
Mean (SE)		-4.7 (1.19)	-5.0 (1.19)	-3.5 (1.19)		-6.2 (1.38)	-9.3 (1.38)		-1.8 (1.27)	-2.8 (1.26)
95% 2-sided CI	--	(-7.1, -2.4)	(-7.3, -2.6)	(-5.9, -1.2)	--	(-8.9, -3.5)	(-12.1, -6.6)	--	(-4.3, 0.7)	(-5.3, -0.3)
P value‡		< 0.001*	< 0.001*	0.003*		< 0.001*	< 0.001*		0.15	0.028*
Health-related Quality of Life Total Score§										
Adjusted Change from Baseline†										
Mean (SE)	13.7 (0.76)	16.1 (0.77)	17.0 (0.77)	14.8 (0.77)	10.7 (0.89)	14.8 (0.90)	17.3 (0.90)	13.0 (0.80)	14.3 (0.79)	14.2 (0.78)
95% 2-sided CI	(12.2, 15.2)	(14.6, 17.6)	(15.5, 18.5)	(13.3, 16.3)	(9.0, 12.5)	(13.1, 16.6)	(15.5, 19.0)	(11.5, 14.6)	(12.8, 15.9)	(12.7, 15.8)
Adjusted Difference vs Placebo†										
Mean (SE)		2.3 (1.08)	3.3 (1.08)	1.1 (1.08)		4.1 (1.26)	6.5 (1.27)		1.3 (1.12)	1.2 (1.12)
95% 2-sided CI	--	(0.2, 4.5)	(1.2, 5.4)	(-1.1, 3.2)	--	(1.6, 6.6)	(4.1, 9.0)	--	(-0.9, 3.5)	(-1.0, 3.4)
P value‡		0.031*	0.002*	0.32		0.001*	< 0.001*		0.26	0.28
Coping§										
Adjusted Change from Baseline†										
Mean (SE)	15.5 (0.93)	18.5 (0.93)	19.9 (0.93)	17.8 (0.93)	12.8 (1.06)	16.9 (1.07)	19.1 (1.08)	14.7 (0.97)	16.9 (0.96)	16.4 (0.95)
95% 2-sided CI	(13.7, 17.3)	(16.6, 20.3)	(18.1, 21.7)	(16.0, 19.6)	(10.7, 14.8)	(14.8, 19.0)	(17.0, 21.2)	(12.8, 16.5)	(15.0, 18.8)	(14.5, 18.2)
Adjusted Difference vs Placebo†										
Mean (SE)		2.9 (1.31)	4.3 (1.31)	2.3 (1.31)		4.1 (1.51)	6.3 (1.51)		2.2 (1.37)	1.7 (1.36)
95% 2-sided CI	--	(0.4, 5.5)	(1.8, 6.9)	(-0.3, 4.8)	--	(1.1, 7.1)	(3.4, 9.3)	--	(-0.5, 4.9)	(-0.9, 4.4)
P value‡		0.025*	<0.001*	0.083		0.007*	<0.001*		0.10	0.20
Concern§										
Adjusted Change from Baseline†										
Mean (SE)	15.7 (0.86)	18.4 (0.87)	19.0 (0.86)	16.2 (0.87)	12.7 (1.03)	18.0 (1.04)	20.5 (1.05)	14.7 (0.92)	15.8 (0.92)	16.2 (0.90)
95% 2-sided CI	(14.1, 17.4)	(16.6, 20.1)	(17.3, 20.7)	(14.5, 17.9)	(10.7, 14.8)	(16.0, 20.1)	(18.4, 22.5)	(12.9, 16.5)	(14.0, 17.6)	(14.4, 18.0)
Adjusted Difference vs Placebo†										
Mean (SE)		2.6 (1.22)	3.2 (1.22)	0.4 (1.22)		5.3 (1.47)	7.7 (1.47)		1.0 (1.30)	1.5 (1.29)
95% 2-sided CI	--	(0.2, 5.0)	(0.8, 5.6)	(-2.0, 2.8)	--	(2.4, 8.2)	(4.8, 10.6)	--	(-1.5, 3.6)	(-1.0, 4.0)
P value‡		0.033*	0.008*	0.74		<0.001*	<0.001*		0.43	0.24

Table continued on next page.

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo (n = 480)	Mirabegron 50 mg (n = 473)	Mirabegron 100 mg (n = 478)	Tolterodine ER 4 mg (n = 475)	Placebo (n = 433)	Mirabegron 50 mg (n = 425)	Mirabegron 100 mg (n = 412)	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)
Sleep§										
Adjusted Change from Baseline†										
Mean (SE)	13.2 (0.86)	15.1 (0.87)	15.8 (0.87)	13.9 (0.87)	9.7(1.07)	14.6 (1.08)	17.5 (1.09)	14.0 (0.96)	14.3 (0.96)	14.5 (0.95)
95% 2-sided CI	(11.5, 14.9)	(13.4, 16.8)	(14.1, 17.5)	(12.2, 15.6)	(7.6, 11.8)	(12.5, 16.7)	(15.4, 19.6)	(12.2,15.9)	(12.4,16.2)	(12.6,16.3)
Adjusted Difference vs Placebo†										
Mean (SE)		1.9 (1.23)	2.6 (1.22)	0.7 (1.23)		4.9 (1.52)	7.8 (1.52)		0.3 (1.36)	0.4 (1.35)
95% 2-sided CI	--	(-0.5, 4.3)	(0.2, 5.0)	(-1.7, 3.1)	--	(1.9, 7.9)	(4.8, 10.8)	--	(-2.4,2.9)	(-2.2,3.1)
P value‡		0.12	0.034*	0.56		0.001*	<0.001*		0.84	0.76
Social§										
Adjusted Change from Baseline†										
Mean (SE)	8.7 (0.68)	10.1 (0.68)	10.9 (0.68)	8.8 (0.68)	6.0 (0.77)	7.4 (0.77)	9.6 (0.78)	7.1 (0.68)	8.2 (0.68)	7.7 (0.67)
95% 2-sided CI	(7.4, 10.0)	(8.8, 11.4)	(9.5, 12.2)	(7.5, 10.2)	(4.4, 7.5)	(5.9, 8.9)	(8.1, 11.2)	(5.7,8.4)	(6.9,9.5)	(6.4,9.0)
Adjusted Difference vs Placebo†										
Mean (SE)		1.4 (0.96)	2.2 (0.96)	0.1 (0.96)		1.4 (1.09)	3.7 (1.09)		1.1 (0.97)	0.6 (0.96)
95% 2-sided CI	--	(-0.5, 3.3)	(0.3, 4.1)	(-1.7, 2.0)	--	(-0.7, 3.6)	(1.5, 5.8)	--	(-0.8,3.0)	(-1.3,2.5)
P value‡		0.15	0.024*	0.88		0.19	<0.001*		0.25	0.54

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

§ A negative change from baseline in Symptom Bother indicated indicats improvement. HRQL total score indicated a better quality of life. A positive change from baseline in HRQL Total Score and the subscales indicated indicates improvement.

--: not applicable; HRQL: Higher Health-related Quality of Life OAB-q: overactive bladder questionnaire.

† Individual study results are taken from the primary analysis of the respective study from an analysis of covariance (ANCOVA) with treatment group, gender and geographical region as fixed factors and baseline value as a covariate.

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

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Table 21 Change from Baseline to Final Visit in TS-VAS, Primary Phase 3 Studies, FAS

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo (n = 480)	Mirabegron 50 mg (n = 473)	Mirabegron 100 mg (n = 478)	Tolt ER 4 mg (n = 475)	Placebo (n = 433)	Mirabegron 50 mg (n = 425)	Mirabegron 100 mg (n = 412)	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)
Adjusted Change from Baseline†										
Mean (SE)	1.89 (0.146)	2.55 (0.149)	2.66 (0.146)	2.44 (0.147)	0.7 (0.16)	1.5 (0.16)	2.1 (0.16)	1.05 (0.154)	1.54 (0.152)	1.88 (0.152)
95% 2-sided CI	(1.60, 2.18)	(2.26, 2.85)	(2.37, 2.94)	(2.15, 2.73)	(0.4, 1.0)	(1.2, 1.9)	(1.8, 2.4)	(0.75, 1.35)	(1.24, 1.84)	(1.58, 2.18)
Adjusted Difference vs Placebo†										
Mean (SE)		0.66 (0.208)	0.77 (0.207)	0.55 (0.207)		0.8 (0.22)	1.4 (0.22)		0.49 (0.216)	0.83 (0.216)
95% 2-sided CI	--	(0.25, 1.07)	(0.36, 1.17)	(0.14, 0.95)	--	(0.4, 1.3)	(1.0, 1.8)	--	(0.07, 0.91)	(0.41, 1.25)
P value‡		0.001*	< 0.001*	0.008*		< 0.001*	< 0.001*		0.024*	< 0.001*

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Treatment satisfaction was assessed by patients on a 10 cm VAS. A score of 10 indicated complete satisfaction. A positive change from baseline in TS-VAS indicated improvement in patient satisfaction.
TS-VAS: Treatment satisfaction visual analog scale; ER: extended release; Min: minimum; Max: maximum; Tolt: tolterodine; --: not applicable.
† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate.
‡ P values were from pairwise comparisons vs placebo within the ANCOVA model.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Table 22 Change from Baseline to Final Visit in PPBC Scores, Primary Phase 3 Studies, FAS

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo (n = 480)	Mirabegron 50 mg (n = 473)	Mirabegron 100 mg (n = 478)	Tolt ER 4 mg (n = 475)	Placebo (n = 433)	Mirabegron 50 mg (n = 425)	Mirabegron 100 mg (n = 412)	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)
Adjusted Change from Baseline†										
Mean (SE)	-0.8(0.05)	-1.0 (0.06)	-1.1 (0.05)	-1.0 (0.06)	-0.5(0.05)	-0.7 (0.05)	-0.8 (0.05)	-0.7 (0.06)	-0.8 (0.06)	-0.7 (0.06)
95% 2-sided CI	(-0.9,-0.7)	(-1.1,-0.9)	(-1.2, -1.0)	(-1.1, -0.9)	(-0.6,-0.4)	(-0.8,-0.6)	(-0.9, -0.7)	(-0.8,-0.6)	(-0.9, -0.6)	(-0.8,-0.6)
Adjusted Difference vs Placebo†										
Mean (SE)		-0.2 (0.08)	-0.2 (0.08)	-0.2 (0.08)		-0.2 (0.07)	-0.3 (0.07)		-0.1 (0.08)	-0.0 (0.08)
95% 2-sided CI	--	(-0.3,-0.0)	(-0.4, -0.1)	(-0.3, -0.0)	--	(-0.3,-0.0)	(-0.4, -0.2)	--	(-0.2, 0.1)	(-0.2,0.1)
P value‡		0.045*	0.001*	0.023*		0.032*	<0.001*		0.49	0.64

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
PPBC: Patient Perception of Bladder Condition.
†Adjusted change from baseline values are generated from the ANCOVA model with treatment group, gender and geographical regions as fixed factors and baseline as a covariate. Differences of the adjusted means are calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.
‡P values are from pairwise comparisons vs. placebo within the ANCOVA model.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Table 23 Responder Analysis for PPBC (at Least 1 Point Improvement from Baseline to Final Visit), Primary Phase 3 Studies, FAS

	Study 178-CL-046				Study 178-CL-047			Study 178-CL-074		
	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolt ER 4 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
n	433	416	429	426	392	388	377	376	391	395
Responder (%)	56.6%	61.3%	62.2%	65.0%	47.4%	50.8%	56.8%	55.1%	52.7%	55.2%
OR vs. Placebo	--	1.36	1.42	1.43	--	1.16	1.47	--	0.95	1.03
P value	--	0.036*	0.018*	0.015*	--	0.31	0.012*	--	0.74	0.87

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
PPBC: Patient Perception of Bladder Condition; OR: odds ratio.
Odds ratios of mirabegron over placebo and P values were derived from a logistic regression model including treatment group, gender, geographical region and baseline measurement.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

4.3.5 Supportive Studies 178-CL-048, 178-CL-044 and 178-CL-045

The efficacy results from supportive studies 178-CL-044 [Table 24], 178-CL-045 [Table 25] and 178-CL-048 [Table 26] are consistent with results from the EU/NA OAB 12-week Phase 3 Population.

In the supportive studies (Study 178-CL-048, 178-CL-044 and 178-CL-045), mirabegron 25, 50 and 100 mg once daily demonstrated statistically significant reductions from baseline to final visit compared with placebo in mean number of incontinence episodes per 24 hours, with the exception of mirabegron 100 mg in Study 178-CL-044, and in mean number of micturitions per 24 hours, with the exception of mirabegron 25 mg in Study 178-CL-044. The supportive studies also demonstrated statistically significant increases in mean volume voided per micturition for all doses across all studies, with the exception of mirabegron 25 mg in Study 178-CL-044.

Table 24 Efficacy Results, Supportive Study 178-CL-044, FAS

	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Tolterodine ER 4 mg§
Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours						
n	106	99	108	111	110	53
Mean Baseline (SD)	2.45 (2.35)	2.92 (3.23)	2.41 (2.30)	2.49 (2.48)	2.47 (2.23)	2.85 (2.76)
Adjusted Mean Difference from Baseline†	-0.53	-1.36	-1.15	-1.06	-1.10	-0.81
Adjusted Mean Difference vs Placebo (SE)†	--	-0.84 (0.31)	-0.62 (0.30)	-0.53 (0.30)	-0.58 (0.30)	-0.28 (0.37)
95% 2-sided CI		(-1.45, -0.23)	(-1.22, -0.02)	(-1.12, 0.06)	(-1.16, 0.01)	(-1.01, 0.45)
P value‡		0.0072*	0.0416*	0.0758	0.0551	0.4468
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours						
n	166	167	167	168	166	85
Mean Baseline (SD)	11.67 (3.39)	11.87 (2.88)	11.85 (3.30)	11.81 (3.51)	11.34 (2.41)	12.31 (3.68)
Adjusted Mean Difference from Baseline†	-1.44	-1.88	-2.08	-2.12	-2.24	-1.99
Adjusted Mean Difference vs Placebo† (SE)	--	-0.45 (0.28)	-0.64 (0.28)	-0.68 (0.28)	-0.80 (0.28)	-0.52 (0.34)
95% 2-sided CI		(-0.99, 0.10)	(-1.19, -0.10)	(-1.22, -0.13)	(-1.34, -0.25)	(-1.18, 0.15)
P value‡		0.1083	0.0205*	0.0152*	0.0041*	0.1291
Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition						
n	165	167	167	168	166	85
Mean Baseline (SD)	161.38 (53.87)	160.83 (55.04)	153.62 (49.39)	152.67 (55.26)	156.10 (50.17)	157.00 (64.40)
Adjusted Mean Difference from Baseline†	7.29	15.32	27.34	25.56	33.34	23.86
Adjusted Mean Difference vs Placebo† (SE)		8.03 (4.87)	20.05 (4.88)	18.28 (4.90)	26.06 (4.87)	16.81 (5.97)
95% 2-sided CI	--	(-1.54, 17.60)	(10.48, 29.63)	(8.66, 27.89)	(16.49, 35.62)	(5.09, 28.5)
P value‡		0.0998	< 0.0001*	0.0002*	< 0.0001*	0.0050

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). While FAS-I was not defined as a separate population, analyses of incontinence endpoints were limited to the subset of the FAS that reported incontinence at baseline.
--: not applicable; ER: extended release.
* Statistically significant at the 0.05 level.
†Analysis of covariance with treatment group and country as fixed factors and baseline as a covariate.
‡ P value from pairwise comparison vs placebo.
§ ANCOVA model estimated the difference versus tolterodine; results displayed are converted to display difference versus placebo.

Table 25 Efficacy Results, Supportive Study 178-CL-045, FAS

	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg
Change from Baseline to End of Study in Mean Number of Incontinence Episodes per 24 Hours (FAS)				
n	140	134	144	150
Mean baseline (SD)	1.68 (1.471)	2.20 (2.499)	2.00 (2.228)	1.86 (1.666)
Adjusted mean difference from baseline†	-0.77	-1.16	-1.17	-1.31
Adjusted mean difference from placebo†	--	-0.39	-0.40	-0.54
95% 2-sided CI		(-0.67, -0.11)	(-0.67, -0.13)	(-0.81, -0.28)
Change from Baseline to End of Study in Mean Number of Micturitions per 24 Hours (FAS)				
n	211	209	208	207
Mean baseline (SD)	11.17 (2.526)	11.47 (2.835)	11.77 (2.606)	11.20 (2.761)
Adjusted mean difference from baseline†	-1.26	-1.92	-2.00	-2.04
Adjusted mean difference from placebo†	--	-0.66	-0.74	-0.78
95% 2-sided CI		(-1.04, -0.28)	(-1.12, -0.36)	(-1.16, -0.40)
Change from Baseline to End of Study in Mean Volume Voided per Micturition (FAS)				
n	211	209	208	207
Mean baseline (SD)	148.95 (42.96)	147.75 (50.46)	151.57 (49.46)	152.70 (46.53)
Adjusted mean difference from baseline†	11.12	23.65	27.33	31.36
Adjusted mean difference from placebo	--	12.52	16.20	20.23
95% 2-sided CI		(4.97, 20.07)	(8.64, 23.77)	(12.66, 27.80)

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). While FAS-I was not defined as a separate population, analyses of incontinence endpoints were limited to the subset of the FAS that reported incontinence at baseline.
† An analysis of covariance with treatment group as a factor and baseline as a covariate.

Table 26 Efficacy Results, Supportive Study 178-CL-048, FAS

	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Change from Baseline to Endpoint Visit in Mean Number of Incontinence Episodes per 24 Hours (FAS)			
n	264	266	240
Mean baseline (SD)	1.91 (1.760)	1.99 (2.054)	1.89 (1.826)
Adjusted mean difference from baseline†	-0.67	-1.09	-0.99
Adjusted mean difference from placebo†	--	-0.42	-0.32
95% CI		(-0.67, -0.17)	(-0.57, -0.06)
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours			
n	368	369	368
Mean baseline (SD)	11.29 (2.748)	11.15 (2.650)	11.10 (2.567)
Adjusted mean difference from baseline †	-0.82	-1.68	-1.43
Adjusted mean difference from placebo†	--	-0.86	-0.61
95% CI		(-1.16, -0.57)	(-0.90, -0.32)
Change from Baseline to Endpoint Visit in Mean Volume Voided per Micturition (FAS)			
n	366	368	367
Mean baseline (SD)	146.791 (44.2336)	149.591 (46.3775)	145.863 (46.8973)
Adjusted mean difference from baseline †	9.675	24.450	28.724
Adjusted mean difference from placebo (SE)†	--	14.775	19.049
95% CI		(9.974, 19.576)	(14.246, 23.852)

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). While FAS-I was not defined as a separate population, analyses of incontinence endpoints were limited to the subset of the FAS that reported incontinence at baseline.
--: not applicable; ER: extended release.
† Analysis of variance with treatment group as a fixed factor and baseline as a covariate.

4.4 Persistence of Efficacy

The data from long-term controlled Study 178-CL-049 provide evidence to demonstrate the persistence of efficacy for mirabegron assessed in parallel with tolterodine over the one-year treatment period. Study 178-CL-049 was a double-blind study with an active-control allowing for

contextualization of results relative to a known treatment for OAB; efficacy analyses were secondary, and there were no statistical comparisons of efficacy between treatment groups.

4.4.1 Design Features of Phase 3 EU/NA Long-term Controlled Study 178-CL-049

The following key features characterized the design and conduct of Study 178-CL-049:

- Patients in Study 178-CL-049 were required to meet the same inclusion/exclusion criteria as patients in primary phase 3 studies (Studies 178-CL-046, 178-CL-047 and 178-CL-074), including the inclusion criterion of ≥ 8 micturitions per 24 hours in the baseline micturition diary.
- Patients who completed the 12-week treatment and safety follow-up periods of studies 178-CL-046 or 178-CL-047, as well as patients that did not participate in the 178-CL-046 or 178-CL-047 studies, could be enrolled into Study 178-CL-049 if they met all inclusion criteria and none of the exclusion criteria at screening (visit 1) and baseline (visit 2).
- A total of 81.3% of patients in Study 178-CL-049 had been previously treated 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 Study 178-CL-049 with regard to prior treatment in either 178-CL-046 or 178-CL-047.
- Relatively few patients discontinued treatment in studies 178-CL-046 or 178-CL-047 due to lack of efficacy (from 0.4% to 1.2% and from 0.2% to 2.0%, respectively, across treatment groups in each study).
- There was no placebo group because it would be impractical to expect patients with symptomatic OAB to remain on placebo for one year. Furthermore, the differential drop-out rate that would have resulted would have compromised the analysis of both safety and efficacy of mirabegron in this study.

Analyses of efficacy endpoints in Study 178-CL-049 adjusted for for gender, geographical region, prior history (prior treatment and study experience), and baseline value.

4.4.2 Efficacy Results: Long-term Safety Study 178-CL-049

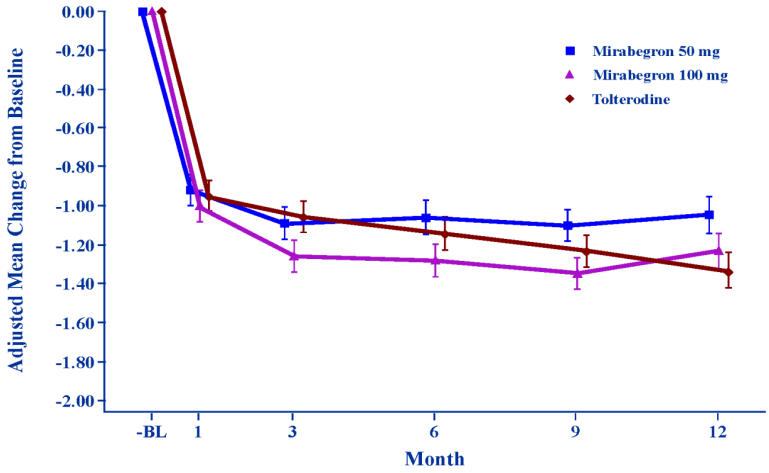
4.4.2.1 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours

The reduction in mean number of incontinence episodes at final visit was similar in both mirabegron treatment groups [Appendix 1, Table 5].

Based on the repeated measurement analysis, each mirabegron group showed a numerical improvement compared with baseline in mean number of incontinence episodes per 24 hours by month 1, with improvement maintained through month 12 [Figure 14].

Results in the tolterodine treatment group were similar to both mirabegron groups [Figure 14 and Appendix 1, Table 5].

Figure 14 Adjusted Mean Change from Baseline to Each Visit in Mean Number of Incontinence Episodes per 24 Hours Based on Repeated Measures, FAS-I



Study included: 178-CL-049.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and who had at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set Incontinence [FAS-I]).
Adjusted means and SE are from a repeated measures model which included terms for treatment group, time (visit), treatment-by-time interaction, baseline measurement, baseline-by-time interaction, gender, gender-by-time interaction, geographical region, and previous study history. SE bars are 1 x SE.
BL: baseline; SE: standard error.

While no study required incontinence at baseline, inclusion in the FAS-I required at least one episode of incontinence in the 3-day baseline micturition diary (equating to a minimum of 0.33 episodes per 24 hours).

Two responder analyses were performed on incontinence episodes, a zero responder analysis (requiring a patient to have zero incontinence episodes per 24 hours at final visit based on the 3-day micturition diary) and a 50% reduction analysis (requiring a patient to have a ≥ 50% decrease from baseline to final visit in mean number of incontinence episodes per 24 hours).

Across all 3 treatment groups, the proportion of patients who were responders for zero incontinence episode at the final visit was 43.4%, 45.8% and 45.1% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively.

Across all 3 treatment groups, the percentage of responders for 50% reduction in incontinence episodes was at the final visit 63.7%, 66.3% and 66.8% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively.

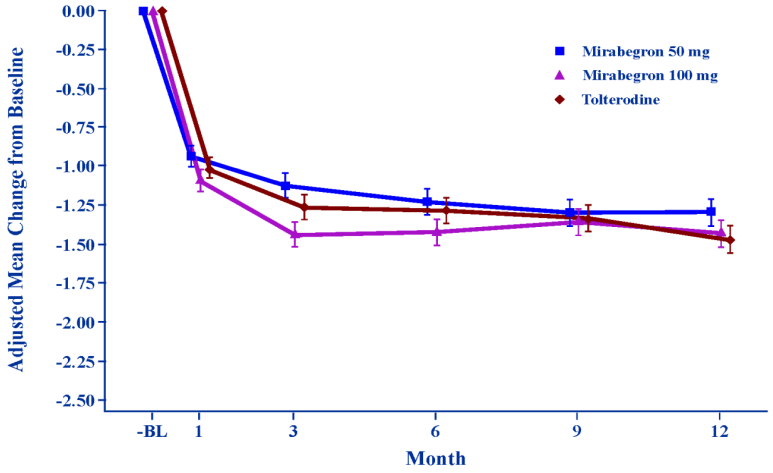
4.4.2.2 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours

Mirabegron 50 and 100 mg showed numeric reductions from baseline to final visit in the mean number of micturitions per 24 hours [Appendix 1, Table 6].

Based on the repeated measurement analysis, each mirabegron group showed a numerical improvement compared with baseline in mean number of micturitions per 24 hours by the first measured time point of month 1, with the improvement maintained through month 12 [Figure 15].

The efficacy results for tolterodine-treated patients were similar to the results observed in mirabegron-treated patients [Figure 15 and Appendix 1, Table 6].

Figure 15 Adjusted Mean Change from Baseline to Each Visit in Mean Number of Micturitions per 24 Hours Based on Repeated Measures, FAS



Study included: 178-CL-049.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Adjusted means and SE are from a repeated measures model which included terms for treatment group, time (visit), treatment-by-time interaction, baseline measurement, baseline-by-time interaction, gender, gender-by-time interaction, geographical region, and previous study history. SE bars are 1 x SE.
BL: baseline; SE: standard error.

A posthoc evaluation of responders for micturition was performed and required that a patient have a value ≤ 8 for mean number of micturition per 24 hours at final visit based on the 3-day micturition diary. The percentage of responders at final visit was 31.3%, 34.2% and 34.4% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively.

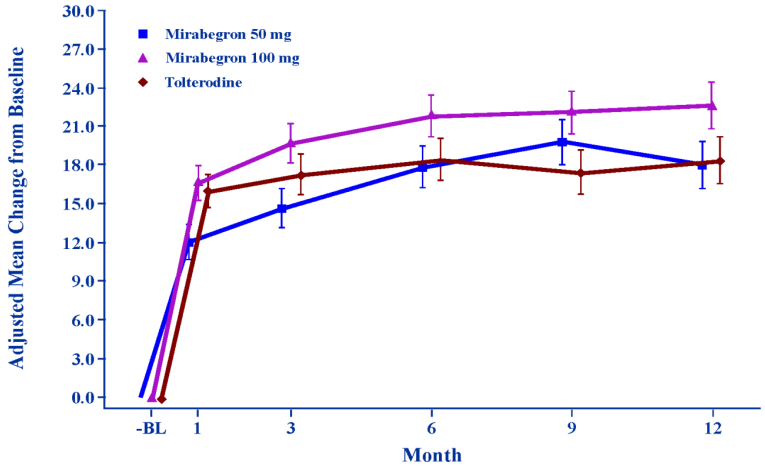
4.4.2.3 Change from Baseline to Final Visit in Mean Volume Voided per Micturition

Mirabegron 50 and 100 mg demonstrated an increase from baseline to final visit in mean volume voided per micturition [Appendix 1, Table 7].

Based on the repeated measurement analysis, each mirabegron group showed a numerical improvement compared with baseline in mean volume voided per micturition by month 1, with the improvement maintained through month 12 [Figure 16].

The efficacy results for tolterodine-treated patients were similar to the results observed in mirabegron-treated patients [Figure 16 and Appendix 1, Table 7].

Figure 16 Adjusted Mean Change from Baseline to Months 1, 3, 6, 9 and 12 in Mean Volume Voided (mL) per Micturition Based on Repeated Measures, FAS



Study included: 178-CL-049.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Adjusted means and SE are from a repeated measures model which included terms for treatment group, time (visit), treatment-by-time interaction, baseline measurement, baseline-by-time interaction, gender, gender-by-time interaction, geographical region, and previous study history. SE bars are 1 x SE.
BL: baseline; SE: standard error.

4.4.2.4 Additional Efficacy Results, Study 178-CL-049

The mirabegron 50 and 100 mg groups showed a numerical improvement compared with baseline at month 1 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.

Improvements in these symptoms were observed by month 1 (first measured time point) and maintained through month 12 for all 3 treatment groups.

Mirabegron 50 and 100 mg also showed similar improvements compared with baseline at final visit for the subjective improvement assessments TS-VAS, HRQL total score and HRQL subscales, PPBC and mean number of pads used.

The tolterodine group showed similar results to the mirabegron treatment groups.

4.4.3 Summary of Persistence of Efficacy Effects, Long-term Safety Study 178-CL-049

Data from this active-controlled, long-term safety study support the persistence of efficacy for mirabegron assessed in parallel with tolterodine over the one-year treatment period.

Mirabegron 50 and 100 mg showed numeric reductions from baseline to final visit in mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours, as well as numerical improvements in mean volume voided per micturition. Improvements in these symptoms were observed by month 1 and maintained through month 12.

Mirabegron 50 mg, 100 mg and tolterodine also showed similar improvements compared with baseline at final visit for the subjective improvement assessments TS-VAS, HRQL total score and HRQL subscales, PPBC, as well as mean number of pads used.

4.5 Efficacy in Special Populations

Pooled analyses of the coprimary efficacy endpoints in the following subpopulation categories were performed:

- Demographics;
- Characteristics of OAB;
- Intrinsic/Extrinsic Factors; and
- Food Status.

The nominal P values for the treatment-by-subpopulation interactions presented were not adjusted for multiplicity and these analyses are designated exploratory in the SAP.

Point estimates and 2-sided 95% CIs of treatment effect for each subpopulation category within each treatment group, as well as compared with placebo, were calculated. The point estimates and 2-sided 95% CIs for each treatment group and subpopulation category were evaluated for the extent to which the CIs were overlapping.

4.5.1 Demographics

An overview of results of pooled analyses for the coprimary efficacy endpoints by subpopulations of demographic and baseline characteristics (gender, age, race, ethnicity, body mass index (BMI) group and geographical region) is provided in [Appendix 2, Figure 9 and Appendix 1, Table 8]. Results are described in detail for age, gender, race and ethnicity.

4.5.1.1 Age

Mean Number of Incontinence Episodes per 24 Hours by Age
The reduction from baseline to final visit in mean number of incontinence episodes per 24 hours was lower within the < 65 years of age group for mirabegron 50 and 100 mg groups as compared with the ≥ 65 years of age group for mirabegron 50 and 100 mg groups [Appendix 1, Table 8].

Mean Number of Micturitions per 24 Hours by Age
In the subpopulation analysis of patients by age group, both mirabegron 50 and 100 mg groups were effective in reducing the mean number of micturitions per 24 hours from baseline to final visit for patients < 65 and ≥ 65 years and for patients < 75 and ≥ 75 years of age, although effects on incontinence were numerically larger in the respective older age groups compared to younger age groups [Appendix 1, Table 8].

4.5.1.2 Gender

Mean Number of Incontinence Episodes per 24 Hours by Gender
Mirabegron 50 and 100 mg were effective in reducing the mean number of incontinence episodes from baseline to final visit for both male and female patients [Appendix 2, Figure 9]. A larger reduction versus placebo in mean number of incontinence episodes per 24 hours was observed in female patients compared with male patients. This effect could be attributed to the lower baseline values (female: 2.83; male: 2.25) observed in male patients and the higher placebo response observed in male patients compared with female patients [Appendix 1, Table 8].

A recent literature review and meta-analysis of clinical studies for a range of currently available pharmacologic treatments for OAB notes that numerous studies have found that incontinence outcomes in men are generally not as favorable as in women [Hartmann et al, 2009]. This is likely to reflect differing anatomy and pathophysiology contributing to symptoms in male and female patients [Hartmann et al, 2009]. Specifically, male patients with urinary symptoms consistent with OAB may have comorbid conditions such as BPH with overlapping symptomatology. Such common comorbid conditions in male patients can precipitate episodes of overflow incontinence or frequency of micturition secondary to mechanisms other than urgency.

Mean Number of Micturitions per 24 Hours by Gender
In the subpopulation analysis by gender, mirabegron 50 and 100 mg were effective in reducing the mean number of micturitions per 24 hours from baseline to final visit for both male and female

patients [Appendix 2, Figure 9].

4.5.1.3 Race

Both mirabegron 50 and 100 mg groups were effective in reducing the mean number of incontinence episodes per 24 hours and reducing the mean number of micturitions per 24 hours from baseline to final visit for Whites [Appendix 2, Figure 9]. There were too few patients in the categories “Black or African American”, "Asian" and "Other" to draw meaningful conclusions about these groups [Table 34].

4.5.1.4 Ethnicity

There were too few Hispanic/Latino patients to draw meaningful conclusions about these groups [Table 34; Appendix 2, Figure 9].

4.5.2 Characteristics of OAB

Analyses demonstrated the efficacy of mirabegron regardless of type of OAB, duration of OAB symptoms, previous surgery for OAB, previous medication for OAB, discontinuation of previous OAB medication due to insufficient effect or discontinuation of previous OAB medication due to poor tolerability [Appendix 2, Figure 10 and Appendix 1, Table 9].

Both mirabegron 50 and 100 mg doses were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours in antimuscarinic treatment naïve patients as well as in patients that had received previous OAB antimuscarinic therapy. In patients with previous OAB antimuscarinic therapy both mirabegron 50 and 100 mg doses were effective in reducing the placebo-corrected mean number of incontinence episodes and mean number of micturitions per 24 hours regardless of the reason for discontinuation (either insufficient effect or poor tolerability as determined by the patient).

4.5.3 Intrinsic/Extrinsic Factors

Analyses demonstrated the efficacy of mirabegron in male patients in general regardless of history of male of BPH, and effectiveness in the general OAB populations regardless of history of diabetes, renal status, with or without the use of concomitant beta-blockers, diuretics or alpha 1-antagonists (males only) [Appendix 2, Figure 11 and Appendix 1, Table 10]. As noted previously with the gender analysis, due to a small number of incontinence episodes at baseline and a relatively larger placebo effect, overall improvement in incontinence relative to placebo is smaller in all male subsets than in the overall OAB population.

For the efficacy evaluations of incontinence episodes and micturitions, an improvement in the placebo-adjusted mean change from baseline was observed for mirabegron 50 and 100 mg for fed and fasted conditions. The decrease in adjusted mean change from baseline to final visit vs placebo for incontinence episodes was larger in patients treated with mirabegron in the fasted state compared with the fed state; however, the opposite was observed for micturitions [Appendix 2, Figure 1]. Examining results for micturitions and incontinence episodes in aggregate, mirabegron was efficacious across food status conditions (fed or fasted) in the primary studies.

4.5.4 Summary of Subpopulation Analyses

Mirabegron at the proposed therapeutic dose of 50 mg orally once daily has demonstrated efficacy for the treatment of OAB. Its efficacy can be generalized to all patients with OAB, regardless of demographic characteristics, OAB characteristics, intrinsic/extrinsic factors comprised of comorbid conditions or concomitant medications that might affect the coprimary efficacy endpoints or administered with or without food. As with many OAB agents, due to differing baseline status and placebo response, efficacy in terms of incontinence episodes in male patients was less robust than female patients, however, results were comparable between males and females for micturition

frequency. Mirabegron is effective in patients who are antimuscarinic treatment naive and in patients who failed previous OAB antimuscarinic treatment. No dose adjustment for reasons of efficacy is required for any of the subpopulations examined.

4.6 Mirabegron Efficacy Comparison to Antimuscarinic OAB Drugs

The effects of mirabegron on incontinence episodes and micturition frequency observed in the 12-week primary studies were compared to the results of an updated systematic review and meta-analysis on the effects of antimuscarinic drugs for the treatment of OAB [Chapple et al, 2008]. Additionally, the effects of mirabegron were compared to efficacy data from studies of OAB patients with a similar duration of treatment (12-weeks), demographic profile and baseline characteristics to those in the mirabegron program for approved OAB products using data from the FDA medical and statistical reviews.

The effects of mirabegron on micturition frequency and episodes of incontinence are consistent with the effects of other approved OAB drugs [Appendix 1, Table 11, Appendix 1, Table 12 and Appendix 1, Table 13]. The mean difference from placebo for incontinence episodes and micturition frequency following administration of mirabegron is within the range of values following administration of approved OAB treatments [Table 27].

Table 27 Mean Difference from Placebo in Primary Endpoints

	Mean Change from baseline in Incontinence Episodes per Day	Mean Change from baseline in the Number of Micturitions per Day
	Mean Difference from Placebo	**Mean Difference from Placebo**
Range of the Means (Literature Meta-analysis)	-0.21 to -1.08	-0.54 to -1.3
Range of the Means (Regulatory Documents)	-0.22 to -1.2	-0.40 to -1.39
Mirabegron 50 mg (95% CI)	-0.40 (-0.21 to -0.58)	-0.55 (-0.36 to -0.75)

Source: Chapple et al, 2008; FDA documents: Medical Review(s) Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Medical Review(s) Application Number 21-518 (VESIcare, Solifenacin Succinate) 2004, Medical Review Application Number 21-595 (Sanctura, Trospium Chloride), Medical Review(s) (Parts 1, 2 and 3) 2004, Medical Review Application Number 22-103 (Sanctura XR, Trospium Chloride) 2007, Medical and Statistical Review(s) Application Number 21-513 (Enablex, Darifenacin Hydrobromide) 2004, Statistical Review(s) (Parts 1 and 2) Application Number 20-771 (Detrol, Tolterodine L-tartrate) 1998, Medical Review(s) (Parts 1 and 2) Application Number 21-228 (Detrol LA, Tolterodine) 2000.

4.7 Efficacy Summary

The primary efficacy studies consistently demonstrated the efficacy of mirabegron 25, 50 and 100 mg compared with placebo for the coprimary endpoints of change from baseline to final visit in mean number of incontinence episodes and mean number of micturitions per 24 hours. Mirabegron 50 mg, the recommended therapeutic dose, demonstrated superiority compared with placebo for key secondary endpoints as defined in the phase 3 program, including change from baseline to final visit in mean volume voided per micturition, change from baseline to week 4 in mean number of incontinence episodes and micturitions per 24 hours, and change from baseline to final visit in measurements of urgency. The effect of mirabegron 25, 50 and 100 mg on the coprimary efficacy endpoints was generally comparable, and a clear incremental efficacy benefit for mirabegron 100 mg compared with mirabegron 50 mg was not demonstrated. The magnitude of effect for the key secondary efficacy endpoints was comparable for mirabegron 50 mg and 100 mg, and notably lower for mirabegron 25 mg. The odds ratio for responders with a $\geq$ 50% reduction from baseline to final visit in incontinence episodes was 1.54 (95% CI: 1.26, 1.89) for the mirabegron 50 mg group.

Standard and clinically established instruments to assess quality of life measures were utilized in these studies to assess the impact of mirabegron on the patient's experience of symptoms and changes in HRQL. Patient-reported outcome measures included the Overactive Bladder Questionnaire (OAB

q), Patient Perception of Bladder Condition (PPBC) and Treatment Satisfaction-Visual Analog Scale (TS-VAS). Mirabegron 50 mg led to significant changes in HRQL measures in parallel with the improvements in objective measures of OAB while mirabegron 25 mg offered little benefit to patients based on HRQL measures and other secondary endpoints.

The directional parallelism between the subjective and objective measures for mirabegron 50 mg substantially supports the clinical significance of the effect of mirabegron.

Pooled analyses of the coprimary efficacy endpoints were conducted for multiple subgroup parameters. These analyses supported the efficacy of mirabegron regardless of demographic characteristics, OAB characteristics, intrinsic/extrinsic factors including comorbid conditions or selected concomitant medications or when administered with or without food. Efficacy with mirabegron was demonstrated in patients who were antimuscarinic treatment naive and in patients who failed previous OAB antimuscarinic therapy.

The durability of effect was demonstrated in the 52-week clinical safety study.

5 OVERVIEW OF SAFETY

The results in this section, including those pertaining to AE of interest, support the safety of mirabegron 50 mg in the treatment of patients with OAB.

5.1 Background

5.1.1 Adverse Effects Characteristic of the Pharmacological Class

Published clinical data on the effects of beta 3-AR agonists in humans are limited [Ursino et al, 2009]. Review of this published data did not reveal additional safety concerns beyond the safety profile observed in the mirabegron clinical development program.

Nonclinical pharmacology data for mirabegron, including safety pharmacology data, are summarized in Section 2.4.

5.1.2 Special Approaches to Monitor and Assess for Particular Adverse Events

The safety evaluations performed in the clinical studies conducted as part of the mirabegron clinical development program were consistent with ICH E1A and allow for sufficient characterization and quantification of the safety profile of mirabegron. Safety data were assessed as per ICH E3, M4 and 21CFR§314.50 and associated guidances and included:

- Extent of exposure.
- Summary of AE, SAE and other significant AE.
- Summary of changes in laboratory parameters, including hematology, serum chemistry, thyroid analytes (where available) and urinalysis (where available). Selected laboratory parameters, including frequency of elevated liver parameters and analyses of liver transaminases and total bilirubin consistent with FDA's Guidance for Industry, Drug Induced Liver Injury: Pre-marketing Clinical Evaluation (July 2009), were summarized.
- Summary of changes in vital signs (specifically pulse rate and blood pressure), electrocardiogram (ECG) data and PVR volume (where available).

AE, SAE and discontinuations due to AE were also analyzed for relationship to special groups and populations (demographics and intrinsic/extrinsic factors).

In addition to the assessments for the evaluation of safety as stated above, potential AE of interest for mirabegron were identified and included AE indicative of cardiovascular effects (specifically, QT prolongation, cardiac arrhythmia [including tachycardia and atrial fibrillation] and hypertension), neoplasm, hypersensitivity reactions, glaucoma, syncope, seizures, urinary tract events (including UTIs, urinary retention and urolithiasis), hepatotoxicity and endocrine/metabolic events (including

glucose dysregulation and thyroid dysfunction). These AEs of interest were identified either due to theoretical concerns based on the underlying pharmacology, or observations in nonclinical or clinical data emerging during development of mirabegron or because of requests raised by regulatory authorities.

The rationale for each AE of interest is presented in Table 28.

To support the evaluation of safety, for AE indicative of cardiovascular, neoplasm, hypersensitivity or glaucoma, expert panels were utilized to review and provide an assessment of the events.

- A Cardiovascular Adjudication Committee evaluated deaths and cardiovascular SAE and classified them using APTC/MACE criteria [See section 5.6.1.5.3].
- An Independent Adjudication Committee comprised of oncology specialists evaluated potential neoplasm events [See Section 5.6.3.2].
- An Expert Committee evaluated events associated with hypersentivity [See Section 5.6.4].
- An Expert Panel reviewed any glaucoma-type AE [See Section 5.6.5].

Table 28 Adverse Events of Interest and Rationale

AE of Interest	Rationale
Cardiovascular events including: • Hypertension • QT prolongation or its sequelae • Cardiac arrhythmia, including tachycardia and atrial fibrillation • Cardiac failure • APTC/MACE	• Increases in blood pressure were observed in clinical pharmacology studies in young healthy volunteers. In addition, hypertension was identified by FDA as an area of potential concern at the End-of-Phase 2 meeting. • QT prolongation is an AE of interest in new therapeutic agents, per ICH E14. In addition, QT effects at supratherapeutic mirabegron doses were observed in a posthoc reanalysis of the first TQT study (178-CL-037). • Cardiac arrhythmia is an AE of interest primarily because dose-related increases in HR were observed in nonclinical and clinical studies. Additionally, there is potential for arrhythmogenicity due to QT effects. • Cardiac failure was included as an AE of interest because of possible hemodynamic effects of beta 3 stimulation on cardiac function. • APTC/MACE were included as an AE of interest because of potential mirabegron effects on pulse rate and blood pressure.
Syncope, postural hypotension and falls	Syncope is recommended for review by ICH E14 and was specifically requested as an event of interest by FDA QT-IRT comments on protocols 178-CL-037 and 178-CL-077, as an imbalance in frequency of syncope between treatment groups could signal a potential proarrythmic effect of an investigational drug. This assessment also includes events potentially related to syncope or undocumented arrhythmias, i.e., postural hypotension and falls (including musculoskeletal injuries which may have occurred as the result of falls).
Seizures	Seizures are recommended for review by ICH E14 and were specifically requested as events of interest by FDA QT-IRT comments on protocols 178-CL-037 and 178-CL-077, as an imbalance in frequency of seizures between treatment groups could be a sequelae of a potential proarrythmic effect of an investigational drug.
Urinary tract events including: • UTI • Urinary retention/acute urinary retention • Urolithiasis	Potential risks of treatment in patients with OAB, specifically: • UTIs are frequent comorbid conditions in patients with OAB [Wagner et al, 2002] • Patients with OAB and comorbid conditions that potentially limit bladder outflow may be at risk for urinary retention [Verhamme et al, 2008; Martin-Merino et al, 2009] • Urolithiasis was selected as an AE of interest because treatments that alter detrusor activity and affect urine storage have the potential to facilitate the development of bladder stones.
Hepatotoxicity	Hepatotoxicity was identified by FDA Division of Reproductive and Urologic Product as an area of potential concern at the End-of-Phase 2 meeting, and is a routine area of interest for any small molecule NME. Astellas has completed an extensive safety evaluation of mirabegron in mice, rats, rabbits, dogs and monkeys. Based on these studies, the liver has been identified as a target organ of concern. With respect to the liver, nonclinical findings were observed at systemic exposures well in excess of those achievable at the MHRD.

Table continued on next page.

AE of Interest	Rationale
Endocrine/metabolic events • Glucose dysregulation • Thyroid dysfunction	• In animals, it has been shown that stimulation of beta 3-ARs prevents or corrects hyperglycemia [Himms-Hagen et al, 1996]. Although no significant effect on blood glucose was demonstrated in two 12-week POC studies in patients with type 2 diabetes mellitus, a comprehensive evaluation of the effect of mirabegron on hyperglycemia and hypoglycemia was conducted because of its potential effects on blood glucose. • Based upon FDA feedback regarding one SAE of hypothyroidism in the phase 2 program, a program-wide evaluation was conducted to assess the potential risk of thyroid dysregulation, including reviewing AE within the Thyroid Dysfunction SMQ.
Hypersensitivity reaction	Two cases of potential hypersensitivity reaction in the global mirabegron development program (SAE of reported Stevens-Johnson syndrome in a phase 2 study, eventually classified as urticaria by adjudication committee, and leukocytoclastic vasculitis in a phase 1 study) prompted a comprehensive program-wide evaluation of potential hypersensitivity events.
Glaucoma	As requested by the FDA following the reported 2 SAE of glaucoma, the Sponsor conducted a systematic evaluation of AE representing glaucoma during the mirabegron clinical program. Subsequently, the FDA requested a dedicated study to assess the effect of mirabegron on IOP.
Neoplasms	Nonclinical findings showed that mirabegron was not mutagenic or clastogenic and had no discernible carcinogenic potential in either mice or rats. In Study 178-CL-049, an imbalance of SAE within the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC was observed in the mirabegron 100 mg group compared with the mirabegron 50 mg and tolterodine groups. An imbalance was also observed in Study 178-CL-047 in the mirabegron 50 mg group compared with placebo and mirabegron 100 mg. Based on these clinical observations, a program-wide evaluation of TEAE of neoplasm was conducted.

APTC: Antiplatelet Trialists' Collaboration; AR; adrenoceptor; ICH: International Conference on Harmonisation; IOP: intraocular pressure; IRT: Interdisciplinary Review Team; MACE: major adverse cardiac events; MHRD: maximum recommended human dose; NDA: New Drug Application; NME: new molecular entity; POC: proof of concept; SMQ: Standardized MedDRA Query; TEAE: treatment-emergent adverse event (s); TQT: thorough QT; UTI: urinary tract infection.

5.2 Safety Population

The clinical development program consisted of 41 studies conducted over approximately 10 years involving 10,552 volunteers, patients with OAB, patients with LUTS/ BOO or patients with type 2 diabetes mellitus [Appendix 1, Table 1]. The safety of mirabegron has been investigated in 5863 patients (5648 patients with OAB) in the phase 2/3 studies and 1462 volunteers in phase 1 studies [Table 5]. A total of 622 of the 5648 patients with OAB received mirabegron for at least one year (365 days).

5.2.1 Safety Populations Evaluated

The overall safety evaluation was based on 6 safety populations, 5 populations for phase 2/3 studies and one population for phase 1 studies. This briefing document will focus primarily on the Global OAB 12-week phase 2/3 population, the EU/NA OAB 12-week Phase 3 population and the EU/NA Long-term Controlled Population.

A description and rationale for these populations are given below:

- **Global OAB 12-week Phase 2/3**: This population consists of the 6 placebo-controlled, double-blind, 12-week phase 2/3 studies conducted globally in Europe, North America, Japan and Australia in patients with OAB. Three of the 6 studies also included tolterodine ER 4 mg as an active comparator group. These studies all used the same formulation (OCAS) and had the same duration (12-weeks), design (double-blind placebo-controlled) and indication (OAB). This population was used to provide an estimate of overall safety in placebo-controlled OAB studies.
- **EU/NA OAB 12-week Phase 3**: This population is a subset of the Global OAB 12-week phase 2/3 studies and includes data from 3 placebo-controlled, double-blind, 12-week phase 3

studies conducted in Europe, North America and Australia (henceforth described as EU/NA) in patients with OAB. One of the 3 studies also included tolterodine ER 4 mg as an active comparator group. This subset of studies may offer more precise estimates of certain safety parameters, such as vital signs and AE of hypertension and tachycardia, and contains the patient population most representative of intended users in North America. It is the largest subset of the Global OAB 12-week Phase 2/3 population and will be used as the safety database referred to most often in this document in assessing 12 week safety in the OAB population.

- **EU/NA Long-term Controlled**: This population consists of Study 178-CL-049, a 12-month, double-blind phase 3 study with an active-controlled tolterodine ER 4 mg comparator arm conducted in EU/NA in patients with OAB. This study also included sites in New Zealand and South Africa. Patients who completed Studies 178-CL-046 or 178-CL-047 and met inclusion and exclusion criteria could be rerandomized in Study 178-CL-049 after a 30-day washout period; patients naive to the mirabegron program could also enter Study 178-CL-049. This population was used to evaluate AE associated with extended exposure in the EU/NA population with an active control (tolterodine ER 4 mg). This database will be the primary source of long-term safety analysis in this document because it uses methodology consistent with the EU/NA 12 week OAB studies and because it contains an active control (tolterodine ER 4 mg).

The number of patients in each phase 2/3 study and the number of patients in each population is displayed [Table 5]. For each population, the safety analysis set (SAF) consists of all patients who took at least one dose of study drug.

The EU/NA OAB 12-week Phase 2/3 Population will be presented for overall AE, certain safety parameters and adverse drug reactions. This population offers a more precise estimate for mirabegron safety for the following reasons: methodology for reporting AE data; vital signs and other safety parameters were measured using consistent methodology across these studies; a prospective definition of certain AEs of interest such as hypertension and tachycardia was used across these studies; closest representation of the OAB population that will be using mirabegron in the US; and large number of OAB patients. The EU/NA OAB 12-week Phase 3 Population is the source population for safety data in the proposed product labeling.

Table 29 Overview of Safety Phase 2/3 OAB Study Populations

Study Number	Phase	Duration of Treatment	Population		
			Global OAB 12-week Phase 2/ 3	EU/NA OAB 12-week Phase 3	EU/NA Long-term Controlled
178-CL-044	2	12 weeks	X		
178-CL-045	2	12 weeks	X		
178-CL-046	**3**	**12 weeks**	**X**	**X**	
178-CL-047	**3**	**12 weeks**	**X**	**X**	
178-CL-074	**3**	**12 weeks**	**X**	**X**	
178-CL-048	3	12 weeks	X		
178-CL-049	**3**	**52 weeks (12 months)**	X		**X**

5.2.2 Disposition

5.2.2.1 EU/NA OAB 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, disposition and reasons for discontinuation of study drug were similar for all treatment groups [Table 30].

Table 30 Patient Disposition, EU/NA OAB 12-week Phase 3 Population

n (%) of Patients	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total Mirabegron	
Randomized and took double-blind medication	1380	432	1375	929	2736	495
Completed double-blind treatment period	1205 (87.3%)	387 (89.6%)	1209 (87.9%)	833 (89.7%)	2429 (88.8%)	445 (89.9%)
Discontinued from double-blind treatment period	175 (12.7%)	45 (10.4%)	166 (12.1%)	96 (10.3%)	307 (11.2%)	50 (10.1%)
Primary Reason for discontinuation						
AE	45 (3.3%)	17 (3.9%)	54 (3.9%)	35 (3.8%)	106 (3.9%)	24 (4.8%)
Withdrawal of consent	59 (4.3%)	12 (2.8%)	49 (3.6%)	32 (3.4%)	93 (3.4%)	9 (1.8%)
Lack of efficacy	25 (1.8%)	4 (0.9%)	10 (0.7%)	7 (0.8%)	21 (0.8%)	3 (0.6%)
Protocol violation	14 (1.0%)	3 (0.7%)	15 (1.1%)	10 (1.1%)	28 (1.0%)	3 (0.6%)
Patient lost to follow up	10 (0.7%)	3 (0.7%)	15 (1.1%)	5 (0.5%)	23 (0.8%)	5 (1.0%)
Not fulfilling inclusion or exclusion criteria	6 (0.4%)	1 (0.2%)	6 (0.4%)	1 (0.1%)	8 (0.3%)	4 (0.8%)
Other	16 (1.2%)	5 (1.2%)	17 (1.2%)	6 (0.6%)	28 (1.0%)	2 (0.4%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
AE: adverse event(s); ER: Extended release; OAB: Overactive bladder.

5.2.2.2 EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, disposition and reasons for discontinuation of study drug were similar for all treatment groups [Table 31]. Patients who completed Studies 178-CL-046 and 178-CL-047 were allowed to participate in Study 178-CL-049 study after a 30-day washout period; patients naive to the mirabegron program were also allowed to participate.

Table 31 Patient Disposition, EU/NA Long-term Controlled Population

n (%) of Patients	Mirabegron		Tolterodine ER 4 mg	Total
	50 mg	100 mg		
Randomized and took double-blind study drug	812	820	812	2444
Completed double-blind treatment period	629 (77.5%)	645 (78.7%)	621 (76.5%)	1895 (77.5%)
Discontinued from double-blind treatment period	183 (22.5%)	175 (21.3%)	191 (23.5%)	549 (22.5%)
Primary reason for discontinuation				
Withdrawal of consent	63 (7.8%)	72 (8.8%)	64 (7.9%)	199 (8.1%)
AE	52 (6.4%)	49 (6.0%)	49 (6.0%)	150 (6.1%)
Lack of efficacy	34 (4.2%)	25 (3.0%)	45 (5.5%)	104 (4.3%)
Patient lost to follow up	14 (1.7%)	7 (0.9%)	7 (0.9%)	28 (1.1%)
Protocol violation	6 (0.7%)	9 (1.1%)	11 (1.4%)	26 (1.1%)
Not fulfilling inclusion or exclusion criteria	7 (0.9%)	6 (0.7%)	9 (1.1%)	22 (0.9%)
Other	7 (0.9%)	7 (0.9%)	6 (0.7%)	20 (0.8%)

Study included: 178-CL-049.
AE: adverse event(s); ER: extended release.

5.2.3 Extent of Exposure

5.2.3.1 EU/NA OAB 12-week Phase 3 Population

Study design features are described in Section 4.1.2. Study drug exposure of this population is presented in Table 32.

Table 32 Summary of Drug Exposure, EU/NA OAB 12-week Phase 3 Population

Characteristic n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)	Total (n = 4611)
Duration (days)							
n	1380	432	1375	929	2736	495	4611
Mean (SD)	78.7 (18.87)	79.1 (19.05)	79.3 (18.80)	80.0 (18.46)	79.5 (18.72)	80.6 (17.30)	79.4 (18.62)
Median	84.0	84.0	84.0	84.0	84.0	84.0	84.0
Min, Max	1, 104	1, 102	1, 108	1, 111	1, 111	1, 124	1, 124
Patient-years of exposure							
Total	297.44	93.51	298.46	203.40	595.36	109.29	1002.09

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder.

5.2.3.2 EU/NA Long-term Controlled Population

A total of 622 of the 5648 patients with OAB received mirabegron continuously for at least 52 weeks (365 days). In addition, 1572 patients had at least 6 months (182 days) of continuous exposure and 1482 patients had at least 9 months (274 days) of continuous exposure to mirabegron [Table 6]. Study drug exposure for the EU/NA Long-term Controlled Population is presented in Table 33.

Table 33 Summary of Study Drug Exposure, EU/NA Long-term Controlled Population

Characteristic	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)	Total (n = 2444)
Duration (days)					
Mean (SD)	311.3 (109.87)	313.6 (108.24)	312.4 (109.03)	308.7 (111.48)	311.2 (109.84)
Median	364.0	364.0	364.0	363.0	364.0
Min, Max	2, 391	1, 396	1, 396	1, 415	1, 415
Patient-years of exposure					
Total	691.96	703.94	1395.90	686.33	2082.23

Study included: 178-CL-049. ER: extended release.

5.2.4 Demographics

5.2.4.1 EU/NA OAB 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, demographics were similar across all treatment groups [Table 34].

Table 34 Demographics, EU/NA OAB 12-week Phase 3 Population

Parameter Category/ Statistic	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)	Total (n = 4611)
Gender, n (%)							
n	1380	432	1375	929	2736	495	4611
Female	1002 (72.6%)	293 (67.8%)	982 (71.4%)	675 (72.7%)	1950 (71.3%)	361 (72.9%)	3313 (71.9%)
Male	378 (27.4%)	139 (32.2%)	393 (28.6%)	254 (27.3%)	786 (28.7%)	134 (27.1%)	1298 (28.2%)
Ethnicity, n (%)							
n	886	432	882	433	1747	0	2633
Not Hispanic or Latino	837 (94.5%)	408 (94.4%)	838 (95.0%)	401 (92.6%)	1647 (94.3%)	0	2484 (94.3%)
Hispanic or Latino	49 (5.5%)	24 (5.6%)	44 (5.0%)	32 (7.4%)	100 (5.7%)	0	149 (5.7%)

Table continued on next page.

Parameter Category/ Statistic	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)	Total (n = 4611)
Race, n (%)							
n	1380	432	1375	929	2736	495	4611
White	1274 (92.3%)	394 (91.2%)	1279 (93.0%)	873 (94.0%)	2546 (93.1%)	490 (99.0%)	4310 (93.5%)
Black or African American	84 (6.1%)	32 (7.4%)	66 (4.8%)	38 (4.1%)	136 (5.0%)	3 (0.6%)	223 (4.8%)
Asian	13 (0.9%)	5 (1.2%)	19 (1.4%)	10 (1.1%)	34 (1.2%)	2 (0.4%)	49 (1.1%)
Other	9 (0.7%)	1 (0.2%)	11 (0.8%)	8 (0.9%)	20 (0.7%)	0	29 (0.6%)
Age (years), n							
n	1380	432	1375	929	2736	495	4611
Mean (SD)	59.2 (13.26)	58.5 (12.85)	59.5 (12.71)	59.9 (12.99)	59.5 (12.83)	59.1 (12.89)	59.4 (12.97)
Min, Max	20, 95	22, 85	21, 91	19, 90	19, 91	18, 83	18, 95
Median	60.0	61.0	61.0	61.0	61.0	61.0	61.0
Weight (kg)							
n	1378	432	1375	928	2735	495	4608
Mean (SD)	80.44 (18.422)	83.10 (19.854)	80.32 (18.350)	80.67 (18.574)	80.88 (18.689)	76.93 (14.865)	80.33 (18.271)
Min, Max	44.0, 188.6	45.0, 172.7	41.3, 171.8	42.0, 170.7	41.3, 172.7	47.0, 132.9	41.3, 188.6
Median	78.00	80.40	78.00	78.00	78.20	75.00	78.00
Geographic region †, n (%)							
n	1380	432	1375	929	2736	495	4611
Europe	693 (50.2%)	197 (45.6%)	686 (49.9%)	494 (53.2%)	1377 (50.3%)	495 (100.0%)	2565 (55.6%)
North America	685 (49.6%)	235 (54.4%)	687 (50.0%)	433 (46.6%)	1355 (49.5%)	0	2040 (44.2%)
Southern Hemisphere	2 (0.1%)	0	2 (0.1%)	2 (0.2%)	4 (0.1%)	0	6 (0.1%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder.
† Europe included: Austria, Belarus, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Portugal, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland, United Kingdom and Ukraine; North America included US and Canada; and Southern Hemisphere included: Australia, New Zealand and South Africa.

5.2.4.2 EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, demographics were consistent across treatment groups [Table 35].

Table 35 Demographics, EU/NA Long-term Controlled Population

Parameter Category/Statistic	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)	Total (n = 2444)
Gender, n (%)				
n	812	820	812	2444
Female	602 (74.1%)	608 (74.1%)	600 (73.9%)	1810 (74.1%)
Male	210 (25.9%)	212 (25.9%)	212 (26.1%)	634 (25.9%)
Age (years), n				
n	812	820	812	2444
Mean (SD)	59.2 (12.56)	60.1 (11.92)	59.6 (12.47)	59.6 (12.32)
Min, Max	21, 87	22, 86	21, 87	21, 87
Median	61.0	61.0	61.0	61.0
Race, n (%)				
n	812	820	812	2444
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%)

Table continued on next page.

Parameter Category/Statistic	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)	Total (n = 2444)
Ethnicity, n (%)				
n	812	820	810	2442
Non-Hispanic/Non-Latino	789 (97.2%)	800 (97.6%)	778 (96.0%)	2367 (96.9%)
Hispanic/Latino	23 (2.8%)	20 (2.4%)	32 (4.0%)	75 (3.1%)
Weight (kg)				
n	811	819	809	2439
Mean (SD)	79.94 (18.368)	79.73 (17.722)	79.10 (17.495)	79.59 (17.861)
Min, Max	44.1, 189.5	44.0, 190.9	44.5, 147.0	44.0, 190.9
Median	77.80	77.00	76.00	77.00
Geographic region, n (%)				
n	812	820	812	2444
Europe	517 (63.7%)	512 (62.4%)	520 (64.0%)	1549 (63.4%)
North America	261 (32.1%)	269 (32.8%)	255 (31.4%)	785 (32.1%)
Southern Hemisphere	34 (4.2%)	39 (4.8%)	37 (4.6%)	110 (4.5%)

Study included: 178-CL-049. The denominators for the percentage calculations of categorical variables were the number of patients with nonmissing values.
ER: extended release; US: United States.

5.3 Overall Safety Profile – Common and Nonserious AE

The safety analysis included all patients who took at least one dose of study drug. TEAE are defined as events that start or worsen after the first dose of study drug through 30 days after the last dose of study drug.

5.3.1 Common and Nonserious Adverse Events in Phase 3 Controlled Studies

5.3.1.1 EU/NA OAB 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, the overview of SAE, TEAE and TEAE leading to permanent discontinuation of study drug are presented in Table 36. The most common TEAE (by preferred term [PT]) reported in the total mirabegron group were hypertension and nasopharyngitis [Table 37].

Table 36 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA OAB 12-week Phase 3 Population

n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)
SAE	29 (2.1%)	7 (1.6%)	29 (2.1%)	26 (2.8%)	62 (2.3%)	11 (2.2%)
Drug-related SAE †	6 (0.4%)	3 (0.7%)	7 (0.5%)	3 (0.3%)	13 (0.5%)	6 (1.2%)
TEAE	658 (47.7%)	210 (48.6%)	647 (47.1%)	402 (43.3%)	1259 (46.0%)	231 (46.7%)
Drug-related TEAE †	232 (16.8%)	87 (20.1%)	256 (18.6%)	172 (18.5%)	515 (18.8%)	131 (26.5%)
TEAE leading to permanent d/c of study drug	46 (3.3%)	17 (3.9%)	53 (3.9%)	34 (3.7%)	104 (3.8%)	22 (4.4%)
Drug-related TEAE leading to permanent d/c of study drug †	27 (2.0%)	11 (2.5%)	35 (2.5%)	25 (2.7%)	71 (2.6%)	20 (4.0%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Drug relatedness was based on investigator assessment.
d/c: discontinuation; ER: extended release; OAB: overactive bladder; SAE: serious adverse event(s); TEAE: treatment-emergent adverse event(s).
† Possible or probable, as assessed by the investigator, or records where relationship was missing.

Table 37 Common TEAE (≥ 1% in Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

MedDRA v12.1 PT†, n (%) of Patients	Placebo (n=1380)	Mirabegron 25 mg (n=432)	Mirabegron 50 mg (n=1375)	Mirabegron 100 mg (n=929)	Total Mirabegron (n=2736)	Tolt ER 4 mg (n=495)
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
Hypertension	105 (7.6%)	49 (11.3%)	103 (7.5%)	48 (5.2%)	200 (7.3%)	40 (8.1%)
Nasopharyngitis	35 (2.5%)	15 (3.5%)	54 (3.9%)	25 (2.7%)	94 (3.4%)	14 (2.8%)
UTI	25 (1.8%)	18 (4.2%)	40 (2.9%)	25 (2.7%)	83 (3.0%)	10 (2.0%)
Headache	42 (3.0%)	9 (2.1%)	44 (3.2%)	22 (2.4%)	75 (2.7%)	18 (3.6%)
Dry mouth	29 (2.1%)	8 (1.9%)	23 (1.7%)	23 (2.5%)	54 (2.0%)	50 (10.1%)
Constipation	20 (1.4%)	7 (1.6%)	22 (1.6%)	15 (1.6%)	44 (1.6%)	10 (2.0%)
Diarrhoea	18 (1.3%)	5 (1.2%)	20 (1.5%)	18 (1.9%)	43 (1.6%)	6 (1.2%)
Upper respiratory tract infection	23 (1.7%)	9 (2.1%)	20 (1.5%)	11 (1.2%)	40 (1.5%)	2 (0.4%)
Influenza	19 (1.4%)	3 (0.7%)	19 (1.4%)	16 (1.7%)	38 (1.4%)	7 (1.4%)
Nausea	24 (1.7%)	5 (1.2%)	19 (1.4%)	14 (1.5%)	38 (1.4%)	6 (1.2%)
Sinusitis	19 (1.4%)	3 (0.7%)	19 (1.4%)	10 (1.1%)	32 (1.2%)	3 (0.6%)
Arthralgia	15 (1.1%)	7 (1.6%)	18 (1.3%)	6 (0.6%)	31 (1.1%)	2 (0.4%)
Back pain	23 (1.7%)	7 (1.6%)	14 (1.0%)	10 (1.1%)	31 (1.1%)	7 (1.4%)
Fatigue	14 (1.0%)	6 (1.4%)	17 (1.2%)	7 (0.8%)	30 (1.1%)	9 (1.8%)
Dizziness	12 (0.9%)	10 (2.3%)	13 (0.9%)	6 (0.6%)	29 (1.1%)	8 (1.6%)
Bronchitis	19 (1.4%)	3 (0.7%)	17 (1.2%)	8 (0.9%)	28 (1.0%)	2 (0.4%)
Tachycardia	8 (0.6%)	7 (1.6%)	17 (1.2%)	4 (0.4%)	28 (1.0%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Mira: mirabegron; Tolt ER: tolterodine extended release; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s). † Sorting order: PT, by decreasing frequency of TEAE in total mirabegron group.

The most common TEAE (≥ 3.0% in the Total Mirabegron Group), including severity and treatment relationship, are listed by PT in Table 38.

Table 38 TEAE by PT (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

MedDRA v12.1 PT†, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Total Mira (n = 2736)	Tolterodine ER 4 mg (n = 495)
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
Mild	365 (26.4%)	123 (28.5%)	361 (26.3%)	200 (21.5%)	684 (25.0%)	129 (26.1%)
Moderate	241 (17.5%)	79 (18.3%)	238 (17.3%)	164 (17.7%)	481 (17.6%)	85 (17.2%)
Severe ‡	52 (3.8%)	8 (1.9%)	48 (3.5%)	38 (4.1%)	94 (3.4%)	17 (3.4%)
Drug-related	232 (16.8%)	87 (20.1%)	256 (18.6%)	172 (18.5%)	515 (18.8%)	131 (26.5%)
Hypertension	**105 (7.6%)**	**49 (11.3%)**	**103 (7.5%)**	**48 (5.2%)**	**200 (7.3%)**	**40 (8.1%)**
Mild	82 (5.9%)	39 (9.0%)	77 (5.6%)	31 (3.3%)	147 (5.4%)	32 (6.5%)
Moderate	23 (1.7%)	9 (2.1%)	25 (1.8%)	17 (1.8%)	51 (1.9%)	8 (1.6%)
Severe ‡	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Drug-related	63 (4.6%)	30 (6.9%)	65 (4.7%)	32 (3.4%)	127 (4.6%)	30 (6.1%)
Nasopharyngitis	**35 (2.5%)**	**15 (3.5%)**	**54 (3.9%)**	**25 (2.7%)**	**94 (3.4%)**	**14 (2.8%)**
Mild	25 (1.8%)	11 (2.5%)	36 (2.6%)	10 (1.1%)	57 (2.1%)	8 (1.6%)
Moderate	10 (0.7%)	4 (0.9%)	14 (1.0%)	12 (1.3%)	30 (1.1%)	6 (1.2%)
Severe ‡	0	0	4 (0.3%)	3 (0.3%)	7 (0.3%)	0
Drug-related	0	0	0	1 (0.1%)	1 (< 0.1%)	0
UTI	**25 (1.8%)**	**18 (4.2%)**	**40 (2.9%)**	**25 (2.7%)**	**83 (3.0%)**	**10 (2.0%)**
Mild	15 (1.1%)	10 (2.3%)	27 (2.0%)	16 (1.7%)	53 (1.9%)	5 (1.0%)
Moderate	9 (0.7%)	8 (1.9%)	13 (0.9%)	9 (1.0%)	30 (1.1%)	5 (1.0%)
Severe ‡	1 (0.1%)	0	0	0	0	0
Drug-related	5 (0.4%)	5 (1.2%)	6 (0.4%)	2 (0.2%)	13 (0.5%)	1 (0.2%)

Footnotes continued on next page.

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Drug relatedness was based on investigator assessment.
ER: extended release; mira: mirabegron; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.
† Sorting order: PT, decreasing frequency of TEAE in total mirabegron group.
‡ Severe category includes TEAE with missing severity.

5.3.1.2 EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, the overview of SAE, TEAE and TEAE leading to permanent discontinuation of study drug are presented in Table 39. The most common TEAE by PT (≥ 3.0% in the Total Mirabegron Group), were UTI and hypertension [Table 40].

Table 39 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA Long-term Controlled Population

	Mirabegron			
n (%) of Patients	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
SAE	42 (5.2%)	51 (6.2%)	93 (5.7%)	44 (5.4%)
Drug-related SAE†	10 (1.2%)	4 (0.5%)	14 (0.9%)	5 (0.6%)
TEAE	485 (59.7%)	503 (61.3%)	988 (60.5%)	508 (62.6%)
Drug-related TEAE†	213 (26.2%)	192 (23.4%)	405 (24.8%)	224 (27.6%)
TEAE leading to permanent d/c of study drug	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Drug-related TEAE leading to permanent d/c of study drug†	35 (4.3%)	29 (3.5%)	64 (3.9%)	31 (3.8%)

Study included: 178-CL-049. Drug relatedness was based on investigator assessment.
d/c: discontinuation; ER: extended release; SAE: serious adverse event(s); TEAE: treatment-emergent adverse event(s).
† Possible or probable, as assessed by the investigator, or records where relationship was missing.

Table 40 TEAE by PT (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-term Controlled Population

	Mirabegron			Tolterodine
MedDRA v12.1 PT†, n (%) of Patients	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	ER 4 mg (n = 812)
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
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%)
Drug-related	213 (26.2%)	192 (23.4%)	405 (24.8%)	224 (27.6%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
Mild	61 (7.5%)	64 (7.8%)	125 (7.7%)	61 (7.5%)
Moderate	14 (1.7%)	15 (1.8%)	29 (1.8%)	17 (2.1%)
Severe‡	0	1 (0.1%)	1 (0.1%)	0
Drug-related	43 (5.3%)	50 (6.1%)	93 (5.7%)	42 (5.2%)
UTI	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
Mild	31 (3.8%)	27 (3.3%)	58 (3.6%)	44 (5.4%)
Moderate	16 (2.0%)	16 (2.0%)	32 (2.0%)	8 (1.0%)
Severe‡	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Drug-related	5 (0.6%)	7 (0.9%)	12 (0.7%)	9 (1.1%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
Mild	20 (2.5%)	22 (2.7%)	42 (2.6%)	17 (2.1%)
Moderate	11 (1.4%)	10 (1.2%)	21 (1.3%)	7 (0.9%)
Severe‡	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)
Drug-related	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
Mild	19 (2.3%)	13 (1.6%)	32 (2.0%)	9 (1.1%)
Moderate	9 (1.1%)	12 (1.5%)	21 (1.3%)	10 (1.2%)
Severe‡	5 (0.6%)	1 (0.1%)	6 (0.4%)	1 (0.1%)
Drug-related	18 (2.2%)	14 (1.7%)	32 (2.0%)	14 (1.7%)

Table continued on next page.

MedDRA v12.1 PT†, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
Mild	10 (1.2%)	13 (1.6%)	23 (1.4%)	9 (1.1%)
Moderate	11 (1.4%)	15 (1.8%)	26 (1.6%)	4 (0.5%)
Severe ‡	2 (0.2%)	1 (0.1%)	3 (0.2%)	0
Drug-related	0	1 (0.1%)	1 (0.1%)	0

Study included: 178-CL-049. Drug relatedness was based on investigator assessment.
ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.
† Sorting order: PT, by decreasing frequency of TEAE in total mirabegron group.
‡ Severe category includes TEAE with missing severity. In this population, there were no patients who reported a TEAE with missing severity.

5.3.2 Adverse Drug Reactions

Common AE (> 1% in any mirabegron-dose group) with frequency in mirabegron 50 mg-treated patients numerically higher than placebo in the EU/NA OAB 12-Week Phase 3 Population were evaluated using The Council for International Organizations of Medical Sciences (CIOMS) III/V threshold criteria to determine common adverse reactions where causality was reasonably associated with mirabegron.

Uncommon AE (≥ 0.1% to < 1.0 %, or ≥ 1/1,000 to < 1/100, in any mirabegron-dose group) with relative risk (RR) ≥ 1.5 compared to placebo in the Global OAB 12-week Phase 2/3 or the EU/NA OAB 12-Week Phase 3 Populations were evaluated using CIOMS III/V threshold criteria to determine uncommon adverse reactions. Rare AE (< 0.1%, or < 1/1,000, in any mirabegron-dose group) in the Global Phase 2/3 or Global Phase 1 Populations were evaluated based on clinical review of AE and CIOMS III/V threshold criteria to determine rare adverse reactions.

Adverse drug reactions for mirabegron are summarized in Table 41.

Table 41 Adverse Drug Reactions for Mirabegron 50 mg, EU/NA OAB 12-week Phase 3 Population

System Organ Class MedDRA v12.1	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Very Rare (<1/10,000)
Infections and infestations		Urinary tract infection	Vaginal infection Cystitis		
Eye disorders				Eyelid oedema	
Cardiac disorders		Tachycardia	Palpitations Atrial fibrillation		
Gastrointestinal disorders			Dyspepsia Gastritis	Lip oedema	
Skin and subcutaneous tissue disorders			Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura	
Musculoskeletal and connective tissue disorders			Joint swelling		
Reproductive system and breast disorders			Vulvovaginal pruritis		
Investigations			Blood pressure increased GGT increased AST increased ALT increased		

ALT: alanine transaminase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; OAB: overactive bladder.

5.4 Overall Safety Profile – Discontinuations, Serious Adverse Events and Deaths

5.4.1 Discontinuations

5.4.1.1 EU/NA OAB 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, one or more TEAE leading to permanent discontinuation of study drug was reported in 104/2736 (3.8%) mirabegron, 46/1380 (3.3%) placebo and 22/495 (4.4%) tolterodine patients, with no apparent mirabegron dose response. The most common TEAE (by PT) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 6/2736 [0.2%]; placebo: 3/1380 [0.2%]; tolterodine: 1/495 [0.2%]), headache (mirabegron: 6/2736 [0.2%]; placebo: 5/1380 [0.4%]; tolterodine: 2/495 [0.4%]) and hypertension (mirabegron: 6/2736 [0.2%]; placebo: 2/1380 [0.1%]; tolterodine: 1/495 [0.2%]) [Table 42].

Temporary discontinuation of study drug due to TEAE is presented in Table 43.

Table 42 TEAE Leading to Permanent Discontinuation of Study Drug (Reported by ≥ 0.1% Patients in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

MedDRA (v12.1) SOC PT †, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Total Mirabegron (n = 2736)	Tolt ER 4 mg (n = 495)
Overall	46 (3.3%)	17 (3.9%)	53 (3.9%)	34 (3.7%)	104 (3.8%)	22 (4.4%)
Cardiac disorders	3 (0.2%)	2 (0.5%)	6 (0.4%)	5 (0.5%)	13 (0.5%)	3 (0.6%)
Atrial fibrillation	1 (0.1%)	0	2 (0.1%)	1 (0.1%)	3 (0.1%)	0
Palpitations	1 (0.1%)	1 (0.2%)	0	2 (0.2%)	3 (0.1%)	1 (0.2%)
Tachycardia	0	1 (0.2%)	2 (0.1%)	1 (0.1%)	4 (0.1%)	0
Gastrointestinal disorders	13 (0.9%)	3 (0.7%)	12 (0.9%)	5 (0.5%)	20 (0.7%)	5 (1.0%)
Constipation	3 (0.2%)	1 (0.2%)	2 (0.1%)	3 (0.3%)	6 (0.2%)	1 (0.2%)
Diarrhoea	0	0	3 (0.2%)	0	3 (0.1%)	1 (0.2%)
Gastritis	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Nausea	8 (0.6%)	1 (0.2%)	3 (0.2%)	0	4 (0.1%)	0
Vomiting	3 (0.2%)	0	2 (0.1%)	0	2 (0.1%)	0
General disorders and administration site conditions	6 (0.4%)	3 (0.7%)	8 (0.6%)	4 (0.4%)	15 (0.5%)	3 (0.6%)
Chest pain	3 (0.2%)	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Malaise	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Oedema peripheral	1 (0.1%)	0	2 (0.1%)	1 (0.1%)	3 (0.1%)	0
Pyrexia	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Investigations	2 (0.1%)	3 (0.7%)	6 (0.4%)	2 (0.2%)	11 (0.4%)	0
ALT increased	1 (0.1%)	0	2 (0.1%)	1 (0.1%)	3 (0.1%)	0
AST increased	0	0	2 (0.1%)	1 (0.1%)	3 (0.1%)	0
Blood pressure increased	1 (0.1%)	0	0	2 (0.2%)	2 (0.1%)	0
GGT increased	1 (0.1%)	0	2 (0.1%)	1 (0.1%)	3 (0.1%)	0
Liver function test abnormal	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Nervous system disorders	7 (0.5%)	2 (0.5%)	8 (0.6%)	3 (0.3%)	13 (0.5%)	5 (1.0%)
Dizziness	1 (0.1%)	1 (0.2%)	2 (0.1%)	0	3 (0.1%)	1 (0.2%)
Headache	5 (0.4%)	0	4 (0.3%)	2 (0.2%)	6 (0.2%)	2 (0.4%)
Respiratory, thoracic and mediastinal disorders	3 (0.2%)	0	4 (0.3%)	1 (0.1%)	5 (0.2%)	0
Dyspnoea	2 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Skin and subcutaneous tissue disorders	2 (0.1%)	2 (0.5%)	4 (0.3%)	6 (0.6%)	12 (0.4%)	1 (0.2%)
Rash	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Skin discolouration	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0

Table continued on next page.

MedDRA (v12.1) SOC PT †, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolt ER 4 mg (n = 495)
Vascular disorders	2 (0.1%)	2 (0.5%)	4 (0.3%)	2 (0.2%)	8 (0.3%)	2 (0.4%)
Hypertension	2 (0.1%)	2 (0.5%)	2 (0.1%)	2 (0.2%)	6 (0.2%)	1 (0.2%)
Hypertensive crisis	0	0	2 (0.1%)	0	2 (0.1%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ER: extended release; GGT: gamma-glutamyl transferase; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); tolt: tolterodine.
† Sorting order: alphabetic by SOC and alphabetic by PT.

Table 43 TEAE Leading to Temporary Discontinuation of Study Drug (Reported by ≥ 0.1% Patients in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)
Overall†	13 (0.9%)	5 (1.2%)	12 (0.9%)	14 (1.5%)	31 (1.1%)	9 (1.8%)
Discontinued from Double-blind Treatment Period‡	4 (30.8%)	0	2 (16.7%)	2 (14.3%)	4 (12.9%)	2 (22.2%)
Completed Double-blind Treatment Period‡	9 (69.2%)	5 (100.0%)	10 (83.3%)	12 (85.7%)	27 (87.1%)	7 (77.8%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder.
† Number and percent of subjects with any treatment emergent adverse event leading to temporary discontinuation of study drug.
‡ Completion status percentages are based on the number of subjects displayed in †.

5.4.1.2 EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, one or more TEAE leading to permanent discontinuation of study drug was reported in 98/1632 (6.0%) mirabegron patients (mirabegron 50 mg: 48/812 [5.9%]; mirabegron 100 mg: 50/820 [6.1%]) and 46/812 (5.7%) tolterodine patients. The most common TEAE (by PT) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 9/1632 [0.6%]; tolterodine: 0/812), headache (mirabegron: 9/1632 [0.6%]; tolterodine: 3/812 [0.4%]), dizziness (mirabegron: 6/1632 [0.4%]; tolterodine: 0/812) and hypertension (mirabegron: 6/1632 [0.4%]; tolterodine: 3/812 [0.4%]) [Table 44].

Temporary discontinuation of study drug due to TEAE is presented in Table 45.

Table 44 TEAE Leading to Permanent Discontinuation of Study Drug (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA Long-term Controlled Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Cardiac disorders	4 (0.5%)	4 (0.5%)	8 (0.5%)	7 (0.9%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
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%)
Eye disorders	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Dry eye	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Vision blurred	3 (0.4%)	1 (0.1%)	4 (0.2%)	1 (0.1%)

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MedDRA v12.1 SOC PT†, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Gastrointestinal disorders	14 (1.7%)	9 (1.1%)	23 (1.4%)	11 (1.4%)
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%)
Constipation	7 (0.9%)	2 (0.2%)	9 (0.6%)	0
Dry mouth	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Gastritis	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nausea	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
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
Infections and infestations	6 (0.7%)	2 (0.2%)	8 (0.5%)	3 (0.4%)
UTI	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
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
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
Nervous system disorders	10 (1.2%)	8 (1.0%)	18 (1.1%)	10 (1.2%)
Dizziness	4 (0.5%)	2 (0.2%)	6 (0.4%)	0
Headache	5 (0.6%)	4 (0.5%)	9 (0.6%)	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
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
Rash	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Urticaria	1 (0.1%)	1 (0.1%)	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%)

Study included: 178-CL-049. ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection. † Sorting order: alphabetic by SOC and alphabetic by PT.

Table 45 TEAE Leading to Temporary Discontinuation of Study Drug (Reported by ≥ 0.1% Patients in the Total Mirabegron Group), EU/NA Long-term Controlled Population

n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall†	29 (3.6%)	24 (2.9%)	53 (3.2%)	37 (4.6%)
Discontinued from Double-blind Treatment Period ‡	12 (41.4%)	5 (20.8%)	17 (32.1%)	12 (32.4%)
Completed Double-blind Treatment Period ‡	17 (58.6%)	19 (79.2%)	36 (67.9%)	25 (67.6%)

Study included: 178-CL-049.
ER: extended release; TEAE: treatment-emergent adverse event(s).
† Number and percent of subjects with any TEAE leading to temporary discontinuation of study drug.
‡ Completion status percentages are based on the number of subjects displayed in (†).

5.4.2 SAE

5.4.2.1 EU/NA OAB 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, one or more SAE was reported for 62/2736 (2.3%) total mirabegron patients, 29/1380 (2.1%) placebo patients and 11/495 (2.2%) tolterodine patients, with no apparent mirabegron dose response [Table 46].

Table 46 SAE (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

MedDRA v12.1 SOC PT, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total Mirabegron (n = 2736)	Tolterodine ER 4 mg (n = 495)
Overall	**29 (2.1%)**	**7 (1.6%)**	**29 (2.1%)**	**26 (2.8%)**	**62 (2.3%)**	**11 (2.2%)**
General disorders and admnistrations site conditions	3 (0.2%)	1 (0.2%)	0	3 (0.3%)	4 (0.1%)	0
Chest pain	2 (0.1%)	1 (0.2%)	0	3 (0.3%)	4 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	1 (0.2%)	3 (0.2%)	3 (0.3%)	7 (0.3%)	1 (0.2%)
Prostate cancer	0	0	2 (0.1%)	0	2 (0.1%)	0
Surgical and medical procedures	3 (0.2%)	0	2 (0.1%)	2 (0.2%)	4 (0.1%)	1 (0.2%)
Bunion operation	0	0	0	2 (0.2%)	2 (0.1%)	0
Cardiac disorders	6 (0.4%)	0	5 (0.4%)	4 (0.4%)	9 (0.3%)	1 (0.2%)
Atrial fibrillation	1 (0.1%)	0	3 (0.2%)	2 (0.2%)	5 (0.2%)	0

Studies included: 178-CL-046, 178-CL-47 and 178-CL-74.
ER: extended release; PT: preferred term; SAE: serious adverse event(s).

5.4.2.2 EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, the frequency of reported SAE was similar across all treatment groups [Table 47].

Table 47 SAE (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA Long-term Controlled Population

MedDRA v12.1 SOC PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	42 (5.2%)	51 (6.2%)	93 (5.7%)	44 (5.4%)
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%)
Gastrointestinal disorders	3 (0.4%)	7 (0.9%)	10 (0.6%)	2 (0.2%)
Gastritis	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Upper gastrointestinal haemorrhage	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Infections and infestations	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Abscess intestinal	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Investigations	1 (0.1%)	3 (0.4%)	4 (0.2%)	0
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
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%)
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

Table continued on next page.

MedDRA v12.1 SOC PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
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 polyp	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Surgical and medical procedures	2 (0.2%)	7 (0.9%)	9 (0.6%)	3 (0.4%)
Hysterectomy	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Vascular disorders	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.2%)
Hypertension	1 (0.1%)	1 (0.1%)	2 (0.1%)	0

Study included: 178-CL-049.
ER: extended release; PT: preferred term; SAE: serious adverse event(s).

5.4.3 Deaths

There were 11 deaths in the mirabegron program, including 2 deaths in the ongoing study 178-CL-090 (one death on placebo and one death that occurred prior to randomization). A brief listing of all 11 deaths is presented by assigned dose group in Table 48.

5.4.3.1 Mortality by Treatment Group

Table 49 describes mortality by treatment groups across the mirabegron program.

It should be noted that the 9 deaths in the Global OAB Phase 2/3 Population are the same 9 deaths as in the Global Phase 2/3 Population, and the 5 deaths in the EU/NA Long-term Controlled Population are a subset of the 9. Patients in Study 178-CL-049 were allowed to have participated in a prior 12 week study (Study 178-CL-046 or 178-CL-047). Table 49 displays a combination of treatment in the prior study and treatment in this Study 178-CL-049 with prior treatment listed first.

Overall, mortality per 1000 patients years of mirabegron exposure was comparable to placebo and tolterodine.

Table 48 Listing of Deaths

Study Type	Study	Patient No.	Prior Treatment	Treatment Group	Age	Gender	MedDRA (v12.1) Preferred Term	Onset/ Stop Day (Last Dose Day)	Day of Death	Relationship to Study Drug by Investigator	Adjudicated Term
12-week Program	178-CL-046	3105-1598	--	Tolterodine ER 4mg	74	Male	Ruptured cerebral aneurysm	68/70 (60)	70	Possible	CV death
	178-CL-047	1597-6697	--	Placebo	76	Female	Cardiac arrest	142/142 (86)	142	Not related	CV death
	178-CL-047	1617-6141	--	Mirabegron 100 mg	66	Female	Bladder cancer§	38/99 (49)	99	Not related	Non-CV event
							Colon cancer metastatic	38/99 (49)		Not related	Non-CV event
Long-term (52 weeks) Program)	178-CL-049	1838-6486	Mirabegron 50 mg	Tolterodine ER 4 mg	57	Female	Coronary artery disease	208/208 (208)	208	Not related	CV death
	178-CL-049	2190-6983	Mirabegron 100 mg	Tolterodine ER 4 mg	68	Male	Cerebrovascular accident	62/72 (62)	72	Not related	CV death
							Pneumonia aspiration	62/72 (62)		Not related	CV death
	178-CL-049	3034-2380	--	Mirabegron 50 mg	72	Female	Cardiac failure	190/190 (190)	190	Not related	CV death
	178-CL-049	3063-3438†	--	Mirabegron 50 mg	27	Female	Completed suicide	359/359 (267 E)	359	Possible	Non-CV event
	178-CL-049	1530-6120	--	Mirabegron 50 mg	64	Female	Pneumonia	104/108 (86 E)	108	Possible	Non-CV event
							Acute respiratory failure, Multi-organ failure, Renal vein thrombosis, Staphylococcal sepsis	107/108 (86 E)		Not related	
	178-CL-051	S01503	--	Mirabegron 50 mg/100 mg	59	Female	Aortic dissection	237/237 (224)	237	Not related‡	CV death
Ongoing Studies	178-CL-090	90701	--	Placebo	57	Male	Sudden death	45/45 (44)	45	Not related	CV death
	178-CL-090	90724	--	Prior to randomization	55	Female	Chemical poisoning	8/10 (2)	10	Not related	Non-CV event

--: not applicable; CV: cardiovascular; E: estimated value; ER: extended release.
† Last dose day for this patient was unknown. Based on the estimated last dose day (per imputation rules described in the Statistical Analysis Plan), the death was nontreatment-emergent.
‡ Investigator's causality determination: there was insufficient information at the time of the event because the subject was dead on arrival at the hospital; the Sponsor concluded that the event (aortic dissection), which occurred during study treatment, was not completely unrelated to the study drug.
§ Patient had metastatic colon cancer with local invasion to the bladder.

Table 49 Mortality by Treatment Group

Treatment Group	Total Number of Patients †	Total Number of Deaths ‡	Patient-years of Exposure §	Mortality per 1000 PYE ¶
Global OAB Phase 2/3 Population				
Placebo	2208	1	469.36	2.1
Total mirabegron	5648	5	2555.57	2.0
Tolterodine	1726	3††	902.54	3.3
EU/NA Long-term Controlled Population				
Tolterodine/mirabegron	237	0	211.90	0.0
Mirabegron only	1395	3	1183.99	2.5
Mirabegron/tolterodine	368	2	310.30	6.4
Tolterodine only	444	0	376.03	0.0

Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060 and 178-CL-074.
Treatment groups indicate treatment in prior study (178-CL-046/047) in addition to current study (178-CL-049), with prior treatment listed first. For example, "Tolterodine/mirabegron" indicates tolterodine taken in prior study, mirabegron in current study. "Mirabegron only" indicates patients who took mirabegron in both studies, and those who took mirabegron in current study and either took placebo or did not participate in prior study; "Tolterodine only" is defined similarly.
OAB: overactive bladder; PYE: patient-years of exposure.
† Patients who received more than one type of study drug will be counted under each treatment received.
‡ The total number of deaths includes deaths for all exposed patients collected up to the database lock for each study.
§ PYE is defined as the sum of exposure to study drug expressed in years for all patients within a treatment group; where duration of exposure is the last dosing date - first dosing date + 1. For patients who took the same study drug in more than one study or who took multiple doses of the same study drug within a study, exposure is added together.
¶ Number of deaths for whom person-time is available divided by PYE for each group and multiplied by 1000.
†† Two of the 3 patients received mirabegron in a prior study.

5.5 Overall Safety Profile – Other Safety Parameters

5.5.1 Laboratory Findings

Routine clinical laboratory parameters were collected on patients/volunteers participating in the mirabegron development program. Laboratory data support that mirabegron does not have a clinically meaningful effect on hematological, serum chemistry or urinalysis parameters.

5.5.1.1 Hematology

Potentially clinically significant (PCS) hematology laboratory abnormalities are presented in Table 50 and Table 51. In general, the frequency of these abnormalities were comparable across treatment groups.

Table 50 PCS Hematology Laboratory Abnormalities, EU/NA OAB 12-week Phase 3 Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
Erythrocytes (10^{12}/L)	< 2.5 x 10^{12}/L	0/1334	0/418	0/1329	0/898	0/480
	> 7.0 x 10^{12}/L	0/1334	0/418	0/1329	1/898 (0.1%)	0/480
Hemoglobin (g/L)	< 80 g/L	0/1334	0/418	0/1329	0/898	0/480
	> 180 g/L	2/1334 (0.1%)	0/418	2/1329 (0.2%)	0/898	0/480
Hematocrit (%)	< 25%	0/1334	0/418	0/1329	0/898	0/480
	> 55%	2/1334 (0.1%)	0/418	1/1329 (0.1%)	0/898	0/480
Platelet count (10^9/L)	< 120 x 10^9/L	4/1330 (0.3%)	2/418 (0.5%)	9/1327 (0.7%)	8/897 (0.9%)	3/480 (0.6%)
	> 500 x 10^9/L	4/1330 (0.3%)	3/418 (0.7%)	4/1327 (0.3%)	4/897 (0.4%)	2/480 (0.4%)
Leukocytes (10^9/L)	< 2.5 x 10^9/L	1/1334 (0.1%)	1/418 (0.2%)	3/1329 (0.2%)	1/898 (0.1%)	2/480 (0.4%)
	> 18 x 10^9/L	2/1334 (0.1%)	1/418 (0.2%)	0/1329	1/898 (0.1%)	1/480 (0.2%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
The denominator is the number of patients who had at least one nonmissing value postbaseline.
ER: extended release; PCS: potentially clinically significant.

Table 51 PCS Hematology Laboratory Abnormalities, EU/NA Long-term Controlled Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Mirabegron		Tolterodine ER 4 mg (n = 812)
		50 mg (n = 812)	100 mg (n = 820)	
Erythrocytes (10^{12}/L)	< 2.5 x 10^{12}/L	0/792	0/803	0/791
	> 7.0 x 10^{12}/L	0/792	0/803	0/791
Hemoglobin (g/L)	< 80 g/L	1/792 (0.1%)	1/803 (0.1%)	0/791
	> 180 g/L	0/792	0/803	0/791
Hematocrit (%)	< 25%	0/792	0/803	0/791
	> 55%	1/792 (0.1%)	0/803	0/791
Platelet count (10^9/L)	< 120 x 10^9/L	11/790 (1.4%)	13/799 (1.6%)	11/790 (1.4%)
	> 500 x 10^9/L	5/790 (0.6%)	3/799 (0.4%)	5/790 (0.6%)
Leukocytes (10^9/L)	< 2.5 x 10^9/L	1/792 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	> 18 x 10^9/L	1/792 (0.1%)	0/803	0/791

Study included: 178-CL-049. The denominator is the number of patients who had at least one nonmissing value postbaseline.
ER: extended release; PCS: potentially clinically significant.

5.5.1.2 Chemistry and Urinalysis

Chemistry laboratory data from the clinical program support the hepatic, renal, glucoregulatory and thyroid function safety of mirabegron 50 mg in the treatment of OAB patients.

PCS chemistry laboratory abnormalities are presented in Table 52 and Table 53. In general, the frequency of these abnormalities was comparable across treatment groups; in the case of hepatic enzymes, when elevations were more common with mirabegron than placebo, the frequency of these occurrences was similar to the active comparator.

Table 52 PCS Chemistry Laboratory Abnormalities, EU/NA OAB 12-week Phase 3 Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Placebo (n = 1380)	Mirabegron			Tolterodine ER 4 mg (n = 495)
			25 mg (n = 432)	50 mg (n = 1375)	100 mg (n = 929)	
ALT or AST (U/L)	> 3 x ULN	9/1335 (0.7%)	4/418 (1.0%)	6/1328 (0.5%)	12/898 (1.3%)	6/480 (1.3%)
	> 5 x ULN	2/1335 (0.1%)	1/418 (0.2%)	2/1328 (0.2%)	1/898 (0.1%)	3/480 (0.6%)
	> 10 x ULN	1/1335 (0.1%)	1/418 (0.2%)	0/1328	0/898	1/480 (0.2%)
	> 20 x ULN	1/1335 (0.1%)	0/418	0/1328	0/898	0/480
ALT (U/L)	> 3 x ULN	8/1335 (0.6%)	4/418 (1.0%)	6/1328 (0.5%)	8/898 (0.9%)	5/480 (1.0%)
	> 5 x ULN	2/1335 (0.1%)	1/418 (0.2%)	2/1328 (0.2%)	1/898 (0.1%)	3/480 (0.6%)
	> 10 x ULN	0/1335	1/418 (0.2%)	0/1328	0/898	1/480 (0.2%)
	> 20 x ULN	0/1335	0/418	0/1328	0/898	0/480
AST (U/L)	> 3 x ULN	2/1335 (0.1%)	1/418 (0.2%)	1/1328 (0.1%)	7/898 (0.8%)	2/480 (0.4%)
	> 5 x ULN	1/1335 (0.1%)	1/418 (0.2%)	0/1328	0/898	0/480
	> 10 x ULN	1/1335 (0.1%)	0/418	0/1328	0/898	0/480
	> 20 x ULN	1/1335 (0.1%)	0/418	0/1328	0/898	0/480
ALP (U/L)	> 1.5 x ULN	2/1335 (0.1%)	1/418 (0.2%)	4/1328 (0.3%)	4/898 (0.4%)	2/480 (0.4%)
Bilirubin (mcmol/L)	> 1.5 x ULN	8/1335 (0.6%)	0/418	10/1328 (0.8%)	5/898 (0.6%)	4/480 (0.8%)
	> 2 x ULN	2/1335 (0.1%)	0/418	3/1328 (0.2%)	0/898	2/480 (0.4%)
Glucose (mmol/L)	< 2.5 mmol/L	5/1335 (0.4%)	2/418 (0.5%)	2/1328 (0.2%)	3/897 (0.3%)	0/480
	> 11.1 mmol/L	41/1335 (3.1%)	17/418 (4.1%)	36/1328 (2.7%)	23/897 (2.6%)	10/480 (2.1%)
HbA1c (%)	> 8%	14/1335 (1.0%)	7/418 (1.7%)	25/1328 (1.9%)	18/898 (2.0%)	7/479 (1.5%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
The denominator is the number of patients who had at least one nonmissing value postbaseline.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ER: extended release; GGT: gamma-glutamyltransferase; HbA1c: glycosylated hemoglobin; PCS: potentially clinically significant; ULN: upper limit of normal.

Table 53 PCS Chemistry Laboratory Abnormalities, EU/NA Long-term Controlled Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Mirabegron		Tolterodine ER 4 mg (n = 812)
		50 mg (n = 812)	100 mg (n = 820)	
ALT or AST (U/L)	> 3 x ULN	10/792 (1.3%)	9/803 (1.1%)	7/791 (0.9%)
	> 5 x ULN	2/792 (0.3%)	3/803 (0.4%)	1/791 (0.1%)
	> 10 x ULN	2/792 (0.3%)	0/803	0/791
	> 20 x ULN	1/792 (0.1%)	0/803	0/791
ALT (U/L)	> 3 x ULN	8/792 (1.0%)	8/803 (1.0%)	6/791 (0.8%)
	> 5 x ULN	1/792 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	> 10 x ULN	1/792 (0.1%)	0/803	0/791
	> 20 x ULN	1/792 (0.1%)	0/803	0/791
AST (U/L)	> 3 x ULN	6/792 (0.8%)	5/803 (0.6%)	3/791 (0.4%)
	> 5 x ULN	2/792 (0.3%)	2/803 (0.2%)	0/791
	> 10 x ULN	2/792 (0.3%)	0/803	0/791
	> 20 x ULN	0/792	0/803	0/791
ALP (U/L)	> 1.5 x ULN	3/791 (0.4%)	3/803 (0.4%)	6/791 (0.8%)
Bilirubin (mcmol/L)	> 1.5 x ULN	5/792 (0.6%)	9/803 (1.1%)	3/791 (0.4%)
	> 2 x ULN	1/792 (0.1%)	3/803 (0.4%)	0/791
Glucose (mmol/L)	< 2.5 mmol/L	6/792 (0.8%)	4/803 (0.5%)	0/792
	> 11.1 mmol/L	27/792 (3.4%)	17/803 (2.1%)	17/792 (2.1%)
HbA1c (%)	> 8%	15/792 (1.9%)	15/803 (1.9%)	11/792 (1.4%)

Study included: 178-CL-049.
The denominator is the number of patients who had at least one nonmissing value postbaseline.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ER: extended release; GGT: gamma-glutamyltransferase; HbA1c: glycosylated hemoglobin; PCS: potentially clinically significant; ULN: upper limit of normal.

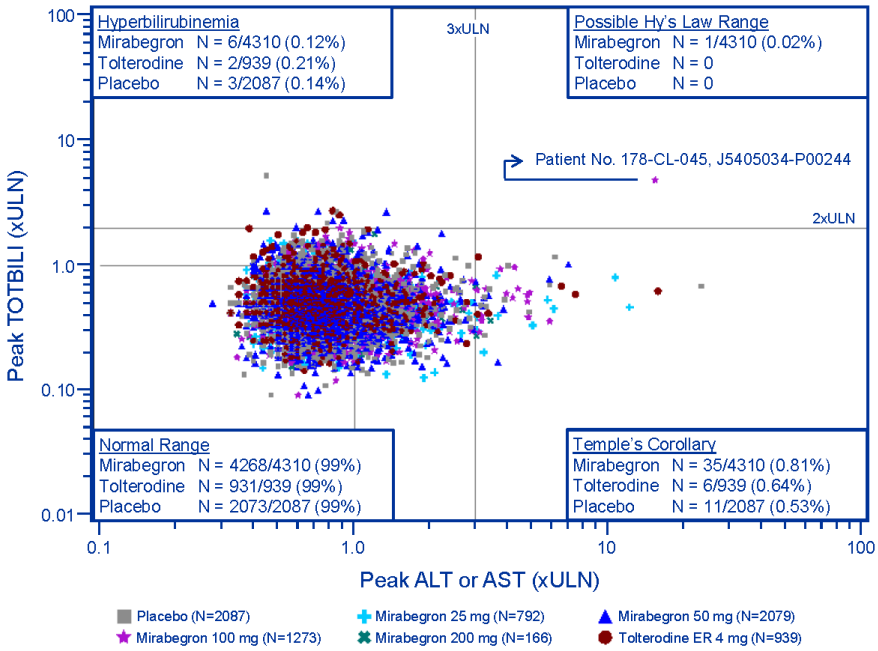
5.5.1.2.1 Hepatotoxicity

Across the entire mirabegron clinical development program, no patient had a 3 x upper limit of normal (ULN) or more transaminase elevation combined with 2 x ULN or more bilirubin elevation in the absence of another underlying cause [Figure 17 and Figure 18]. Two patients had elevations in transaminases 3 x ULN or higher combined with an elevation in total bilirubin 2 x ULN or higher.

- Patient No. 178-CL-045, J5405034-P00244, elevations in transaminases and total bilirubin based on local laboratory data; review by expert hepatologists did not classify this case as consistent with typical drug-induced liver injury (DILI), but rather, a cholestatic pattern of liver chemistry increases possibly in association with drug hypersensitivity [Section 5.6.4]. The patient also took Kyufu Gold, an herbal remedy which contains 600 mg acetaminophen, to treat nasopharyngitis concomitantly with mirabegron [Kyufu Gold package insert, 2009].
- Patient No. 178-CL-049, 3353-1381 in the EU/NA Long-term Controlled Population had these laboratory parameter elevations throughout the study and in the prior study (178-CL-046) where he received tolterodine ER 4 mg. This patient had ongoing viral hepatitis as an alternate etiology and a history of alchohol abuse.

In the Global Phase 2/3 Population, 5/5863 (0.1%) mirabegron-treated patients reported one or more SAE of hepatotoxicity. The most common report was liver function test abnormality and no cases diagnosed as DILI without alternative explanation were reported in the mirabegron clinical development program.

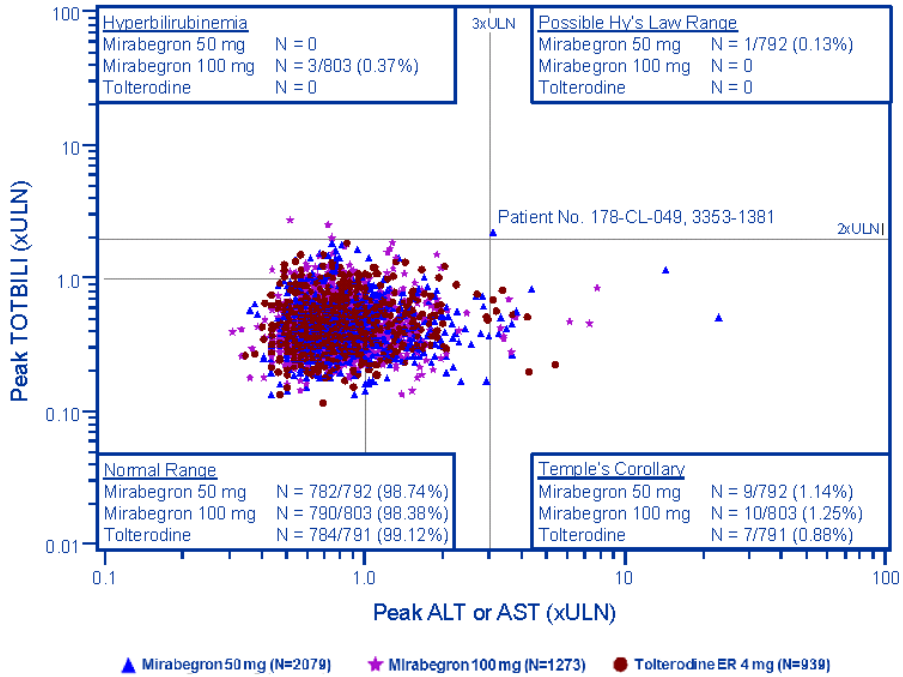
Figure 17 Scatterplot of Peak Total Bilirubin Values by Peak AST or ALT Values, Global OAB 12-Week Phase 2/3 Population



Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.

ALT: alanine transaminase; aspartate transaminase; ER: extended release; OAB: overactive bladder; TOTBILI: total bilirubin; ULN: upper limit of normal.

Figure 18 Scatterplot of Peak Total Bilirubin Values by Peak AST or ALT Values, EU/NA Long-term Controlled Population



Study included: 178-CL-049.

ALT: alanine transaminase; aspartate transaminase; ER: extended release; OAB: overactive bladder; TOTBILI: total bilirubin; ULN: upper limit of normal.

5.5.1.2.2 Glucose Dysregulation and Thyroid Function

The number of patients who met a PCS criterion for blood glucose and glycosylated hemoglobin in the EU/NA OAB 12-week Phase 3 Population and in the EU/NA Long-term Controlled Population were similar across treatment groups [Table 52 and Table 53]. The frequency of hypoglycemia or hyperglycemia TEAE was similar across the treatment groups.

Overall, data from the clinical program do not suggest that mirabegron 50 mg has the potential to cause hyperglycemia or hypoglycemia in OAB patients.

Thyroid function tests (T4 and thyroid stimulating hormone) were measured routinely in Study 178-CL-074. Evaluation of means, shifts from baseline to postbaseline and PCS data for thyroid analytes collected during Study 178-CL-074 did not suggest differences across total mirabegron, placebo and tolterodine treatment groups. Thyroid function TEAE occurred in EU/NA OAB 12-week Phase 3 Population at a comparable frequency across treatment groups. Data from the clinical program support the safety of mirabegron with regard to thyroid associated TEAE and thyroid function.

5.5.1.3 Post Void Residual Volume

In the Global OAB 12-week Phase 2/3 Population, there were no clinically meaningful differences between treatment groups (placebo, mirabegron 25, 50, 100 or 200 mg and tolterodine) in mean changes from baseline to any postbaseline visit in PVR volume [Table 54] or in overall shifts from baseline to postbaseline PVR volume [Appendix 1, Table 27].

Table 54 Change from Baseline to Week 12 and Final Visit in PVR Volume (mL), Global OAB 12-week Phase 2/3 Population

	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolterodine ER 4 mg (n = 958)
Baseline						
n	2130	810	2118	1297	167	956
Mean (SD)	20.2 (35.07)	19.4 (35.58)	20.0 (34.12)	20.6 (33.36)	15.9 (25.24)	16.6 (27.91)
Change from baseline to Week 12						
n	1868	725	1864	1155	147	869
Mean (SD)	-1.3 (35.52)	-2.8 (33.53)	-0.7 (34.82)	-1.1 (34.86)	-2.8 (26.00)	-0.1 (32.18)
95% CI	(-2.9, 0.3)	(-5.3, -0.4)	(-2.3, 0.8)	(-3.1, 0.9)	(-7.1, 1.4)	(-2.3, 2.0)
Change from baseline to Final Visit						
n	1988	760	1964	1208	155	907
Mean (SD)	-1.0 (35.58)	-2.7 (33.09)	-0.7 (35.09)	-0.4 (35.88)	-2.9 (25.67)	0.1 (32.23)
95% CI	(-2.6, 0.6)	(-5.1, -0.3)	(-2.2, 0.9)	(-2.4, 1.6)	(-6.9, 1.2)	(-2.0, 2.2)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
ER: extended release; OAB: overactive bladder; PVR: postvoid residual (volume).

In a urodynamic study in male patients with LUTS/BOO (Study 178-CL-060), mirabegron 50 mg and 100 mg administered ocne daily for 12 weeks did not affect detrusor pressure at maximum urinary flow rate or urinary flow rate in men with LUTS and BOO. A statistically significant increase in PVR volume (31 ± 10.6 mL, P=0.0459) was observed at week 12 with mirabegron 100 mg treatment compared with placebo; no significant changes in PVR volume were observed with mirabegron 50 mg.

Urinary retention TEAE are discussed in Section 5.6.2.

5.5.2 ECGs, Pulse Rate and Blood Pressure

ECGs, pulse rate and blood pressure are described in Section 5.6.1.

5.6 TEAE of Interest

5.6.1 Cardiovascular Safety with Mirabegron

5.6.1.1 Cardiovascular Comorbidities in the Population Evaluated in the Mirabegron Studies

The population studied in the mirabegron OAB trials is representative of the general OAB population with regards to cardiovascular risk factors and concomitant therapies. Publications have described the cardiovascular comorbidities in OAB patients that are age and gender matched to a non-OAB population from the EPIC study and the HealthCore Integrated Research Database (HIRD) [Coyne, Sexton et al, 2008; Andersson et al, 2009]. Diabetes and hypertension were the 2 most common cardiovascular comorbidities in the OAB population with prevalence rates significantly higher than the non-OAB age and gender matched group [Coyne, Sexton et al, 2008 and Andersson et al, 2009].

Baseline demographics and comorbities for OAB patients in the mirabegron program and OAB and non-OAB patients from the HIRD database and EPIC study are presented in Table 55. The mean patient age was higher in the mirabegron studies compared with the typical OAB population from the HIRD database and EPIC study. There were a higher percentage of male patients in mirabegron studies compared with the HIRD database and EPIC study. The percentage of patients with hypertension at baseline was higher in the mirabegron studies compared with OAB populations from the HIRD database and EPIC study. The percentage of patients with diabetes at baseline in the mirabegron OAB studies was similar to that reported in the OAB populations. Additionally, patients in the mirabegron OAB studies received many of the common concomitant medications/classes of medications used to manage these cardiovascular comorbidities [Table 56]. Therefore, the safety of mirabegron has been assessed in a study population that is representative of the OAB population and includes similar or greater prevalence of the 2 most common cardiovascular comorbidities.

Table 55 Cardiovascular Risk Factors in the Mirabegron OAB Population Compared with Populations Evaluated in Other OAB Programs

	EU/NA OAB 12-week Phase 3 (n = 4611)	EU/NA Long-Term Controlled (n = 2444)	HIRD OAB (n = 6607)	HIRD No OAB (n = 6607)	EPIC OAB (n = 1434)	EPIC No OAB (n =1434)
Male Gender	1298 (28.2%)	634 (25.9%)	1102 (16.7%)	1102 (16.7%)	502 (35.0%)	502 (35.0%)
Mean Age (years)	59.4	59.6	50.8	50.8	53.8	53.7
Heart Failure	21 (0.5%)	9 (0.4%)	85 (1.3%)	38 (0.6%)	NR	NR
Hypertension	1776 (38.5%)	969 (39.6%)	1790 (27.1%)	983 (14.9%)	418 (29.3%)	325 (22.7%)
Diabetes	377 (8.2%)	187 (7.7%)	538 (8.1%)	303 (4.6%)	128 (8.9%)	87 (6.1%)

HIRD: Health Core Integrated Database; OAB: overactive bladder; NR: not reported.
Source: Andersson et al. 2009; Coyne, Sexton et al, 2008

Table 56 Concomitant Medications During the Double-Blind Period in Mirabegron OAB Studies

	EU/NA OAB 12-week Phase 3 Population (n = 4611)	EU/NA Long-Term Controlled Population (n = 2444)
ACE/ARB	1311 (28.4%)	714 (29.2%)
Beta Blockers	778 (16.9%)	451 (18.5%)
Calcium Channel Blockers	552 (12.0%)	317 (13.0%)
Diuretics	477 (10.3%)	289 (11.8%)
Lipid Lowering Agents	1317 (28.6%)	631 (25.8%)
Antithrombotics	963 (20.9%)	501 (20.5%)
Antidiabetics	409 (8.9%)	217 (8.9%)

OAB: overactive bladder; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers.

5.6.1.2 Cardiovascular Assessments in Nonclinical and Clinical Studies of Mirabegron

Results from the nonclinical studies showed that increased heart rates were observed after administration of mirabegron in the safety pharmacology and toxicity studies. In the cynomolgus monkey, heart rate measurements were performed in a total of 6 studies. In 4 of those studies, mirabegron was administered orally. A statistically significant increase in heart rate was observed in only one of these studies, the single dose safety pharmacology study, at a dose of 10 mg/kg (heart rate increase of 27.7% vs vehicle treated controls). This dose resulted in a systemic exposure that was 6.3-fold higher than the human systemic exposure at the MRHD. In the remaining monkey studies, no significant heart rate increases were observed at doses up to 30 mg/kg (systemic exposures 5.4- to 16.4-fold higher than the human exposure at MRHD). Inconsistent elevations of heart rates were described in individual animals; however, these reports were not reproducible in other animals, other studies, or in the same animals at different observation time points. These data indicate that the heart rate effects of mirabegron varied by species and that mirabegron administered orally was associated with an increase in heart rate at supratherapeutic dose.

Diastolic pressures were not altered following oral administration of mirabegron to conscious dogs, however, systolic and mean arterial blood pressures were significantly decreased at doses of 0.3 to 10 mg/kg (human equivalent dose 0.2 to 6.5-fold the MRHD). In contrast, neither the safety pharmacology study nor the single dose oral pharmacology study in conscious cynomolgus monkeys, showed significant alterations in blood pressure (systolic, diastolic, or mean arterial blood pressures) when compared with vehicle treated controls at doses up to 100 mg/kg (human equivalent dose 38.4-fold the MRHD).

The Phase 3 mirabegron studies for the treatment of OAB included a comprehensive assessment of heart rate and blood pressure. Patients in the EU/NA OAB 12-week Phase 3 Population (Studies 178-CL-046, 178-CL-047 and 178-CL-074) and the EU/NA Long-term Controlled Population (Study 178-CL-049), were provided an automatic blood pressure monitoring device and asked to collect 3 consecutive measurements of pulse and blood pressure in both the morning and afternoon for 5 consecutive days prior to each study visit and record these data in a diary. This resulted in the collection of 935,561 pulse rate measures, 935,950 systolic blood pressure measurements and 935,745 diastolic blood pressure measurements in these 4 studies. These measurements were analyzed per the methodology described by Verberk et al [2006] to provide AM/PM values for each visit. Table 57 depicts the methods for calculating the mean pulse and blood pressure measurement for each visit during the 12-week studies; the same methodology was used for the long-term study. This approach was chosen based on the high correlation of this technique with ambulatory blood pressure measurements.

To supplement and corroborate the assessments by the patients, additional vital signs were collected during study office visits using both the patient's automatic blood pressure device and the study office device. Only the patient diary data are included herein. ECG measurements were routinely assessed for the EU/NA OAB 12-week Phase 3 Population at screening and week 12 and for the EU/NA Long-term Controlled Population at screening, month 6 and month 12. In addition, for the EU/NA Long-term Controlled Population, continuous 24 hour ambulatory blood pressure monitoring was assessed in a subset of patients at baseline, month 6 and month 12.

A summary of pulse rate and blood pressure data from the healthy volunteer studies is provided in Appendix 3.

Table 57 Scheme of Values Included in Calculation of Average Vital Sign Values for Each Visit and Time of Day (Diary Data) for EU/NA OAB 12-week Phase 3 Studies

Morning/ Afternoon	Sequence	Visit																			
		Baseline					Week 4					Week 8					Week 12				
		Diary Day					Diary Day					Diary Day					Diary Day				
		1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
AM	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	2	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
	3	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
PM	1	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	2	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●
	3	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●	○	○	●	●	●

The 6 shaded values are averaged to calculate the visit value.
○: An individual vital sign measurement that was not included in the calculation of a patient's average value per visit and time of day.
●: An individual vital sign measurement that was included in the calculation of a patient's average value per visit and time of day.
OAB: overactive bladder

The analysis of the pulse and blood pressure data are presented separately for central tendency, regression analysis of the exposure response, outlier analyses and assessment of reported AE.

5.6.1.3 Pulse Rate Assessments

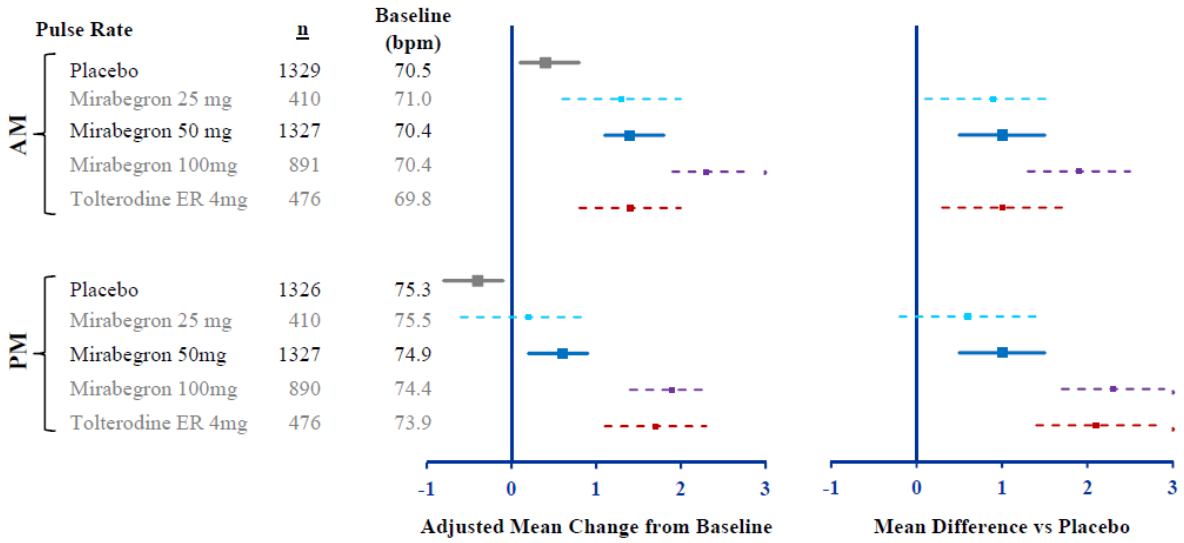
5.6.1.3.1 Analysis of Covariance Results Based on Central Tendency

The adjusted mean change from baseline to final visit and adjusted mean difference vs placebo for changes from baseline to final visit measured in the patient's diary using an analysis of covariance (ANCOVA) model was summarized for pulse rate for the EU/NA OAB 12-week Phase 3 Population [Figure 19] and EU/NA Long-term Controlled Population [Figure 20].

In the EU/NA OAB 12-week Phase 3 Population for AM measurements, dose-dependent increases from baseline in adjusted mean difference vs placebo of 0.9, 1.0, 1.9 and 1.0 bpm were observed for mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. For PM measurements, dose-dependent increases from baseline in adjusted mean difference vs placebo of 0.6, 1.0, 2.3 and 2.1 bpm were observed for mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. Mirabegron 50 mg was comparable to tolterodine for AM measures; mirabegron 100 mg was comparable to tolterodine for PM measures. Increases from baseline in adjusted mean difference vs placebo for all treatment groups for AM/PM pulse rate values had 95% CI excluding zero, with the exception of PM values for the mirabegron 25 mg group.

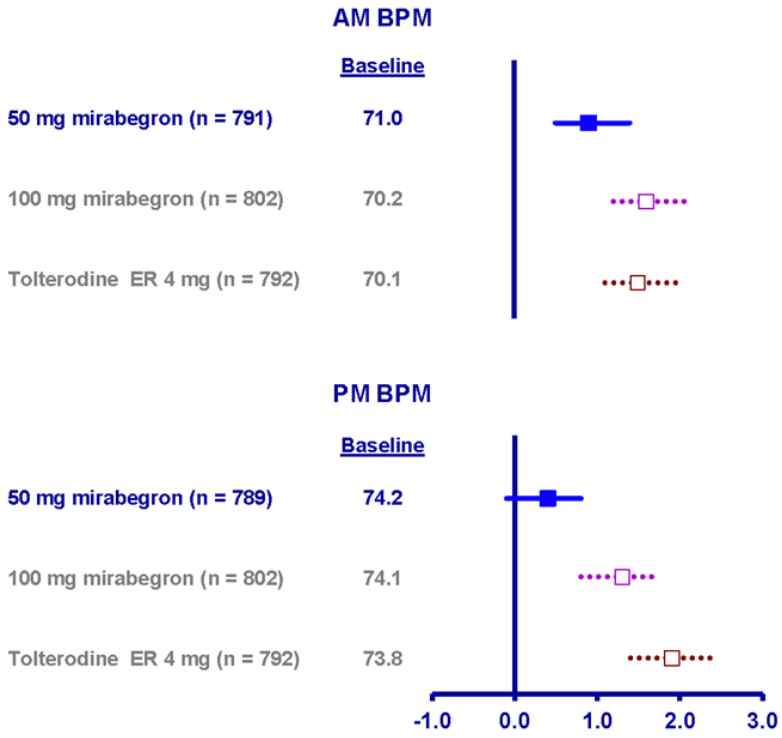
For the EU/NA Long-term Controlled Population, overall, an increase in adjusted mean change from baseline for pulse rate was observed across all treatment groups for both AM/PM measurements. For AM measurements, adjusted mean changes from baseline of 0.9, 1.6 and 1.5 bpm were observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. For PM measurements, adjusted mean changes from baseline of 0.4, 1.3 and 1.9 bpm were observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. Increases in adjusted mean change from baseline for all treatment groups for AM/PM pulse rate values had 95% CI excluding zero with the exception of PM values for the mirabegron 50 mg group.

Figure 19 Change from Baseline to Final Visit for Pulse Rate, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled analysis results are from an ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute; ER: extended release; OAB: overactive bladder.

Figure 20 Change from Baseline to Final Visit for Pulse Rate, EU/NA Long-term Controlled Population



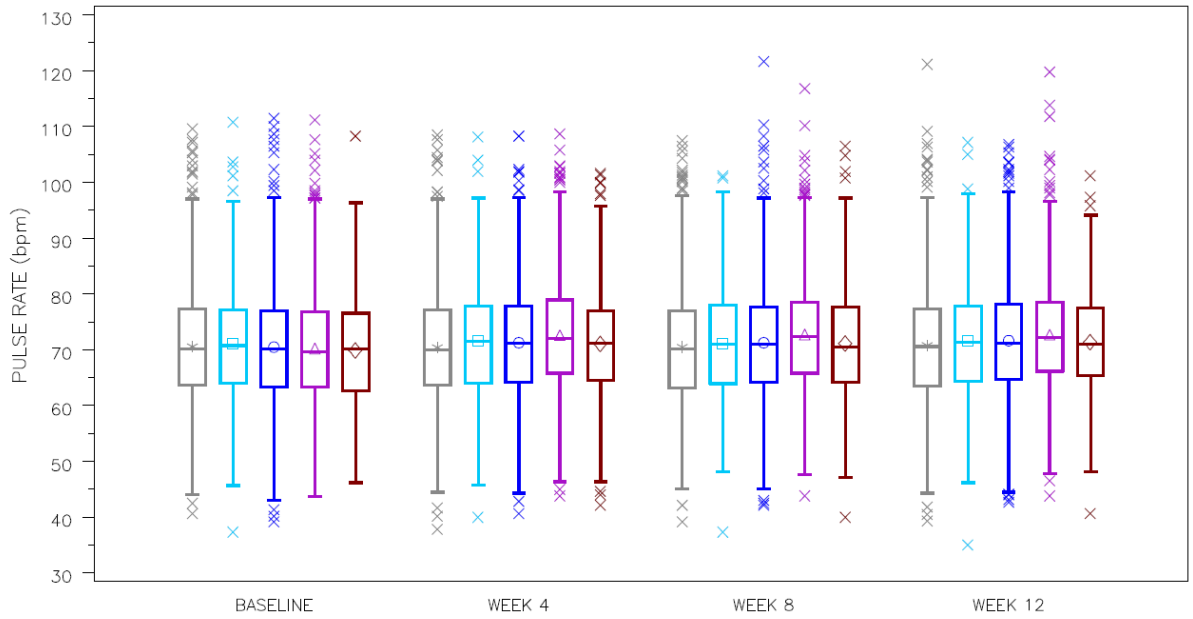
Study included: 178-CL-049.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline. The adjusted mean change from baseline and 95% CI were calculated using an ANCOVA model with treatment group, gender, previous study history and expanded geographical region as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute; ER: extended release.

For the EU/NA OAB 12-week Phase 3 Population, AM/PM pulse rate values and change from baseline to each visit are displayed in Figure 21 and Figure 22. The display uses a box-and-whisker approach. The box spans the pulse rate values between the first quartile (25th percentile) and the third quartile (75th percentile). Median pulse rate values are indicated by the line within the box and mean pulse rate values are indicated by the symbol within the box. The whisker from the box extends to the smallest observation not more than 1.5 times the interquartile range below the 25th percentile and largest observation that are not more than 1.5-times the interquartile range above the 75th percentile. Pulse rate values outside the range of the whiskers are shown individually as the symbol x. Scatterplots illustrating the maximum change from baseline values versus baseline values are displayed in Figure 23, with the x axis representing the baseline value and the y axis the maximum change from baseline value.

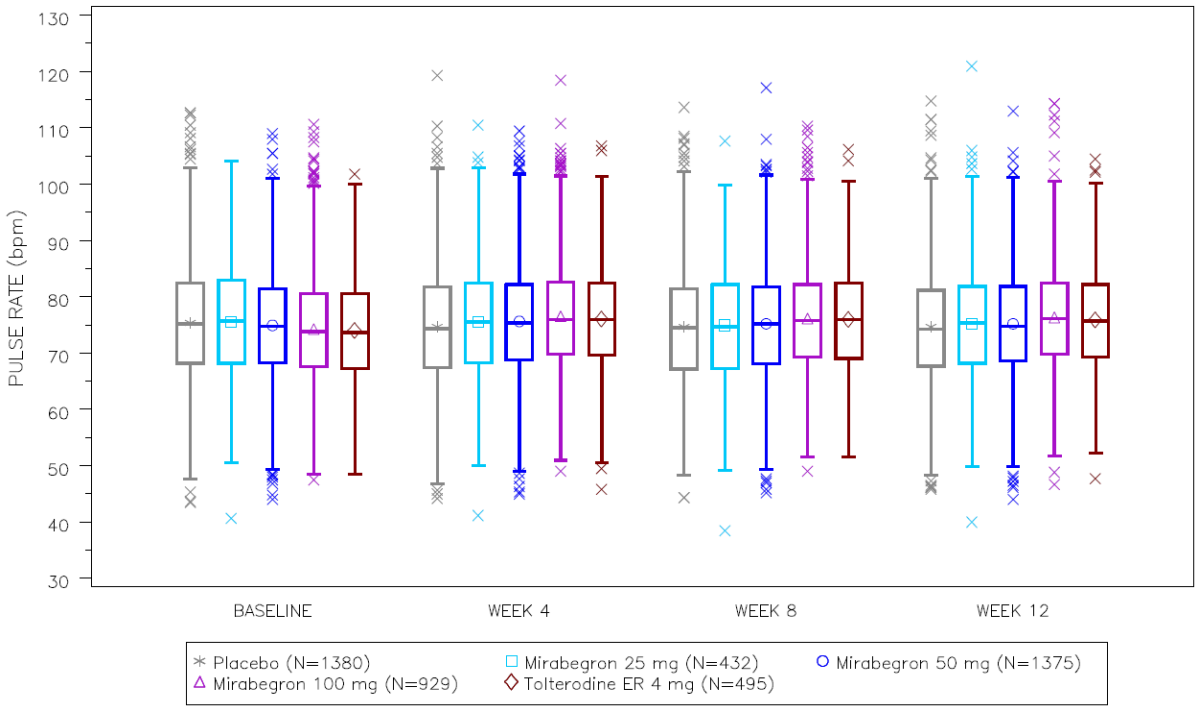
This analysis was also performed for the EU/NA Long-term Controlled Population, AM/PM pulse rate values, change from baseline to each visit value and the maximum change from baseline value are displayed in Figure 24, Figure 25 and Figure 26, respectively.

Figure 21 Boxplots of AM and PM Pulse Rate Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) AM



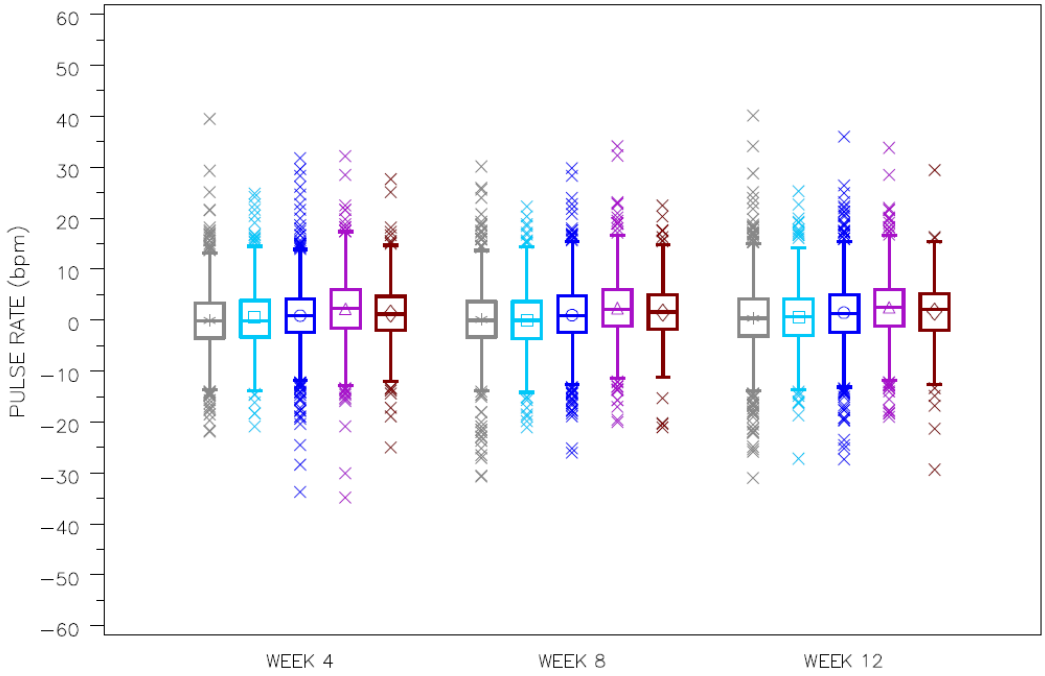
(B) PM



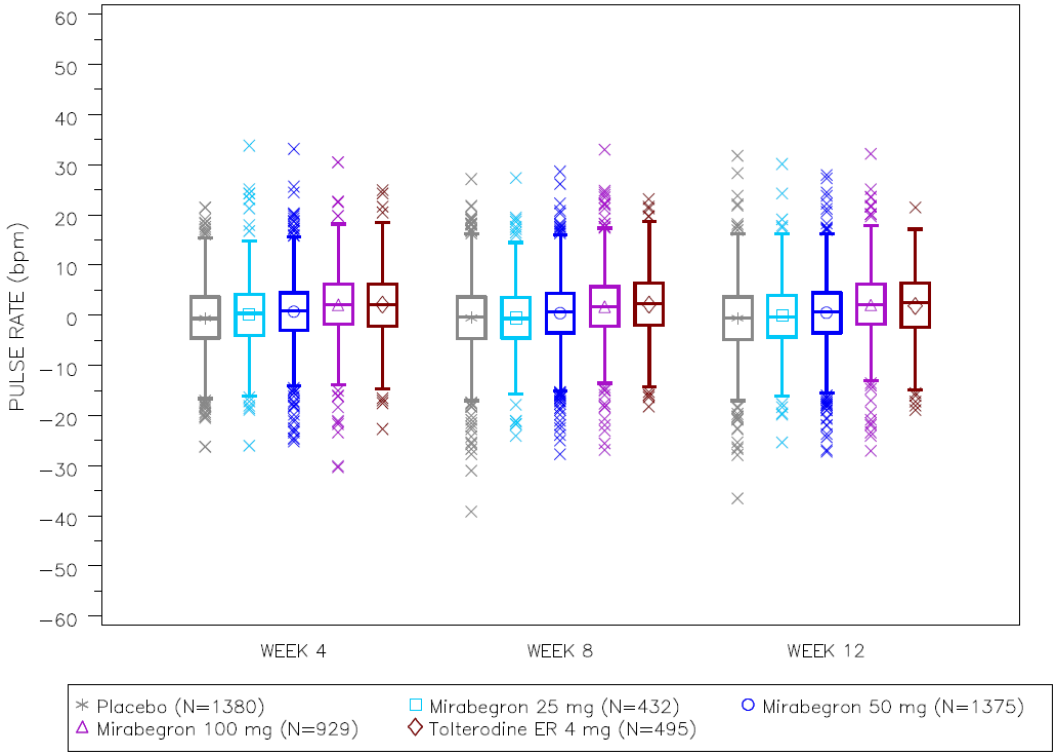
Studies included 178-CL-046, 178-CL-047 and 178-CL-074.
ER; extended release; OAB: overactive bladder.

Figure 22 Boxplots of Change from Baseline in AM and PM Pulse Rate Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) AM



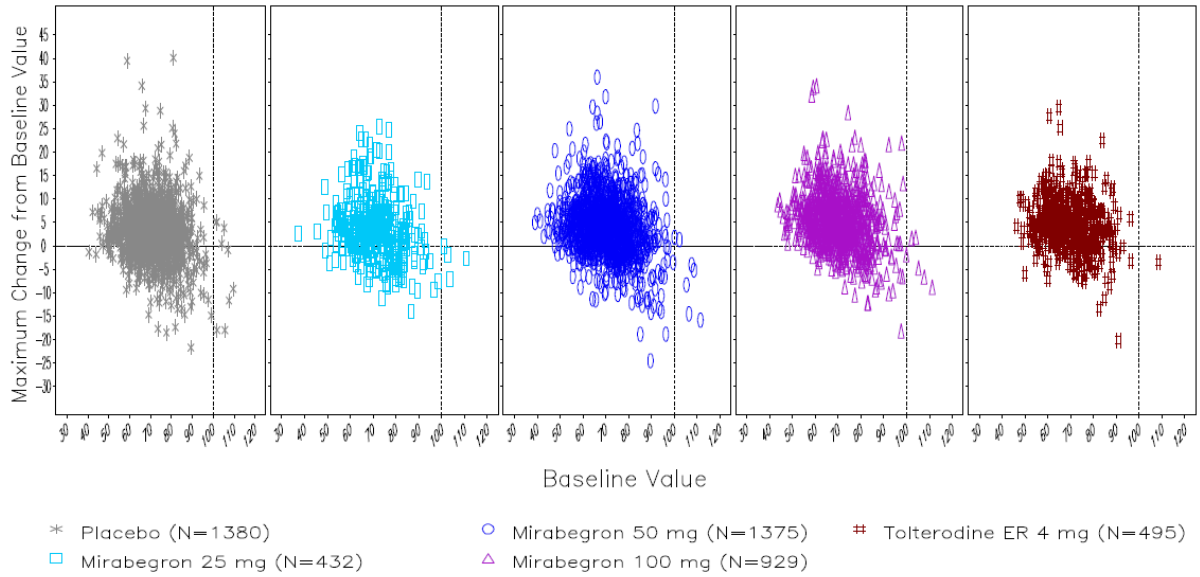
(B) PM



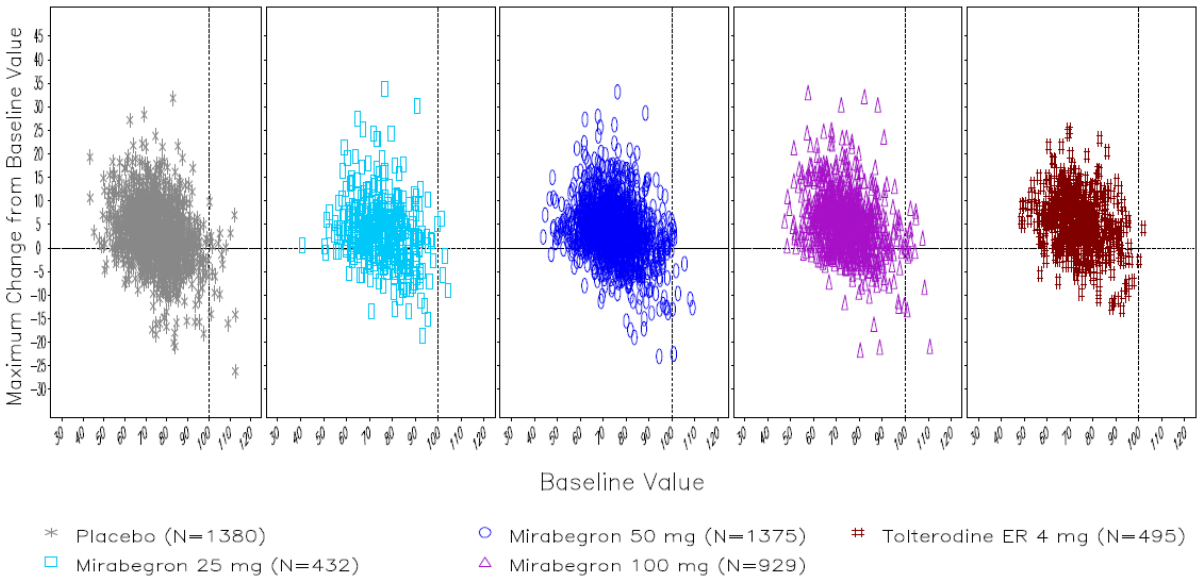
Studies included 178-CL-046, 178-CL-047 and 178-CL-074.
ER; extended release; OAB: overactive bladder.

Figure 23 Scatterplots of Maximum Change from Baseline Values versus Baseline Values in AM and PM Pulse Rate, EU/NA OAB 12-week Phase 3 Population

(A) AM



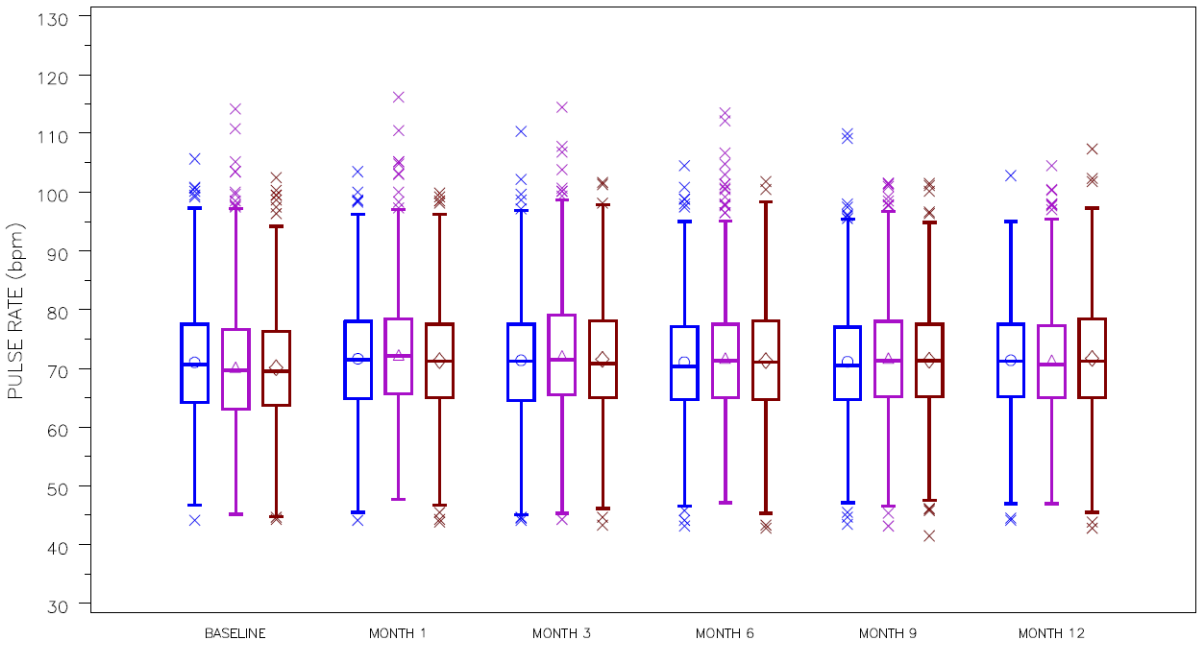
(B) PM



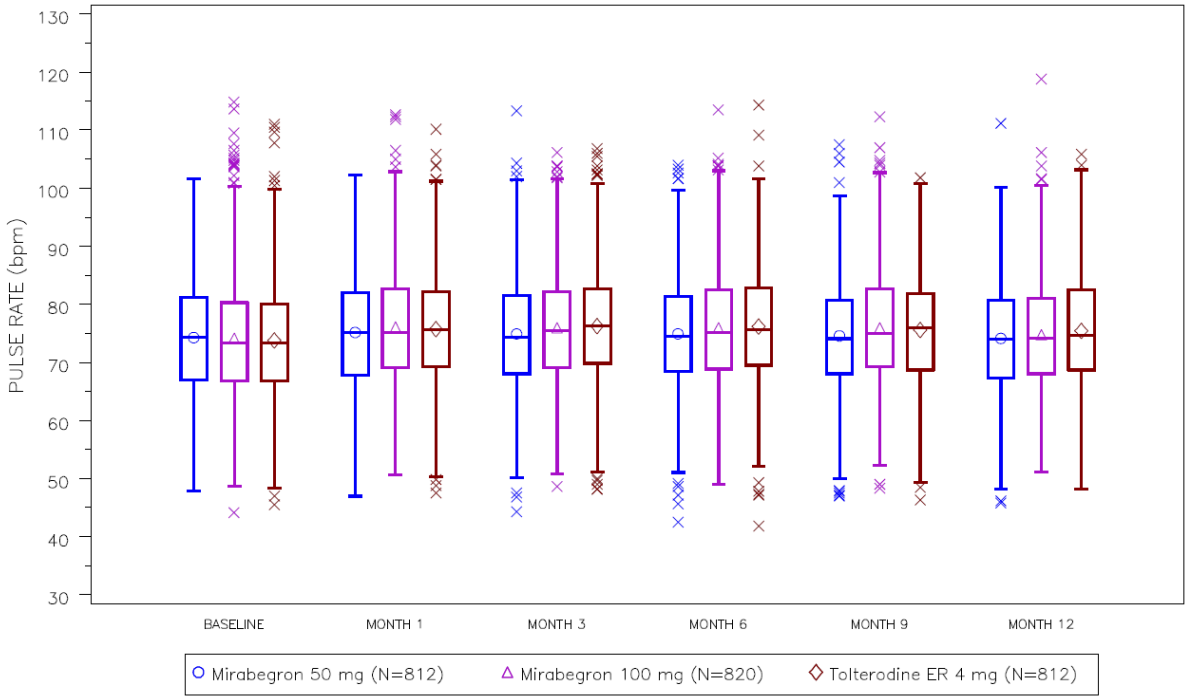
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder.

Figure 24 Boxplots of AM and PM Pulse Rate Values at Each Visit, EU/NA Long-term Controlled Population

(A) AM



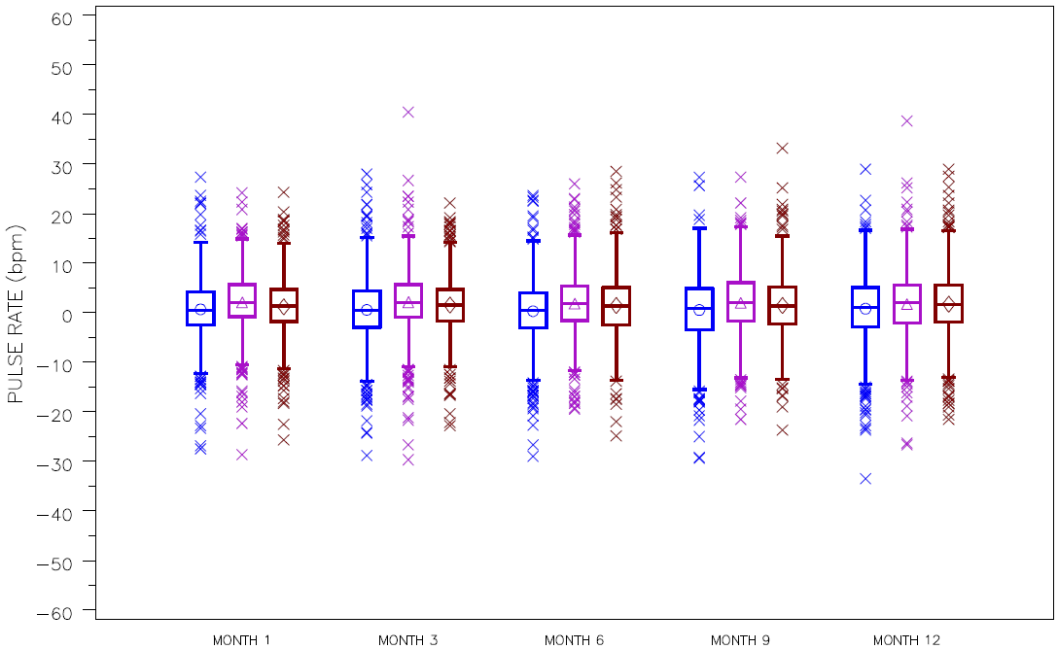
(B) PM



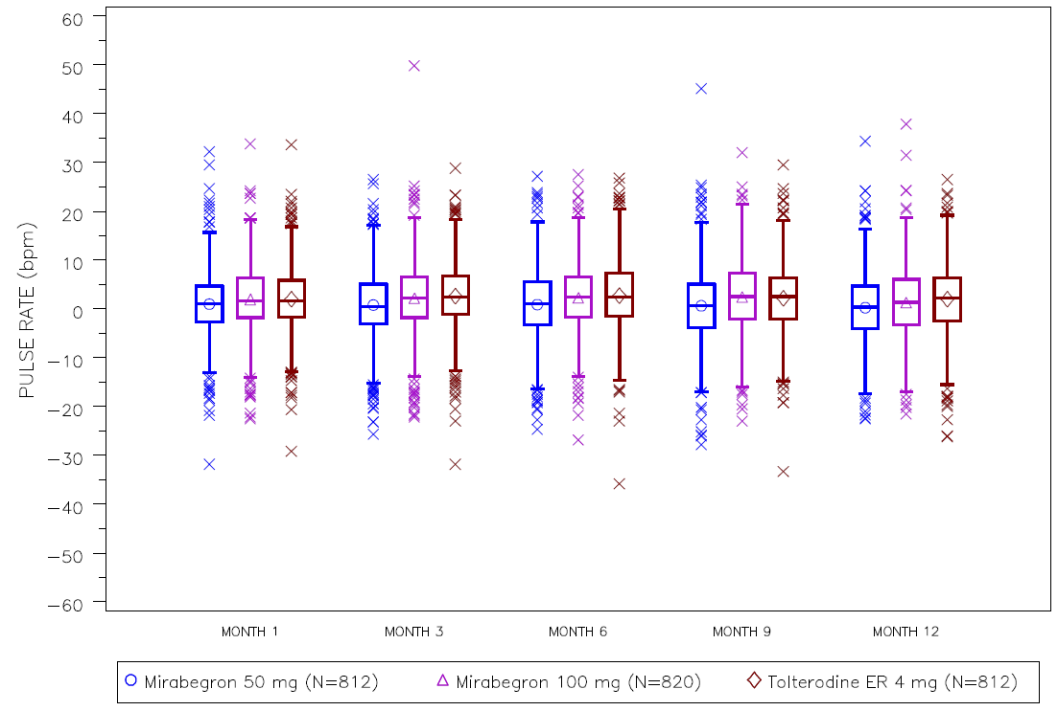
Study included: 178-CL-049.
ER; extended release.

Figure 25 Boxplot of Change from Baseline in AM and PM Pulse Rate Values at Each Visit, EU/NA Long-term Controlled Population

(A) AM



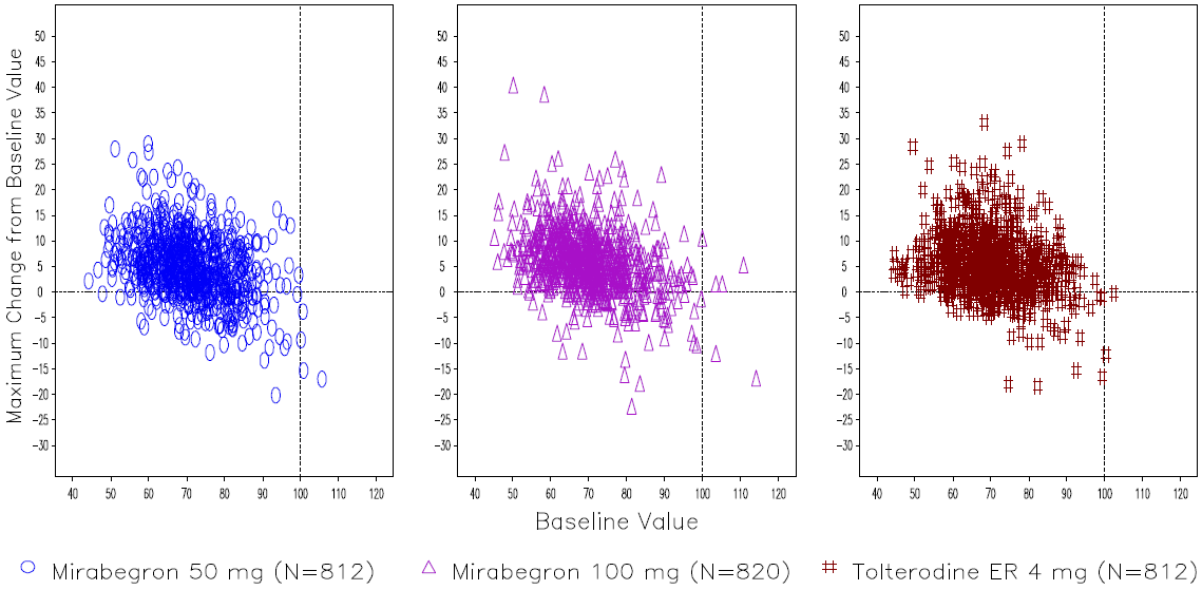
(B) PM



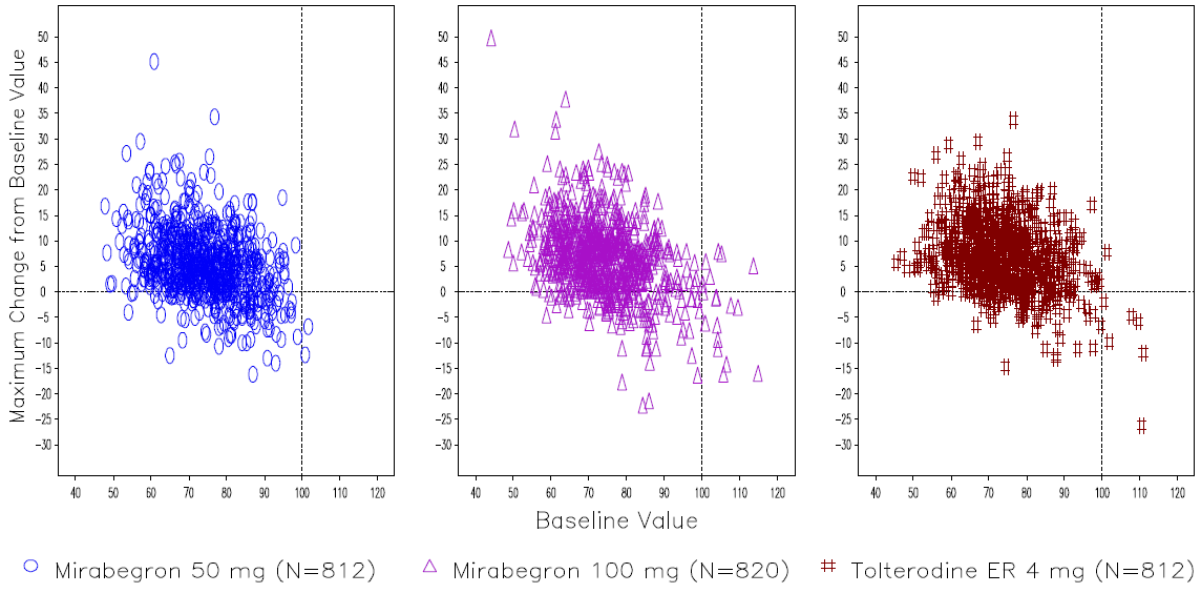
Study included: 178-CL-049.
ER: extended release.

Figure 26 Scatterplots of Maximum Change from Baseline Values versus Baseline Values in AM and PM Pulse Rate, EU/NA Long-term Controlled Population

(A) AM



(B) PM



Study included: 178-CL-049.
Bpm: beats per minute; ER: extended release.

5.6.1.3.2 Exposure Response for Pulse Rate

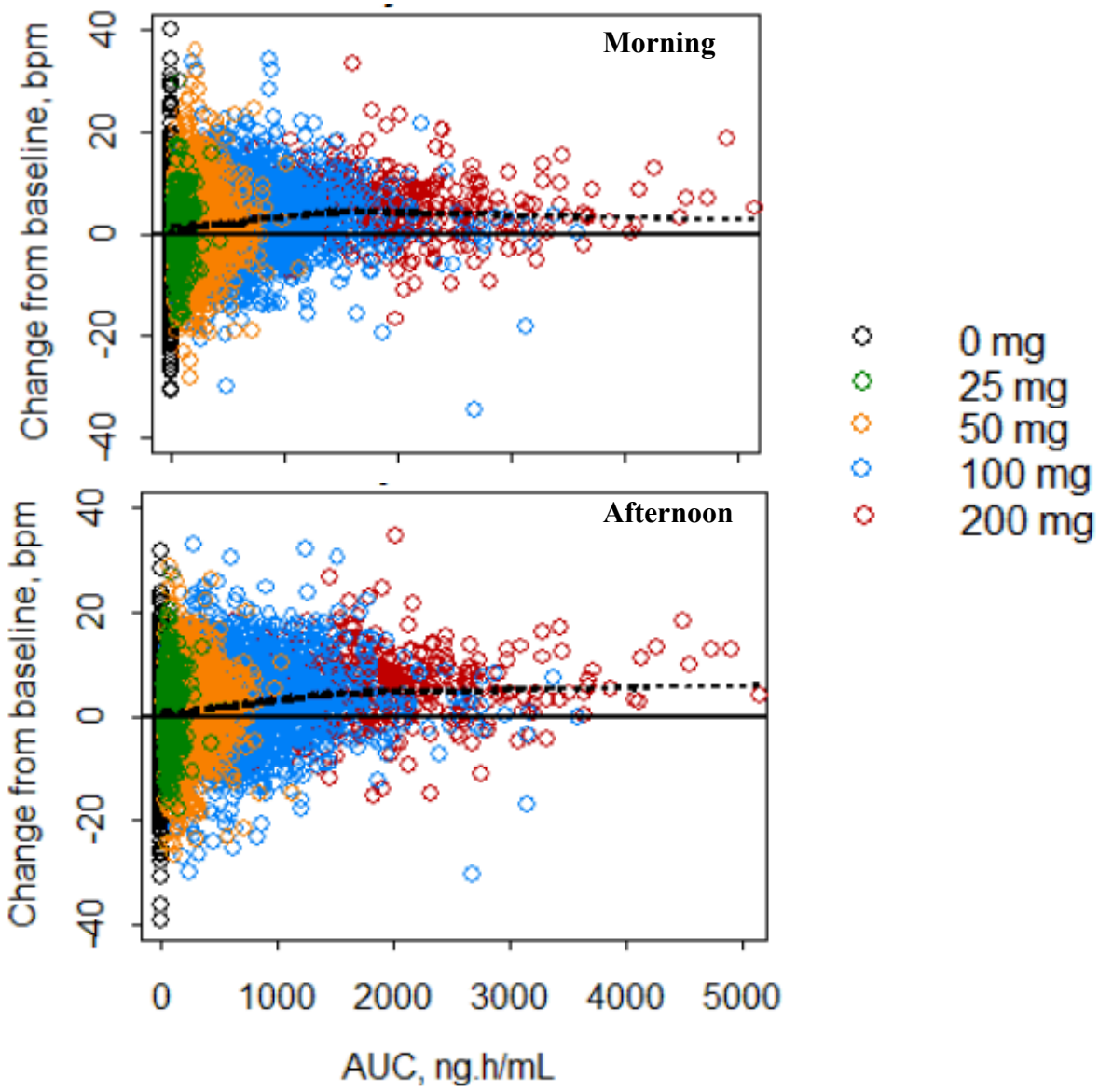
Analyses were conducted to determine the impact of mirabegron exposure as measured by AUC on the change from baseline in pulse rate (Study 178-PK-016). The population PK/PD model for pulse rate consisted of a 'baseline' model that described the morning and afternoon pulse rate during the run-in period, a 'placebo' model that described the placebo effect additive to the baseline during the treatment period (afternoon only) and a 'drug' E_{max} (maximum response) model additive to the baseline and placebo model that described the relationship between mirabegron exposure (AUC) and

pulse rate increase. The parameters of the 'drug' E_{max} model were E_{max} and AU_{50} (the AUC that gives rise to half the maximum response).

The final estimated value for E_{max} was 6.97 bpm (95% CI: 5.38 to 8.56 bpm). The final estimated value for AU_{50} was 1086 ng•hr/mL (95% CI: 721 to 1635 ng•hr/mL).

Regression analysis exposure response for pulse rate in patients with OAB confirmed the trend for increasing change from baseline pulse rate with increasing mirabegron AUC [Figure 27].

Figure 27 Graphical Analysis of AUC vs Change from Baseline in Pulse Rate



Figures represent the individual AM/PM pulse rate changes from baseline as a function of mirabegron AUC (log scale) in patients with OAB from Studies 178-CL-044, 178-CL-046 and 178-CL-047.
IOVAUC values are the individual specific AUC data. The dashed black lines represent smooths through the data. The solid black line represents no change from baseline.
OAB: overactive bladder.

5.6.1.3.3 Categorical Analysis of Increases from Baseline in Pulse Rate

Table 58 and Table 59 summarize the number and percent of patients whose AM/PM pulse rate measurements met selected criteria at final visit or at 2 or 3 consecutive visits for the EU/NA OAB 12-week Phase 3 Population and EU/NA Long-term Controlled Population, respectively.

For the EU/NA OAB 12-week Phase 3 Population, in general, a higher proportion of patients treated with mirabegron met criteria for increases from baseline in pulse rate than placebo patients [Table 58]. The proportion of patients who met criteria for increases from baseline in pulse rate for mirabegron 25 and 50 mg was generally similar to tolterodine, while the proportion of patients who met criteria for mirabegron 100 mg was higher than tolterodine.

For the EU/NA Long-term Controlled Population, dose-related changes in the percentages of patients meeting selected AM and PM pulse rate criteria were generally observed in the mirabegron groups [Table 59]. The proportion of patients treated with mirabegron 50 mg who met criteria for increases in pulse rate was lower than that observed for tolterodine, while the proportion of patients who met criteria for mirabegron 100 mg was similar or higher than tolterodine.

Table 58 Patients Whose AM or PM Pulse Rate Measurements Met Selected Criteria, EU/NA OAB 12-week Phase 3 Population

Parameter, n/n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
AM					
Final visit					
Change from baseline ≥ 10 bpm	81/1329 (6.1%)	34/410 (8.3%)	123/1327 (9.3%)	92/891 (10.3%)	32/476 (6.7%)
3 consecutive postbaseline visits					
Change from baseline ≥ 2 bpm	171/1196 (14.3%)	61/387 (15.8%)	247/1202 (20.5%)	265/821 (32.3%)	106/439 (24.1%)
Change from baseline ≥ 5 bpm	77/1196 (6.4%)	25/387 (6.5%)	87/1202 (7.2%)	98/821 (11.9%)	40/439 (9.1%)
Change from baseline ≥ 10 bpm	13/1196 (1.1%)	4/387 (1.0%)	13/1202 (1.1%)	16/821 (1.9%)	4/439 (0.9%)
Change from baseline ≥ 15 bpm	4/1196 (0.3%)	0/387	2/1202 (0.2%)	3/821 (0.4%)	1/439 (0.2%)
2 consecutive postbaseline visits					
Change from baseline ≥ 2 bpm	344/1242 (27.7%)	116/396 (29.3%)	444/1247 (35.6%)	390/852 (45.8%)	188/463 (40.6%)
Change from baseline ≥ 5 bpm	165/1242 (13.3%)	55/396 (13.9%)	193/1247 (15.5%)	198/852 (23.2%)	92/463 (19.9%)
Change from baseline ≥ 10 bpm	32/1242 (2.6%)	16/396 (4.0%)	37/1247 (3.0%)	41/852 (4.8%)	12/463 (2.6%)
Change from baseline ≥ 15 bpm	9/1242 (0.7%)	7/396 (1.8%)	6/1247 (0.5%)	10/852 (1.2%)	3/463 (0.6%)
PM					
Final visit					
Change from baseline ≥ 10 bpm	81/1326 (6.1%)	25/410 (6.1%)	103/1327 (7.8%)	92/890 (10.3%)	47/476 (9.9%)
3 consecutive postbaseline visits					
Change from baseline ≥ 2 bpm	167/1194 (14.0%)	52/387 (13.4%)	234/1201 (19.5%)	225/820 (27.4%)	126/439 (28.7%)
Change from baseline ≥ 5 bpm	61/1194 (5.1%)	16/387 (4.1%)	83/1201 (6.9%)	97/820 (11.8%)	62/439 (14.1%)
Change from baseline ≥ 10 bpm	12/1194 (1.0%)	1/387 (0.3%)	12/1201 (1.0%)	20/820 (2.4%)	8/439 (1.8%)
Change from baseline ≥ 15 bpm	1/1194 (0.1%)	0/387	1/1201 (0.1%)	4/820 (0.5%)	1/439 (0.2%)
2 consecutive postbaseline visits					
Change from baseline ≥ 2 bpm	317/1239 (25.6%)	111/396 (28.0%)	398/1247 (31.9%)	358/851 (42.1%)	211/463 (45.6%)
Change from baseline ≥ 5 bpm	151/1239 (12.2%)	53/396 (13.4%)	194/1247 (15.6%)	187/851 (22.0%)	128/463 (27.6%)
Change from baseline ≥ 10 bpm	35/1239 (2.8%)	9/396 (2.3%)	42/1247 (3.4%)	56/851 (6.6%)	28/463 (6.0%)
Change from baseline ≥ 15 bpm	6/1239 (0.5%)	2/396 (0.5%)	6/1247 (0.5%)	7/851 (0.8%)	3/463 (0.6%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
bpm: beats per minute; ER: extended release; OAB: overactive bladder.

Table 59 Patients Whose AM or PM Pulse Rate Measurements Met Selected Criteria, EU/NA Long-term Controlled Population

Parameter, n/n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
AM			
Final visit			
Change from baseline ≥ 10 bpm	63/791 (8.0%)	72/802 (9.0%)	68/792 (8.6%)
3 consecutive postbaseline visits			
Change from baseline ≥ 2 bpm	179/686 (26.1%)	268/704 (38.1%)	217/683 (31.8%)
Change from baseline ≥ 5 bpm	69/686 (10.1%)	112/704 (15.9%)	87/683 (12.7%)
Change from baseline ≥ 10 bpm	14/686 (2.0%)	20/704 (2.8%)	19/683 (2.8%)
Change from baseline ≥ 15 bpm	6/686 (0.9%)	1/704 (0.1%)	2/683 (0.3%)
2 consecutive postbaseline visits			
Change from baseline ≥ 2 bpm	331/742 (44.6%)	396/741 (53.4%)	373/735 (50.7%)
Change from baseline ≥ 5 bpm	161/742 (21.7%)	208/741 (28.1%)	177/735 (24.1%)
Change from baseline ≥ 10 bpm	29/742 (3.9%)	57/741 (7.7%)	46/735 (6.3%)
Change from baseline ≥ 15 bpm	10/742 (1.3%)	9/741 (1.2%)	13/735 (1.8%)
PM			
Final Visit			
Change from baseline ≥ 10 bpm	59/789 (7.5%)	91/802 (11.3%)	89/792 (11.2%)
3 consecutive postbaseline visits			
Change from baseline ≥ 2 bpm	204/685 (29.8%)	280/704 (39.8%)	269/683 (39.4%)
Change from baseline ≥ 5 bpm	102/685 (14.9%)	151/704 (21.4%)	129/683 (18.9%)
Change from baseline ≥ 10 bpm	28/685 (4.1%)	29/704 (4.1%)	38/683 (5.6%)
Change from baseline ≥ 15 bpm	4/685 (0.6%)	4/704 (0.6%)	3/683 (0.4%)
2 consecutive postbaseline visits			
Change from baseline ≥ 2 bpm	329/742 (44.3%)	427/741 (57.6%)	416/735 (56.6%)
Change from baseline ≥ 5 bpm	178/742 (24.0%)	253/741 (34.1%)	246/735 (33.5%)
Change from baseline ≥ 10 bpm	48/742 (6.5%)	73/741 (9.9%)	86/735 (11.7%)
Change from baseline ≥ 15 bpm	17/742 (2.3%)	15/741 (2.0%)	18/735 (2.4%)

Study included: 178-CL-049.
bpm: beats per minute; ER: extended release.

5.6.1.3.4 Subgroup Analyses of Pulse Rate Data

For the EU/NA OAB 12-week Phase 3 Population, mean change from baseline to final visit in AM/PM pulse rate is presented in [Appendix 2, Figure 12] for age; [Appendix 2, Figure 13] for gender, race and ethnicity; [Appendix 2, Figure 14] for BMI and geographic region; [Appendix 2, Figure 15] for baseline hypertension status; and [Appendix 2, Figure 16] for baseline concomitant use of alpha antagonist therapy and concomitant use of beta blocker therapy.

Female patients had generally larger changes in pulse rate consistent with their higher exposure following oral administration of mirabegron in the EU/NA OAB 12-week Phase 3 Population, although this finding was inconsistent across treatment groups and AM/PM measurements. In some analyses, younger patients had a larger change in pulse rate than older patients. Concomitant beta blocker therapy reduced the effect of mirabegron on pulse rate. None of the remaining subgroup analyses were remarkable for differences in the effect on pulse rate.

5.6.1.3.5 AE Related to Changes in Pulse Rate

The overall occurrence of tachycardia events in the EU/NA OAB 12-week Phase 3 Population, either based on TEAE or observations of pulse rates captured by patient diary is summarized in Table 60. The occurrence of tachycardia was higher in the mirabegron treatment groups than in the placebo and tolterodine treatment groups. No trends by dose for patients in the mirabegron groups were observed in the occurrence of TEAE and tachycardia based on vital signs.

In the EU/NA Long-term Controlled Population, the overall occurrence of tachycardia events either based on TEAE or observations of pulse rates captured by patient diary is summarized in Table 61. A dose-related trend for both TEAE of tachycardia and tachycardia based on vital signs was observed

for patients in the mirabegron groups. The occurrence of TEAE and tachycardia based on vital signs in the tolterodine group was similar to or higher than either of the mirabegron treatment groups.

Table 60 Combined Summary of Tachycardia Events Based on TEAE and Pulse Rate, EU/NA OAB 12-week Phase 3 Population

Type of Event Event, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Any occurrence of tachycardia	43 (3.1%)	21 (4.9%)	52 (3.8%)	43 (4.6%)	116 (4.2%)	16 (3.2%)
Tachycardia as TEAE	9 (0.7%)	10 (2.3%)	18 (1.3%)	7 (0.8%)	35 (1.3%)	3 (0.6%)
Atrial tachycardia	0	0	0	1 (0.1%)	1 (< 0.1%)	0
Sinus tachycardia	0	3 (0.7%)	0	1 (0.1%)	4 (0.2%)	2 (0.4%)
Supraventricular tachycardia	1 (< 0.1%)	0	1 (< 0.1%)	1 (0.1%)	2 (< 0.1%)	0
Tachycardia	8 (0.6%)	7 (1.6%)	17 (1.2%)	4 (0.4%)	28 (1.0%)	0
Tachycardia paroxysmal	0	0	0	0	0	1 (0.2%)
Tachycardia as pulse rate ≥ 100 bpm	36 (2.6%)	15 (3.5%)	39 (2.8%)	36 (3.9%)	90 (3.3%)	13 (2.6%)
Tachycardia as TEAE and pulse rate ≥ 100 bpm	2 (0.1%)	4 (0.9%)	5 (0.4%)	0	9 (0.3%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Pulse rate tachycardia was based on vital signs diary measurements, defined as an average pulse rate ≥ 100 bpm at any postbaseline visit in the AM and/or PM diary measurements.
AE: adverse event(s); bpm: beats per minute; ER: extended release; OAB: overactive bladder.

Table 61 Combined Summary of Tachycardia Events Based on TEAE and Pulse Rate, EU/NA Long-term Controlled Population

MedDRA v12.1 Type of Event Event, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Any occurrence of tachycardia	25 (3.1%)	49 (6.0%)	74 (4.5%)	53 (6.5%)
Tachycardia as TEAE	10 (1.2%)	19 (2.3%)	29 (1.8%)	26 (3.2%)
Sinus tachycardia	1 (0.1%)	0	1 (< 0.1%)	1 (0.1%)
Tachycardia	8 (1.0%)	19 (2.3%)	27 (1.7%)	25 (3.1%)
Tachyarrhythmia	1 (0.1%)	0	1 (< 0.1%)	0
Tachycardia as pulse rate ≥ 100 bpm	19 (2.3%)	35 (4.3%)	54 (3.3%)	32 (3.9%)
Tachycardia as TEAE and pulse rate ≥ 100 bpm	4 (0.5%)	5 (0.6%)	9 (0.6%)	5 (0.6%)

Study included: 178-CL-049.
Pulse rate tachycardia was based on vital signs diary measurements, defined as an average pulse rate ≥ 100 bpm at any postbaseline visit in the AM and/or PM diary measurements.
AE: adverse event(s); bpm: beats per minute; ER: extended release.

TEAE, SAE and TEAE leading to discontinuation of study drug based on the Standardized MedDRA Query (SMQ) of cardiac arrhythmias are summarized for the Global OAB 12-week Phase 2/3 Population and the EU/NA Long-term Controlled Population in Table 62 and Table 63, respectively.

In the Global OAB 12-week Phase 2/3 Population, the overall frequency of cardiac arrhythmia TEAE was lower in the placebo group (39/2142 [1.8%]) than in the mirabegron or tolterodine treatment groups (mirabegron 25 mg: 25/811 [3.1%]; mirabegron 50 mg: 55/2131 [2.6%]; mirabegron 100 mg: 31/1305 [2.4%]; mirabegron 200 mg: 11/167 [6.6%]; and tolterodine: 30/958 [3.1%]) [Table 62]. The most common TEAE in the Global OAB 12-week Phase 2/3 Population for the total mirabegron group were tachycardia (46/4414 [1.0%]) and palpitations (26/4414 [0.6%]). The proportion of patients with atrial fibrillation noted as a TEAE was 2/2142 (0.1%), 0/811 (0.0%), 5/2131 (0.2%),

4/1305 (0.3%), 1/167 (0.6%) and 2/958 (0.2%) in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. Of the 10/4414 (0.2%) patients in the total mirabegron group who experienced a TEAE of atrial fibrillation, 5/4414 (0.1%) were SAE and 3/4414 (0.1%) led to discontinuation of study drug.

In the EU/NA Long-term Controlled Population, the overall frequency of cardiac arrhythmia TEAE was higher in the tolterodine group (49/812 [6.0%]) compared with the mirabegron treatment groups (mirabegron 50 mg: 32/812 [3.9%] and mirabegron 100 mg: 34/820 [4.1%]) [Table 63]. The higher proportion of patients with TEAE of cardiac arrhythmias in the tolterodine group compared with the mirabegron groups was partially attributable to the higher frequency of reported tachycardia in the tolterodine group, which occurred in 8/812 (1.0%), 19/820 (2.3%) and 25/812 (3.1%) of patients in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Of the 4/1632 (0.2%) patients in the total mirabegron group who experienced a TEAE of atrial fibrillation, 2/1632 (0.1%) were SAE; none led to discontinuation of study drug.

A listing of all patients with an SAE of atrial fibrillation and/or TEAE adjudicated as atrial fibrillation is provided in Appendix 1, Table 15.

Table 62 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the SMQ of Cardiac Arrhythmias, Global OAB 12-week Phase 2/3 Population

MedDRA v 12.1 Category PT, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolterodine ER 4 mg (n = 958)
Patients with any cardiac arrhythmia TEAE	39 (1.8%)	25 (3.1%)	55 (2.6%)	31 (2.4%)	11 (6.6%)	122 (2.8%)	30 (3.1%)
Tachycardia	8 (0.4%)	10 (1.2%)	23 (1.1%)	7 (0.5%)	6 (3.6%)	46 (1.0%)	1 (0.1%)
Palpitations	4 (0.2%)	7 (0.9%)	12 (0.6%)	5 (0.4%)	2 (1.2%)	26 (0.6%)	4 (0.4%)
Supraventricular extrasystoles	6 (0.3%)	2 (0.2%)	5 (0.2%)	5 (0.4%)	0	12 (0.3%)	7 (0.7%)
Atrial fibrillation	2 (0.1%)	0	5 (0.2%)	4 (0.3%)	1 (0.6%)	10 (0.2%)	2 (0.2%)
Patients with cardiac arrhythmia SAE	3 (0.1%)	0	3 (0.1%)	3 (0.2%)	0	6 (0.1%)	1 (0.1%)
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Atrioventricular block first degree	1 (< 0.1%)	0	0	0	0	0	0
Loss of consciousness	1 (< 0.1%)	0	0	0	0	0	0
Patients discontinued study drug due to cardiac arrhythmia TEAE	3 (0.1%)	2 (0.2%)	6 (0.3%)	8 (0.6%)	0	16 (0.4%)	3 (0.3%)
Palpitations	2 (0.1%)	1 (0.1%)	1 (< 0.1%)	3 (0.2%)	0	5 (0.1%)	1 (0.1%)
Tachycardia	0	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Atrial fibrillation	1 (< 0.1%)	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)	0
Atrioventricular block first degree	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Conduction disorder	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
ECG abnormal	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1%)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
PTs presented in the table include those ≥ 0.2% for any cardiac arrhythmia TEAE in the total mirabegron group and all PTs for cardiac arrhythmia SAE or TEAE leading to discontinuation of study drug. MedDRA v12.1.
ECG: electrocardiogram; ER: extended release; OAB: overactive bladder; PT: preferred term; SAE: serious adverse event(s); SMQ: Standardized MedDRA Query; TEAE: treatment-emergent adverse event(s).

Table 63 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the SMQ of Cardiac Arrhythmias, EU/NA Long-term Controlled Population

Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Patients with any cardiac arrhythmia TEAE	32 (3.9%)	34 (4.1%)	66 (4.0%)	49 (6.0%)
Tachycardia	8 (1.0%)	19 (2.3%)	27 (1.7%)	25 (3.1%)
Palpitations	5 (0.6%)	4 (0.5%)	9 (0.6%)	4 (0.5%)
Atrioventricular block first degree	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.2%)
Atrial fibrillation	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Heart rate increased	2 (0.2%)	2 (0.2%)	4 (0.2%)	2 (0.2%)
Arrhythmia	2 (0.2%)	1 (0.1%)	3 (0.2%)	2 (0.2%)
Bundle branch block right	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
ECG QT prolonged	1 (0.1%)	2 (0.2%)	3 (0.2%)	1 (0.1%)
Patients with cardiac arrhythmia SAE	6 (0.7%)	1 (0.1%)	7 (0.4%)	4 (0.5%)
Atrial fibrillation	2 (0.2%)	0	2 (0.1%)	3 (0.4%)
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Atrioventricular block first degree	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Sick sinus syndrome	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Patients discontinued study drug due to cardiac arrhythmia TEAE	3 (0.4%)	4 (0.5%)	7 (0.4%)	2 (0.2%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	0
ECG QT prolonged	0	1 (0.1%)	1 (0.1%)	0
Supraventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Atrial fibrillation	0	0	0	2 (0.2%)

Study included: 178-CL-049.
PTs presented in the table include those ≥ 0.2% for any cardiac arrhythmia TEAE in the total mirabegron group and all PTs for cardiac arrhythmia SAE or TEAE leading to discontinuation of study drug.
ECG: electrocardiogram; ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); SMQ: Standardized MedDRA Query; SAE: serious adverse event(s).

5.6.1.3.6 Discussion of Pulse Rate

Mirabegron administered at the proposed therapeutic dose of 50 mg once daily is associated with an approximately 1 bpm increased adjusted mean change from baseline pulse rate vs placebo in patients with OAB with a low proportion of patients experiencing tachycardia AE. Similar results were observed with mirabegron 25 mg. This pharmacologic effect is consistent across the analyses of central tendency, regression analysis of the exposure response, categorical outlier analysis and TEAE with no differences between the mirabegron 25, 50 and 100 mg dose groups.

The increase in pulse rate with mirabegron compared with antimuscarinic therapies for OAB is presented in Table 64. The change from baseline pulse rate following treatment with mirabegron at doses of 50 mg was similar to or less than the change from baseline pulse rate following treatment with tolterodine, fesoterodine and trospium [Table 64].

Table 64 Impact of OAB Treatments on Pulse Rate in OAB Patients

Generic Name	Trade Name	Dose	Mean Increase in Pulse Rate (bpm)
Mirabegron†		25 mg	0.9
		50 mg	1.0
Fesoterodine‡	Toviaz	4 mg	3 – 4
		8 mg	3 – 5
Trospium‡	Sanctura XR	60 mg	3
Tolterodine†	Detrol LA	4 mg	1.0-2.1

OAB: overactive bladder; XR: extended release; LA: long acting.
† Results from mirabegron development program.
‡ Results from Sanctura XR package insert 09/2011 or Toviaz 12/2011 approved US labels.

5.6.1.4 Blood Pressure Assessments

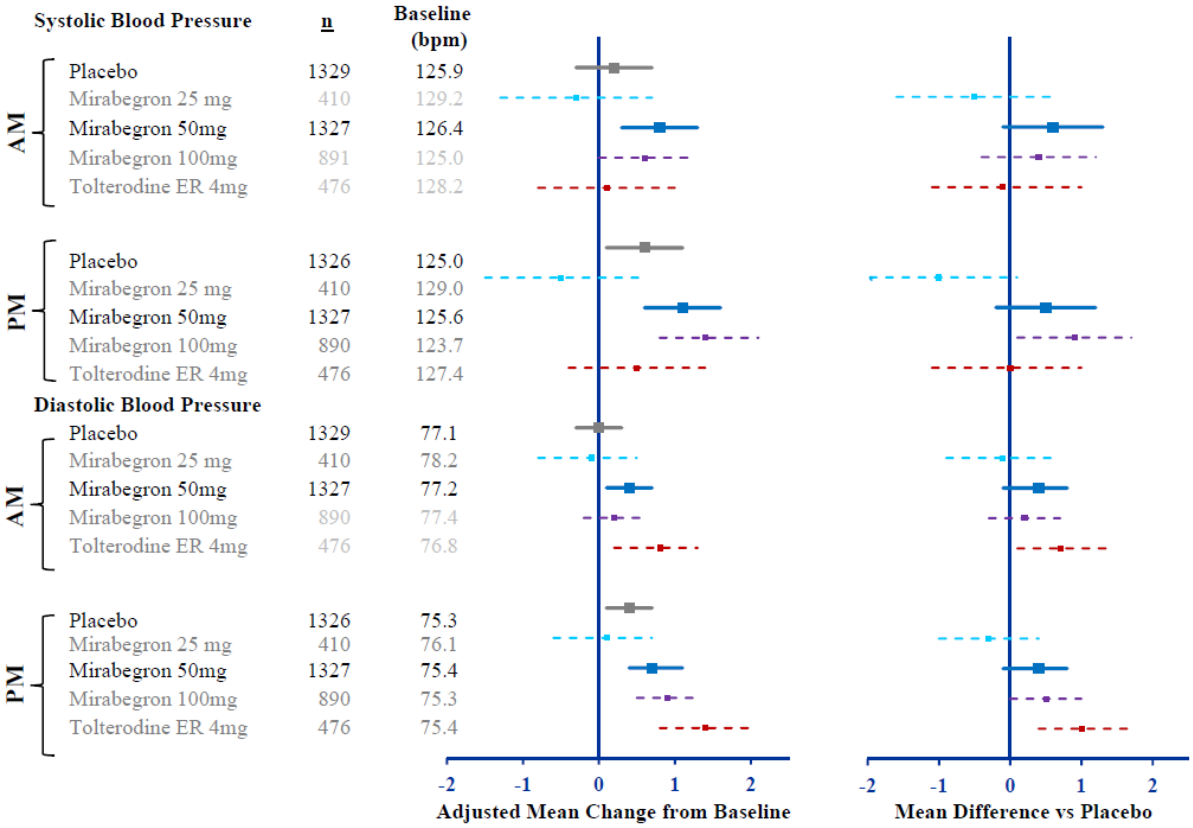
5.6.1.4.1 Analysis of Covariance Results Based on Central Tendency

The adjusted mean change from baseline to final visit in SBP/DBP measured in the patient's diary using the ANCOVA model is presented in Figure 28 for the EU/NA OAB 12-week Phase 3 Population and in Figure 29 for the EU/NA Long-term Controlled Population.

In the mirabegron 50 mg treatment group of the EU/NA OAB 12-week Phase 3 Population, the magnitude of the adjusted mean difference vs placebo in SBP was 0.5-0.6 mm Hg and the 95% CI included zero [Figure 28]. In the mirabegron 50 mg treatment group, the adjusted mean difference vs placebo in DBP was 0.4 mm Hg and the 95% CI included zero.

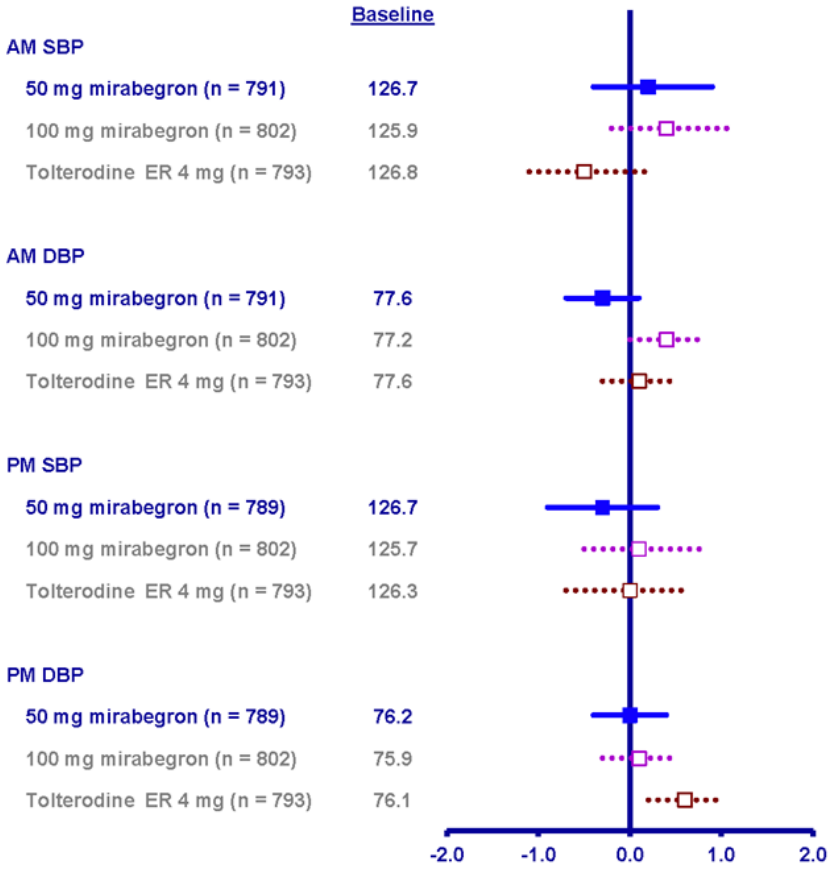
In EU/NA Long-term Controlled Population, the adjusted mean change from baseline in SBP was 0.3-0.2 mm Hg for the mirabegron 50 mg group and the 95% CI included zero. For the mirabegron 50 mg group, the adjusted mean change from baseline in DBP was -0.3-0.0 mm Hg and the 95% CI included zero [Figure 29].

Figure 28 Change from Baseline to Final Visit for AM and PM SBP and DBP, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled analysis results are from an ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

Figure 29 Change from Baseline to Final Visit for AM and PM SBP and DBP, EU/NA Long-term Controlled Population



Study included: 178-CL-049.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline. The adjusted mean change from baseline and 95% CI were calculated using an ANCOVA model with treatment group, gender, previous study history and expanded geographical region as fixed factors and baseline as a covariate.
ER: extended release; DBP: diastolic blood pressure; ANCOVA: analysis of covariance; SBP: systolic blood pressure.

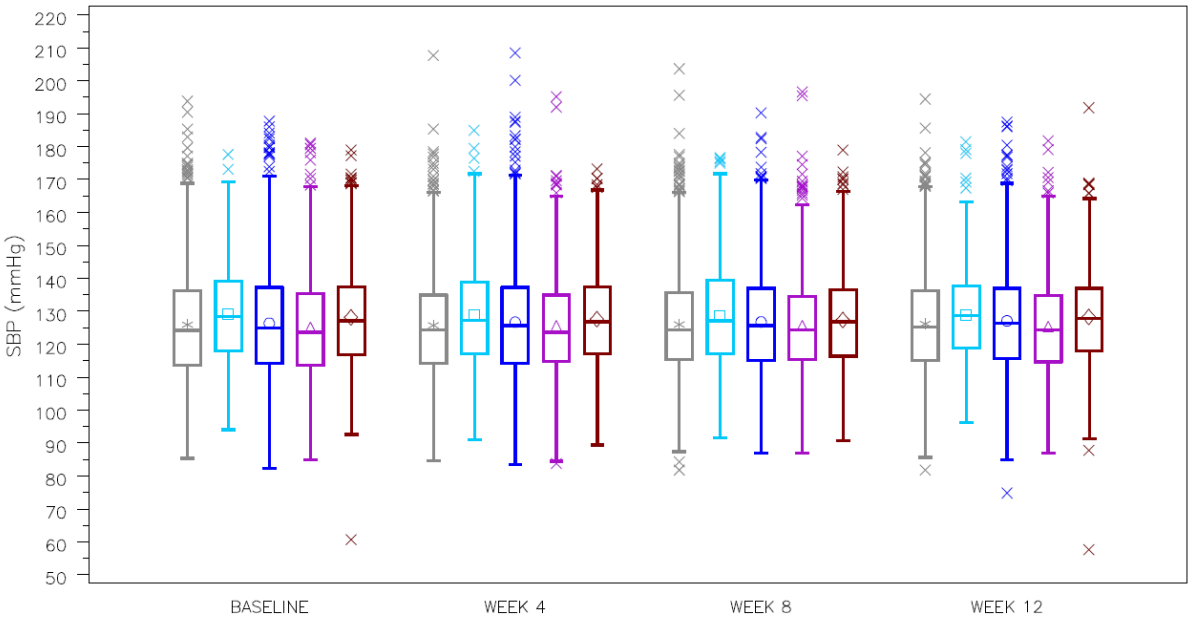
For the EU/NA OAB 12-week Phase 3 Population, SBP/DBP (AM) values and change from baseline to each visit are displayed in Figure 30 and Figure 31, respectively. PM SBP/DBP values, which follow a similar trend to AM SBP/DBP values are presented in [Appendix 2, Figure 17] and [Appendix 2, Figure 18].

Scatterplots illustrating the maximum change from baseline values versus baseline values in SBP/DBP (AM) values are displayed in Figure 32 and PM values are presented in [Appendix 2, Figure 19], with the x axis representing the baseline value and the y axis the maximum change from baseline value.

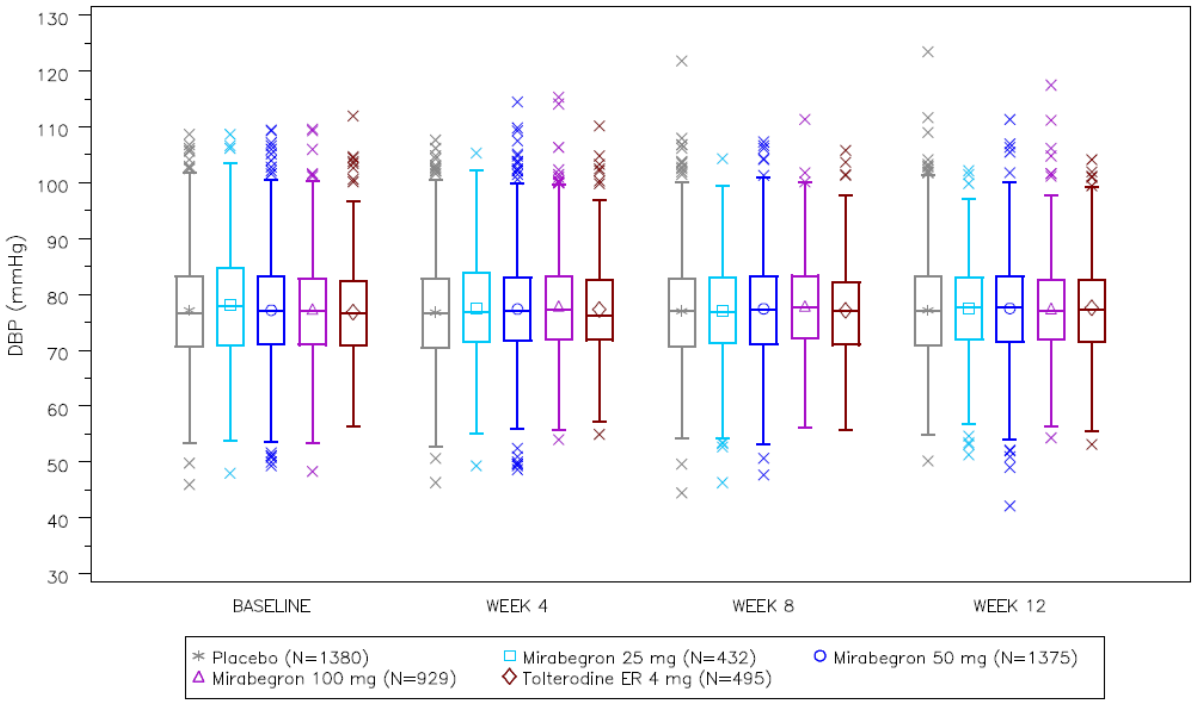
This analysis was also performed for the EU/NA Long-term Controlled Population, SBP/DBP (AM/PM) values displayed in Figure 33 and [Appendix 2, Figure 20], change from baseline to each visit in SBP/DBP (AM/PM) values are displayed inFigure 34 and [Appendix 2, Figure 21] and the maximum change from baseline in SBP/DBP (AM/PM) are presented in Figure 35 and [Appendix 2, Figure 22].

Figure 30 Boxplots of AM SBP/DBP Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) SBP



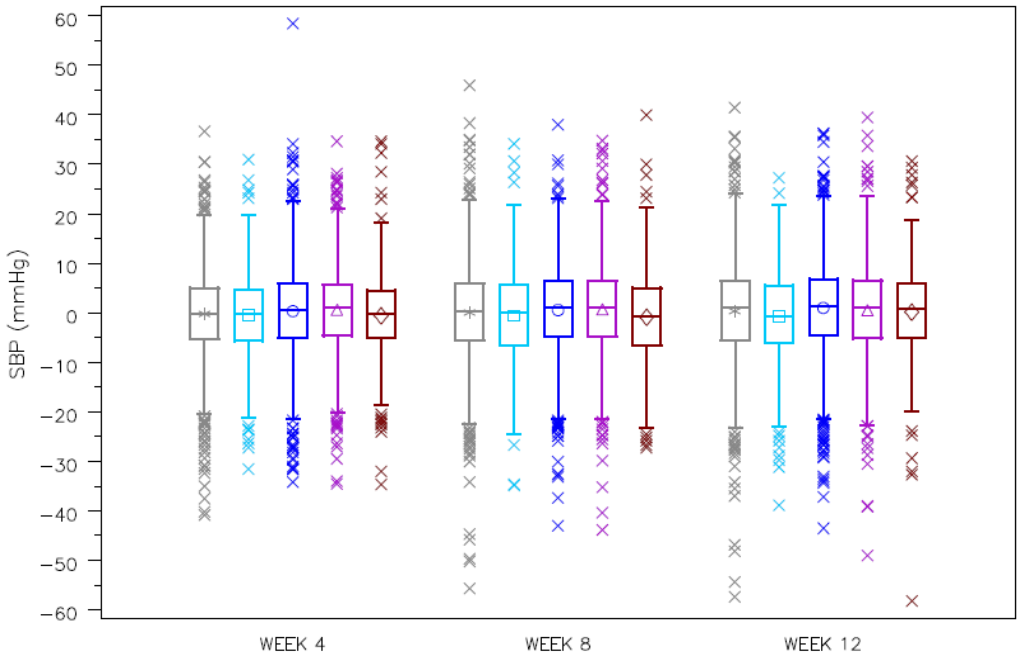
(B) DBP



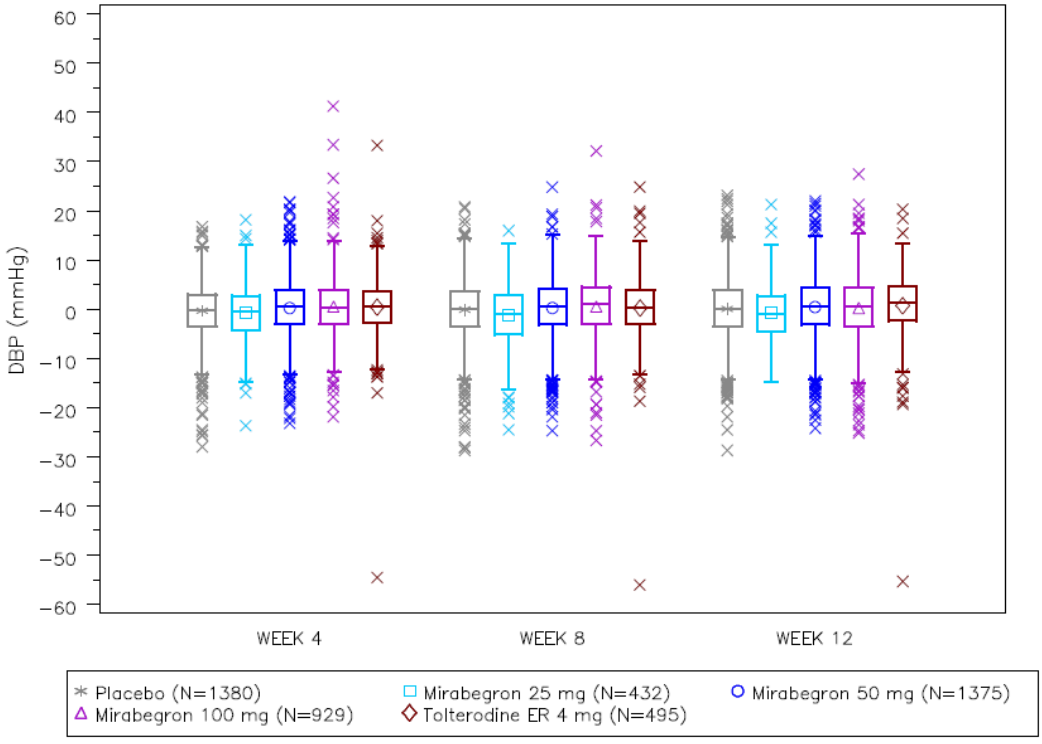
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
DBP: diastolic blood pressure; ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

Figure 31 Boxplots of Change from Baseline in AM SBP/DBP Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) SBP



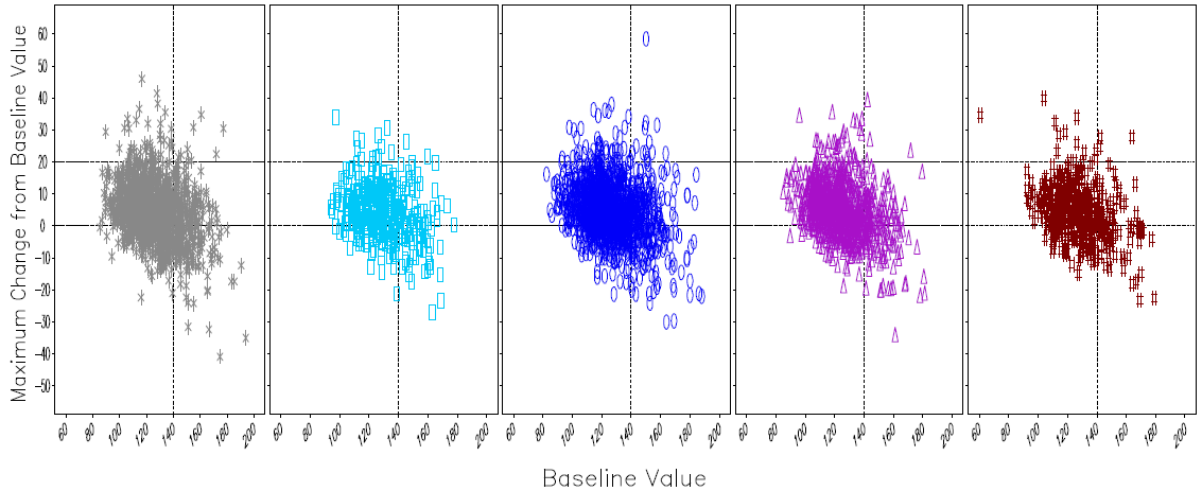
(B) DBP



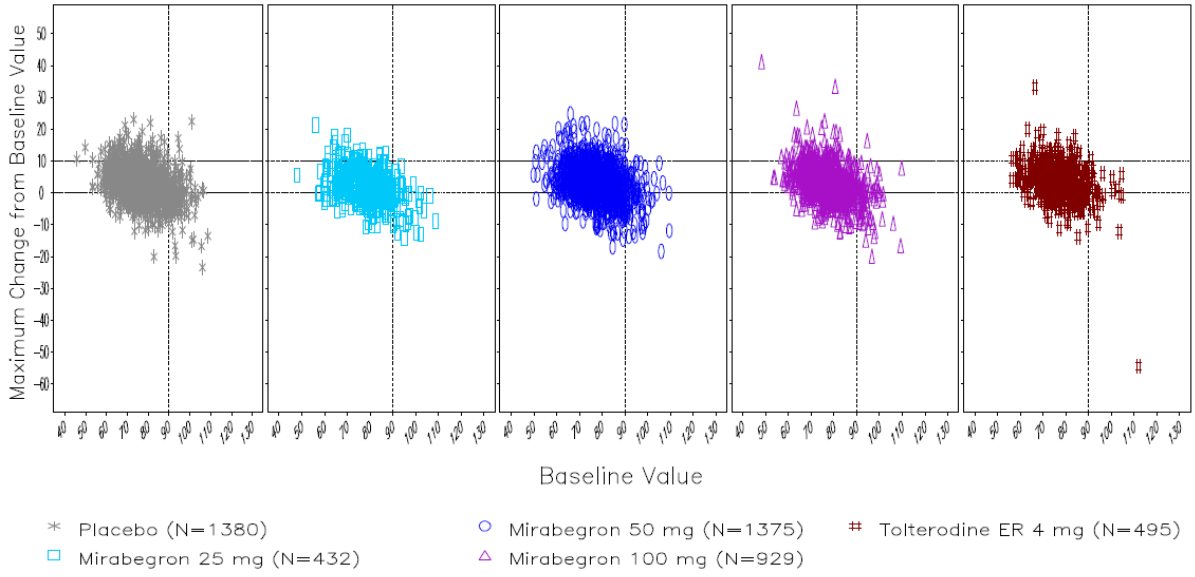
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
DBP: diastolic blood pressure; ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

Figure 32 Scatterplots of Maximum Change from Baseline Value vs Baseline Value in AM SBP/DBP, EU/NA OAB 12-week Phase 3 Population

(A) SBP



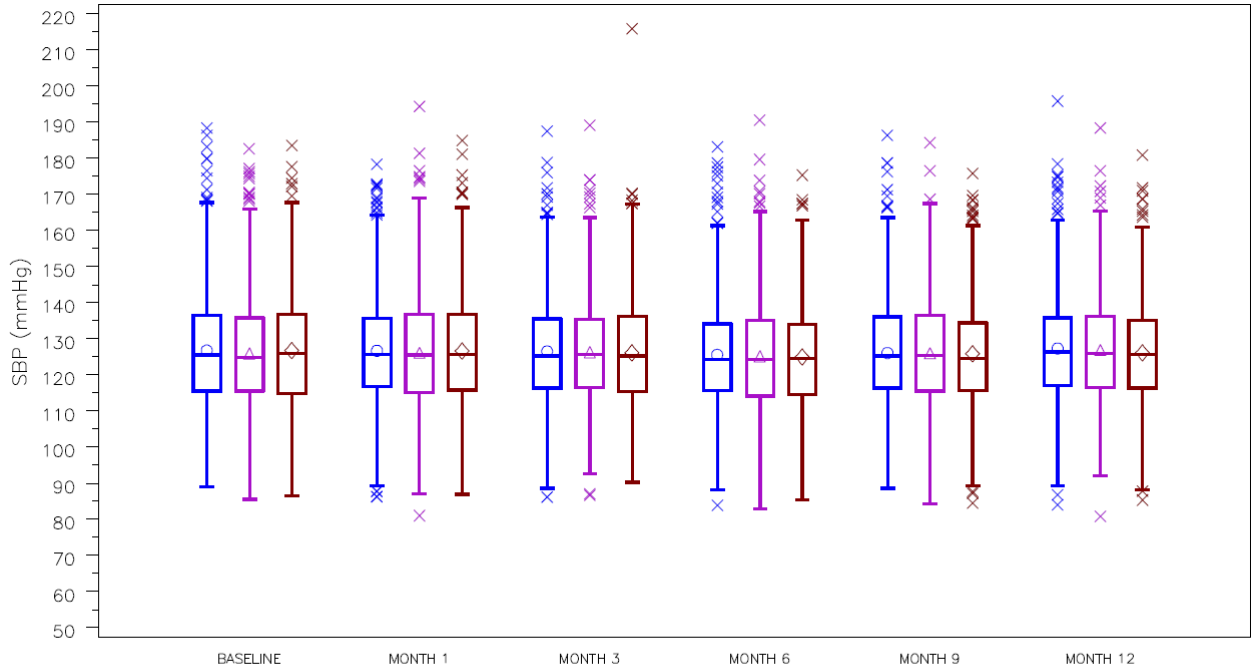
(B) DBP



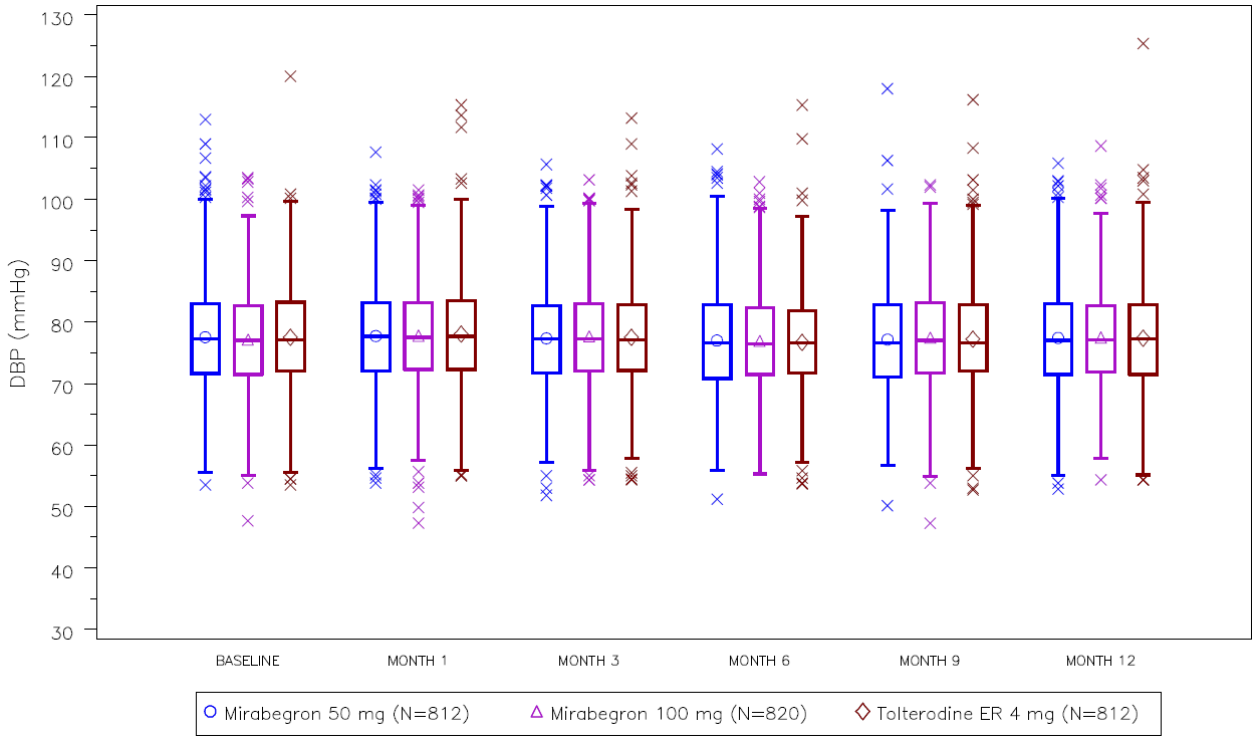
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
DBP: diastolic blood pressure; ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

Figure 33 Boxplot of AM SBP/DBP Values at Each Visit, EU/NA Long-term Controlled Population

(A) SBP



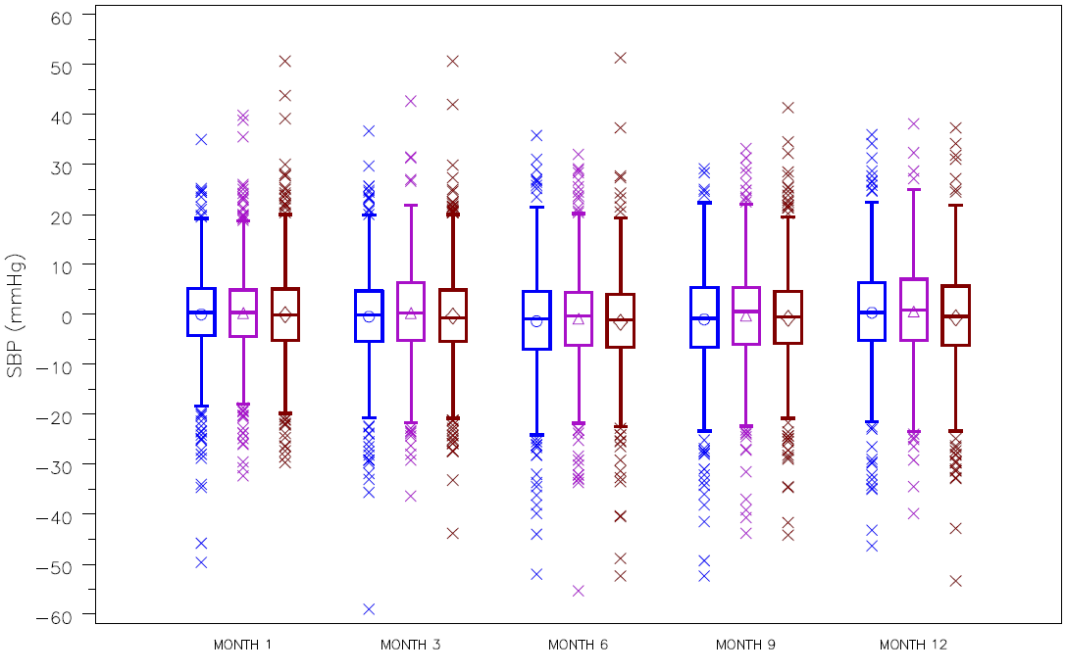
(B) DBP



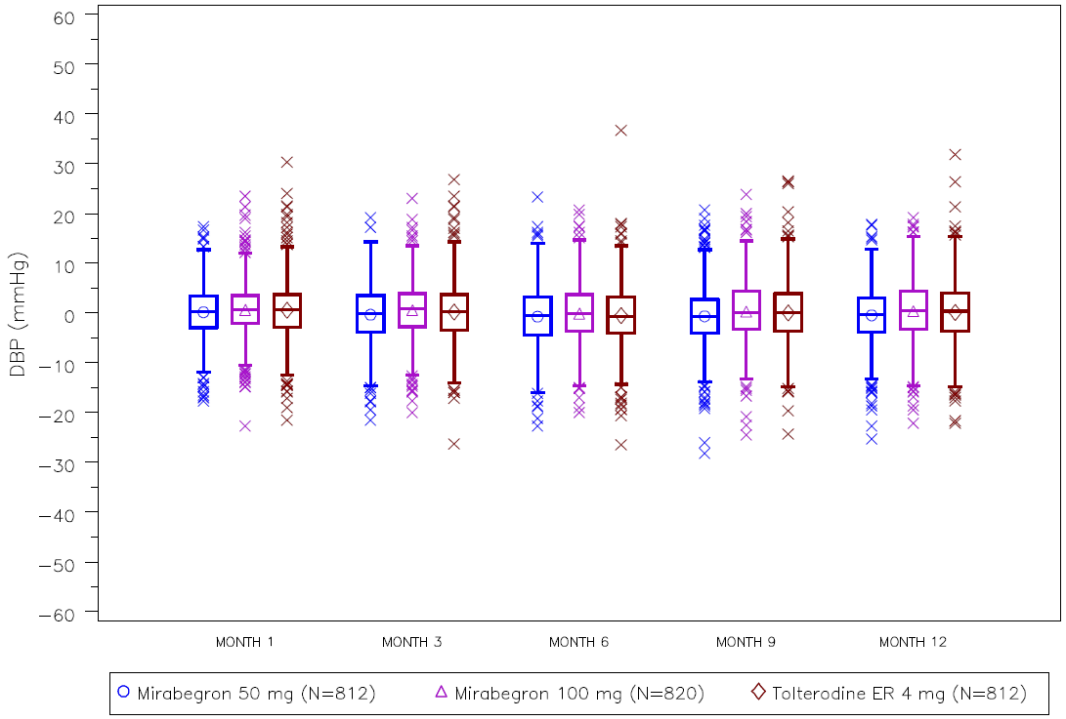
Study included: 178-CL-049.
DBP: diastolic blood pressure; ER: extended release; SBP: systolic blood pressure.

Figure 34 Boxplot of Change from Baseline in AM SBP/DBP Values at Each Visit, EU/NA Long-term Controlled Population

(A) SBP



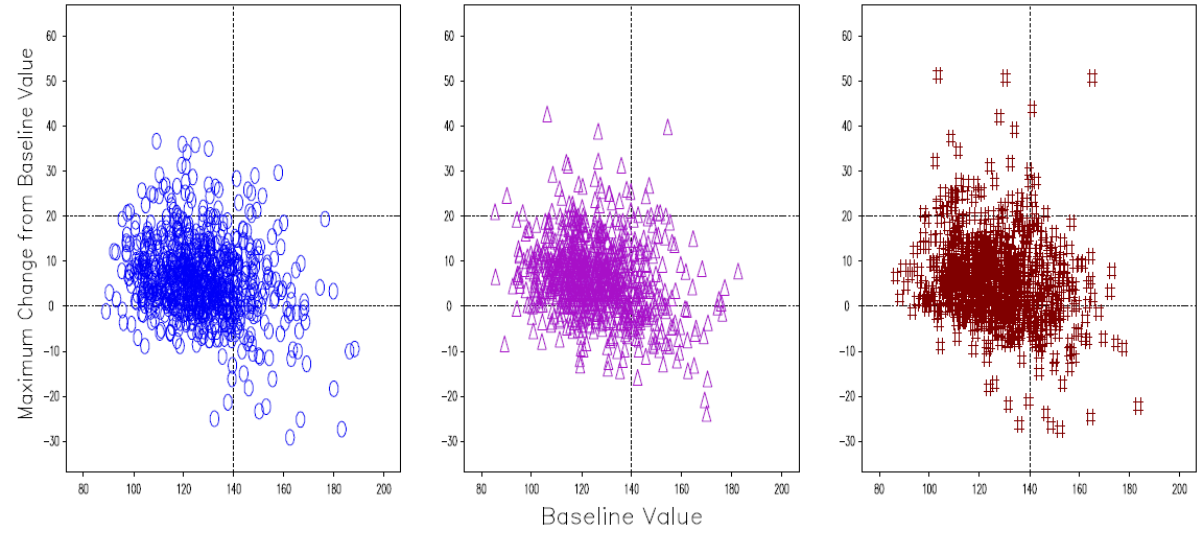
(B) DBP



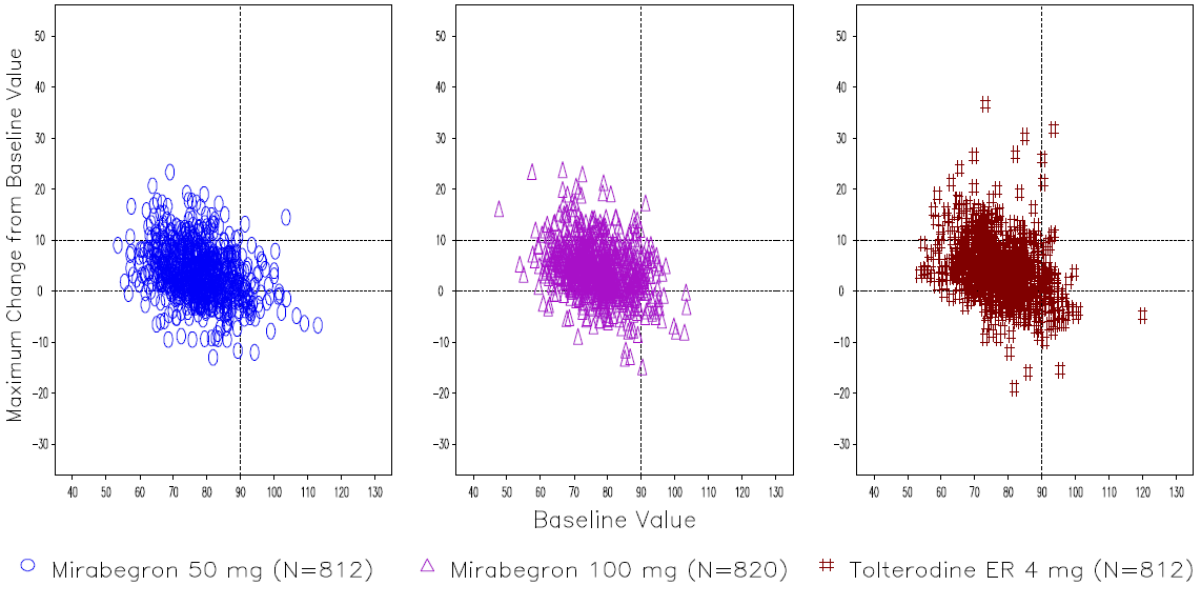
Study included: 178-CL-049.
DBP: diastolic blood pressure; ER: extended release; SBP: systolic blood pressure.

Figure 35 Scatterplots of Maximum Change from Baseline Values vs Baseline Values in AM SBP/DBP, EU/NA Long-term Controlled Population

(A) SBP



(B) DBP

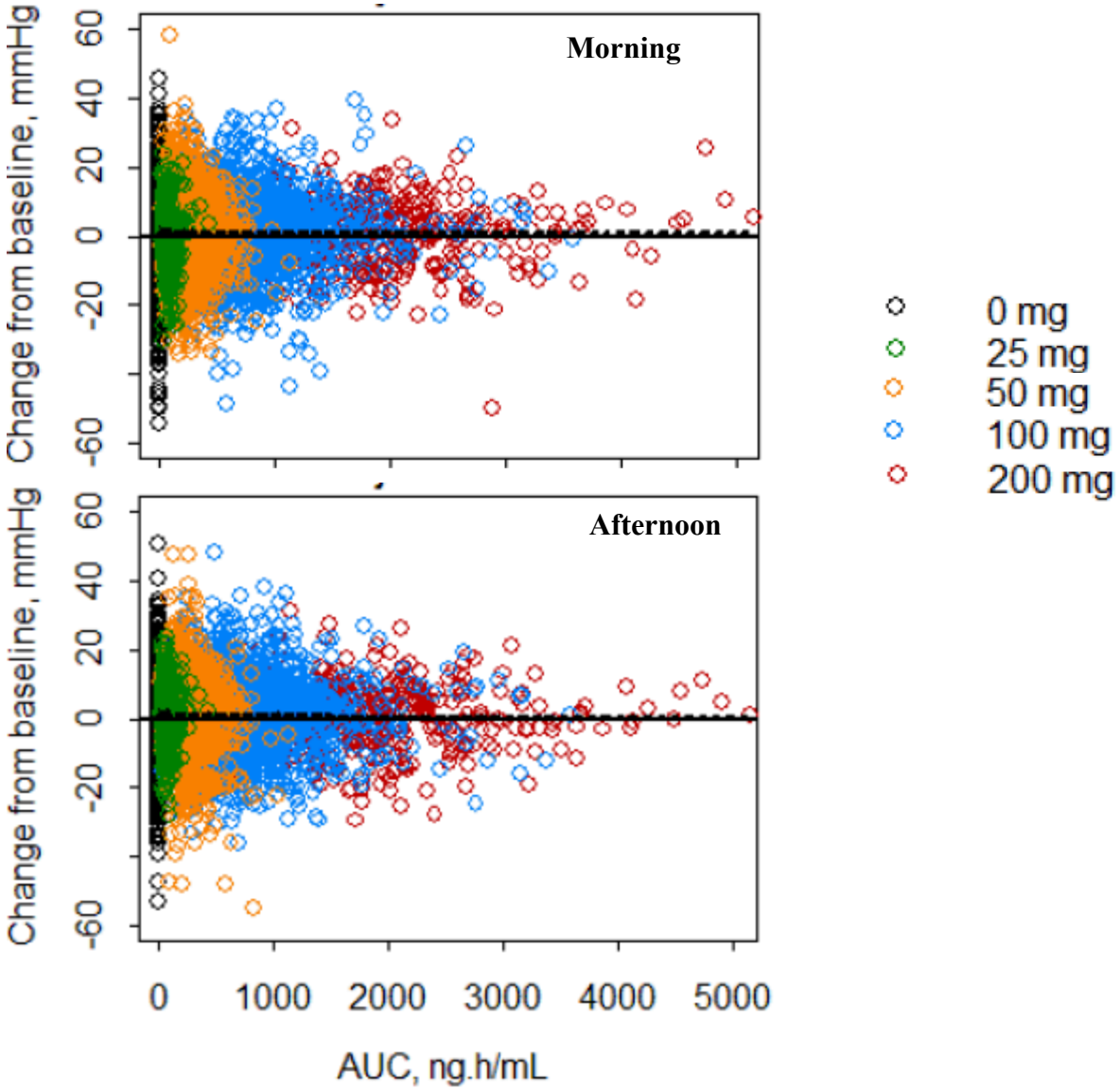


Study included: 178-CL-049
DBP: diastolic blood pressure; ER: extended release; SBP: systolic blood pressure.

5.6.1.4.2 Regression Analysis of the Exposure Response for SBP/DBP

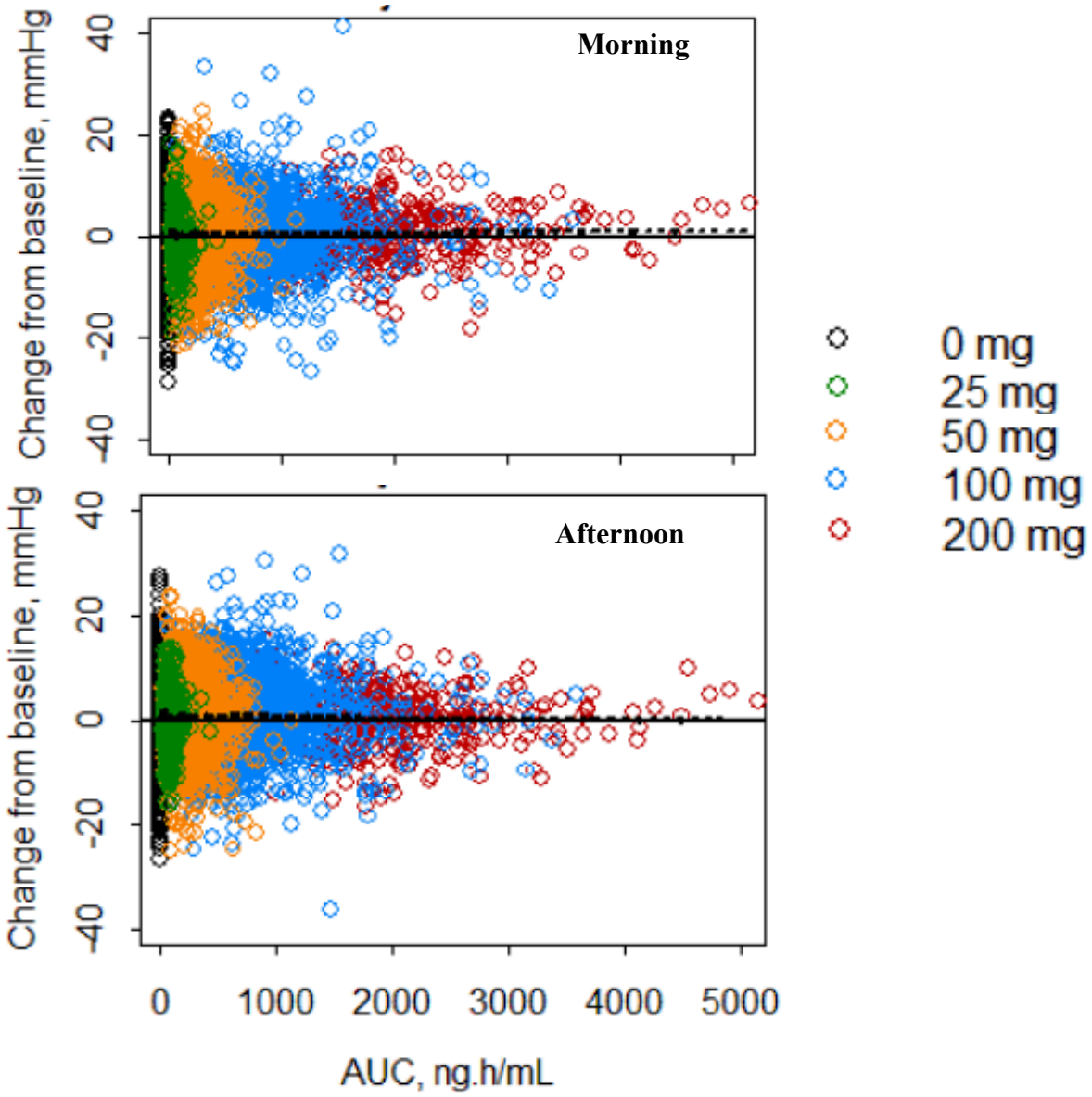
Graphical exposure-effect analysis of SBP in patients with OAB indicated that there was no overall trend for change from baseline in SBP with increasing mirabegron AUC [Figure 36]. Similarly for DBP, the graphical exposure-effect analysis revealed no trends that change in DBP from baseline increased with increasing mirabegron AUC [Figure 37]. Covariate testing was not performed for either SBP or DBP since no overall trend was observed for either in relation to increasing mirabegron exposure.

Figure 36 Graphical Analysis of AUC vs Change from Baseline in SBP



Figures represent the individual AM and PM SBP changes from baseline as a function of mirabegron AUC (log scale) in patients with OAB from Studies 178-CL-044, 178-CL-046 and 178-CL-047.
IOVAUC values are the individual specific AUC data. The dashed black lines represent smooths through the data. The solid black line represents no change from baseline.
SBP: systolic blood pressure; OAB: overactive bladder.

Figure 37 Graphical Analysis of AUC vs Change from Baseline in DBP



Figures represent the individual AM and PM DBP changes from baseline as a function of mirabegron AUC (log scale) in patients with OAB from Studies 178-CL-044, 178-CL-046 and 178-CL-047.
IOVAUC values are the individual specific AUC data. The dashed black lines represent smooths through the data. The solid black line represents no change from baseline.
DBP: diastolic blood pressure; OAB: overactive bladder.

5.6.1.4.3 Categorical Analysis of Increases from Baseline in Blood Pressure

Table 65 and Table 66 summarize the number and percent of patients whose AM/PM SBP or DBP measurements met selected criteria at final visit or at 2 or 3 consecutive visits for the EU/NA OAB 12-week Phase 3 Population and EU/NA Long-term Controlled Population, respectively.

For both the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled populations, the percentages of patients meeting criteria for increases in SBP/DBP were generally comparable across the treatment groups.

Table 65 Patients Whose AM or PM SBP/DBP Measurements Met Selected Criteria, EU/NA OAB 12-week Phase 3 Population

Parameter, n/n (%) of Patients		Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
SBP AM	**Final visit**					
	Change from baseline ≥ 15 mm Hg	70/1329 (5.3%)	21/410 (5.1%)	89/1327 (6.7%)	53/891 (5.9%)	17/476 (3.6%)
	3 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	252/1196 (21.1%)	71/387 (18.3%)	255/1202 (21.2%)	184/821 (22.4%)	84/439 (19.1%)
	Change from baseline ≥ 5 mm Hg	136/1196 (11.4%)	39/387 (10.1%)	140/1202 (11.6%)	96/821 (11.7%)	36/439 (8.2%)
	Change from baseline ≥ 10 mm Hg	28/1196 (2.3%)	10/387 (2.6%)	35/1202 (2.9%)	26/821 (3.2%)	8/439 (1.8%)
	Change from baseline ≥ 15 mm Hg	8/1196 (0.7%)	1/387 (0.3%)	8/1202 (0.7%)	6/821 (0.7%)	2/439 (0.5%)
	Change from baseline ≥ 20 mm Hg	6/1196 (0.5%)	0/387	5/1202 (0.4%)	3/821 (0.4%)	2/439 (0.5%)
	2 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	438/1242 (35.3%)	128/396 (32.3%)	483/1247 (38.7%)	315/852 (37.0%)	142/463 (30.7%)
	Change from baseline ≥ 5 mm Hg	263/1242 (21.2%)	78/396 (19.7%)	303/1247 (24.3%)	204/852 (23.9%)	83/463 (17.9%)
	Change from baseline ≥ 10 mm Hg	94/1242 (7.6%)	34/396 (8.6%)	100/1247 (8.0%)	63/852 (7.4%)	26/463 (5.6%)
	Change from baseline ≥ 15 mm Hg	27/1242 (2.2%)	6/396 (1.5%)	28/1247 (2.2%)	20/852 (2.3%)	7/463 (1.5%)
	Change from baseline ≥ 20 mm Hg	13/1242 (1.0%)	2/396 (0.5%)	15/1247 (1.2%)	10/852 (1.2%)	3/463 (0.6%)
SBP PM	**Final visit**					
	Change from baseline ≥ 15 mm Hg	86/1326 (6.5%)	23/410 (5.6%)	94/1327 (7.1%)	69/890 (7.8%)	35/476 (7.4%)
	3 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	243/1194 (20.4%)	64/387 (16.5%)	252/1201 (21.0%)	225/820 (27.4%)	90/439 (20.5%)
	Change from baseline ≥ 5 mm Hg	129/1194 (10.8%)	37/387 (9.6%)	143/1201 (11.9%)	113/820 (13.8%)	48/439 (10.9%)
	Change from baseline ≥ 10 mm Hg	31/1194 (2.6%)	12/387 (3.1%)	46/1201 (3.8%)	34/820 (4.1%)	16/439 (3.6%)
	Change from baseline ≥ 15 mm Hg	8/1194 (0.7%)	4/387 (1.0%)	15/1201 (1.2%)	8/820 (1.0%)	4/439 (0.9%)
	Change from baseline ≥ 20 mm Hg	3/1194 (0.3%)	1/387 (0.3%)	4/1201 (0.3%)	4/820 (0.5%)	2/439 (0.5%)
	2 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	444/1239 (35.8%)	118/396 (29.8%)	448/1247 (35.9%)	362/851 (42.5%)	167/463 (36.1%)
	Change from baseline ≥ 5 mm Hg	285/1239 (23.0%)	74/396 (18.7%)	307/1247 (24.6%)	240/851 (28.2%)	105/463 (22.7%)
	Change from baseline ≥ 10 mm Hg	101/1239 (8.2%)	26/396 (6.6%)	109/1247 (8.7%)	85/851 (10.0%)	41/463 (8.9%)
	Change from baseline ≥ 15 mm Hg	31/1239 (2.5%)	8/396 (2.0%)	31/1247 (2.5%)	25/851 (2.9%)	11/463 (2.4%)
	Change from baseline ≥ 20 mm Hg	10/1239 (0.8%)	4/396 (1.0%)	11/1247 (0.9%)	9/851 (1.1%)	4/463 (0.9%)
DBP AM	**Final visit**					
	Change from baseline ≥ 10 mm Hg	61/1329 (4.6%)	17/410 (4.1%)	88/1327 (6.6%)	53/890 (6.0%)	25/476 (5.3%)
	3 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	170/1196 (14.2%)	49/387 (12.7%)	219/1202 (18.2%)	149/820 (18.2%)	81/439 (18.5%)
	Change from baseline ≥ 5 mm Hg	62/1196 (5.2%)	23/387 (5.9%)	80/1202 (6.7%)	55/820 (6.7%)	28/439 (6.4%)
	Change from baseline ≥ 10 mm Hg	11/1196 (0.9%)	0/387	10/1202 (0.8%)	11/820 (1.3%)	2/439 (0.5%)
	Change from baseline ≥ 15 mm Hg	0/1196	0/387	1/1202 (0.1%)	2/820 (0.2%)	1/439 (0.2%)
	2 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	329/1242 (26.5%)	99/396 (25.0%)	410/1247 (32.9%)	292/851 (34.3%)	151/463 (32.6%)
	Change from baseline ≥ 5 mm Hg	150/1242 (12.1%)	47/396 (11.9%)	180/1247 (14.4%)	122/851 (14.3%)	61/463 (13.2%)
	Change from baseline ≥ 10 mm Hg	29/1242 (2.3%)	5/396 (1.3%)	31/1247 (2.5%)	25/851 (2.9%)	8/463 (1.7%)
	Change from baseline ≥ 15 mm Hg	3/1242 (0.2%)	1/396 (0.3%)	2/1247 (0.2%)	5/851 (0.6%)	2/463 (0.4%)
DBP PM	**Final visit**					
	Change from baseline ≥ 10 mm Hg	71/1326 (5.4%)	18/410 (4.4%)	91/1327 (6.9%)	78/890 (8.8%)	38/476 (8.0%)
	3 consecutive postbaseline visits					
	Change from baseline ≥ 2 mm Hg	189/1194 (15.8%)	52/387 (13.4%)	222/1201 (18.5%)	175/820 (21.3%)	100/439 (22.8%)
	Change from baseline ≥ 5 mm Hg	61/1194 (5.1%)	19/387 (4.9%)	831201 (6.9%)	72/820 (8.8%)	43/439 (9.8%)
	Change from baseline ≥ 10 mm Hg	9/1194 (0.8%)	0/387	8/1201 (0.7%)	11/820 (1.3%)	7/439 (1.6%)
	Change from baseline ≥ 15 mm Hg	0/1194	0/387	1/1201 (0.1%)	3/820 (0.4%)	1/439 (0.2%)
DBP PM	**2 consecutive postbaseline visits**					
	Change from baseline ≥ 2 mm Hg	374/1239 (30.2%)	99/396 (25.0%)	393/1247 (31.5%)	319/851 (37.5%)	186/463 (40.2%)
	Change from baseline ≥ 5 mm Hg	166/1239 (13.4%)	43/396 (10.9%)	193/1247 (15.5%)	173/851 (20.3%)	86/463 (18.6%)
	Change from baseline ≥ 10 mm Hg	26/1239 (2.1%)	9/396 (2.3%)	31/1247 (2.5%)	38/851 (4.5%)	12/463 (2.6%)
	Change from baseline ≥ 15 mm Hg	0/1239	1/396 (0.3%)	5/1247 (0.4%)	5/851 (0.6%)	1/463 (0.2%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 66 Patients Whose AM or PM SBP or DBP Measurements Met Selected Criteria, EU/NA Long-term Controlled Population

Parameter, n/n (%) of Patients		Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
SBP AM	**Final visit**			
	Change from baseline ≥ 15 mm Hg	52/791 (6.6%)	48/802 (6.0%)	45/793 (5.7%)
	3 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	160/686 (23.3%)	166/704 (23.6%)	148/684 (21.6%)
	Change from baseline ≥ 5 mm Hg	84/686 (12.2%)	87/704 (12.4%)	81/684 (11.8%)
	Change from baseline ≥ 10 mm Hg	25/686 (3.6%)	26/704 (3.7%)	17/684 (2.5%)
	Change from baseline ≥ 15 mm Hg	9/686 (1.3%)	7/704 (1.0%)	9/684 (1.3%)
	Change from baseline ≥ 20 mm Hg	1/686 (0.1%)	4/704 (0.6%)	2/684 (0.3%)
	2 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	304/742 (41.0%)	334/741 (45.1%)	283/736 (38.5%)
	Change from baseline ≥ 5 mm Hg	189/742 (25.5%)	206/741 (27.8%)	179/736 (24.3%)
	Change from baseline ≥ 10 mm Hg	73/742 (9.8%)	72/741 (9.7%)	63/736 (8.6%)
	Change from baseline ≥ 15 mm Hg	27/742 (3.6%)	22/741 (3.0%)	30/736 (4.1%)
	Change from baseline ≥ 20 mm Hg	9/742 (1.2%)	9/741 (1.2%)	11/736 (1.5%)
SBP PM	**Final visit**			
	Change from baseline ≥ 15 mm Hg	46/789 (5.8%)	48/802 (6.0%)	51/793 (6.4%)
	3 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	149/685 (21.8%)	160/704 (22.7%)	144/684 (21.1%)
	Change from baseline ≥ 5 mm Hg	89/685 (13.0%)	97/704(13.8%)	81/684 (11.8%)
	Change from baseline ≥ 10 mm Hg	25/685 (3.6%)	30/704 (4.3%)	19/684 (2.8%
	Change from baseline ≥ 15 mm Hg	5/685 (0.7%)	9/704 (1.3%)	8/684 (1.2%)
	Change from baseline ≥ 20 mm Hg	1/685 (0.1%)	2/704 (0.3%)	5/684 (0.7%)
	2 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	290/742 (39.1%)	312/741 (42.1%)	283/736 (38.5%)
	Change from baseline ≥ 5 mm Hg	178/742 (24.0%)	195/741 (26.3%)	182/736 (24.7%)
	Change from baseline ≥ 10 mm Hg	72/742 (9.7%)	74/741 (10.0%)	68/736 (9.2%)
	Change from baseline ≥ 15 mm Hg	23/742 (3.1%)	22/741 (3.0%)	28/736 (3.8%)
	Change from baseline ≥ 20 mm Hg	7/742 (0.9%)	10/741 (1.3%)	10/736 (1.4%)
DBP AM	**Final visit**			
	Change from baseline ≥ 10 mm Hg	36/791 (4.6%)	45/802 (5.6%)	47/793 (5.9%)
	3 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	131/686 (19.1%)	159/704 (22.6%)	139/684 (20.3%)
	Change from baseline ≥ 5 mm Hg	47/686 (6.9%)	56/704 (8.0%)	55/684 (8.0%)
	Change from baseline ≥ 10 mm Hg	5/686 (0.7%)	7/704 (1.0%)	12/684 (1.8%)
	Change from baseline ≥ 15 mm Hg	0/686	1/704 (0.1%)	3/684 (0.4%)
	2 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	250/742 (33.7%)	297/741 (40.1%)	278/736 (37.8%)
	Change from baseline ≥ 5 mm Hg	112/742 (15.1%)	127/741 (17.1%)	128/736 (17.4%)
	Change from baseline ≥ 10 mm Hg	18/742 (2.4%)	20/741 (2.7%)	30/736 (4.1%)
	Change from baseline ≥ 15 mm Hg	2/742 (0.3%)	6/741 (0.8%)	5/736 (0.7%)
DBP PM	**Final visit**			
	Change from baseline ≥ 10 mm Hg	48/789 (6.1%)	44/802 (5.5%)	59/793 (7.4%)
	3 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	127/685 (18.5%)	140/704 (19.9%)	166/684 (24.3%)
	Change from baseline ≥ 5 mm Hg	55/685 (8.0%)	56/704 8.0%)	73/684 (10.7%)
	Change from baseline ≥ 10 mm Hg	10/685 (1.5%)	8/704 (1.1%)	17/684 (2.5%)
	Change from baseline ≥ 15 mm Hg	0/685	2/704 (0.3%)	2/684 (0.3%)
	2 consecutive postbaseline visits			
	Change from baseline ≥ 2 mm Hg	265/742 (35.7%)	279/741 (37.7%)	289/736 (39.3%)
	Change from baseline ≥ 5 mm Hg	119/742 (16.0%)	143/741 (19.3%)	154/736 (20.9%)
	Change from baseline ≥ 10 mm Hg	28/742 (3.8%)	29/741 (3.9%)	33/736 (4.5%)
	Change from baseline ≥ 15 mm Hg	7/742 (0.9%)	3/741 (0.4%)	7/736 (1.0%)

Study included: 178-CL-049. ER: extended release; SBP: systolic blood pressure; DBP: diastolic blood pressure.

An analysis of the percent of patient with increases in SBP above the criteria established by The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7, 2004] for systolic hypertension was performed for the EU/NA OAB 12-week Phase 3 Population [Table 67] and the EU/NA Long-term Controlled Population [Table 68]. The percentage of patients with SBP (AM or PM) increased from baseline > 5 mm Hg and an actual value > 140 mm Hg at 3 consecutive postbaseline visits were similar across all treatments groups in both the EU/NA OAB 12-week Phase 3 Population and the EU/NA Long-term Controlled Population.

Table 67 Patients With AM or PM SBP Increase from Baseline > 5 mm Hg and Actual Value > 140 mm Hg, EU/NA OAB 12-week Phase 3 Population

Parameter n (%) of Patients	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
3 Consecutive Postbaseline visits (AM)	57/1067 (5.3%)	21/311 (6.8%)	73/1057 (6.9%)	42/726 (5.8%)	26/378 (6.9%)
3 Consecutive Postbaseline visits (PM)	12/1022 (1.2%)	4/305 (1.3%)	12/1012 (1.2%)	11/724 (1.5%)	16/382 (4.2%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder; SBP: systolic blood pressure.

Table 68 Patients With AM or PM SBP Increase from Baseline > 5 mm Hg and Actual Value > 140 mm Hg, EU/NA Long-term Controlled Population

Parameter, n (%) of Patients	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
3 Consecutive Postbaseline visits (AM)	10/555 (1.8%)	11/577 (1.9%)	14/556 (2.5%)
3 Consecutive Postbaseline visits (PM)	6/592 (1.0%)	11/599 (1.8%)	11/584 (1.9%)

Study included: 178-CL-049.
ER: extended release; SBP: systolic blood pressure.

5.6.1.4.4 Subgroup Analyses of SBP/DBP Data

For the EU/NA OAB 12-week Phase 3 Population, mean change from baseline to final visit in AM/PM SBP/DBP measurements is presented in [Appendix 2, Figure 23] for age; [Appendix 2, Figure 24] for gender, race, ethnicity; [Appendix 2, Figure 25] for BMI, geography; [Appendix 2, Figure 26] for baseline hypertension; and [Appendix 2, Figure 27] for baseline concomitant alpha antagonist therapy and concomitant beta blocker therapy.

The mean changes were generally similar in both age groups. Male patients had generally larger changes in SBP/DBP than females. None of the remaining subgroup analyses were remarkable for differences in the effect on SBP/DBP.

5.6.1.4.5 AE Related to Increases in Blood Pressure

Blood pressure monitoring, characteristics of diary data collection and evaluation of hypertension AE have been conducted in accordance with guidance received from the FDA Division of Reproductive and Urologic Products in February 2008 in response to the SPA for studies 178-CL-046 and 178-CL-047. These definitions were also applied to Studies 178-CL-074 and 178-CL-049.

The following prespecified criteria for recording hypertension AE were included in the protocols for the EU/NA OAB 12-week Phase 3 Population (Study 178-CL-046, 178-CL-047, 178-CL-049 and 178-CL-074):

1. If the average SBP was ≥ 140 mm Hg and/or the average DBP was ≥ 90 mm Hg at 2 consecutive visits after baseline in patients who were normotensive (average SBP < 140 mm Hg and average DBP < 90 mm Hg) at baseline.
2. If the average SBP was increased ≥ 20 mm Hg and/or the average DBP was increased ≥ 10 mm Hg at 2 consecutive visits as compared with baseline in patients with hypertension at baseline.

3. If treatment with antihypertensive drugs was initiated for the treatment of hypertension, or if the dose of prior antihypertensive medication was increased due to an increase in blood pressure.

If any of these criteria were met, then an AE of hypertension was recorded on the AE electronic case report form by the investigator. In addition, the investigator could record an AE of hypertension based on clinical assessment.

Because specific criteria for determining TEAE of hypertension were provided to investigators for the phase 3 studies conducted in North America and Europe (Studies 178-CL-046, 178-CL-047, 178-CL-049 and 178-CL-074), providing a consistent definition for hypertension TEAE in the phase 3 population compared with the overall phase 2/3 population, results are presented below for the EU/NA OAB 12-week Phase 3 Population and the EU/NA Long-term Controlled Population. AEs summarized for hypertension are based on the Hypertension SMQ.

The overall frequency of hypertension TEAE in the 12-week phase 3 studies was similar for the total mirabegron group (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]); there was no dose response observed across all doses of mirabegron [Table 69].

Two TEAE in the hypertension SMQ were reported as SAE in 2 different patients: 1/1375 (0.1%) patient in the mirabegron 50 mg group (hypertensive crisis), Patient No. 178-CL-046, 3028-2446; and 1/495 (0.2%) patient in the tolterodine group (hypertension), Patient No. 178-CL-046, 3113-3207 [Table 69]:

- Patient No. 178-CL-046, 3028-2446, a 62-year old woman treated with mirabegron 50 mg, was hospitalized for an SAE of hypertensive crisis on day 13. The patient had a relevant medical history of hypertension. The event, which was considered by the investigator to be severe and possibly related to treatment, led to discontinuation of study drug on day 24. The patient recovered from the event of hypertensive crisis on day 28. Predose SBP diary data in this patient ranged from 132 mm Hg (day -4) to 190 mm Hg (day -4); no postdose blood pressure data were available in the clinical database for this patient. However, blood pressure on the day of hospital admission was 170/90 mm Hg, comparable to the predose diary data. The event of hypertensive crisis was adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a non-APTC/MACE cardiovascular event/other serious non-MACE cardiovascular event (Section 5.6.1.5.3).
- Patient No. 178-CL-046, 3113-3207, 75-year old woman treated with tolterodine, with a history of arterial hypertension and coronary disease, was hospitalized for an SAE of hypertension on day 68. The event, which was considered by the investigator to be moderate and possibly related to treatment, led to discontinuation of study drug on day 68. Average blood pressure measurements at week 8 (based on diary data) were 150/91 mm Hg (AM) and 146/84 mm Hg (PM). At an unspecified time during the event, it was reported that a blood pressure of 240/140 mm Hg was obtained. The event was reported as resolved on day 71. The event of hypertension was adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a non-APTC/MACE cardiovascular event/other serious non-MACE cardiovascular event [see Section 5.6.1.5.3].

Fifteen patients discontinued study drug due to a TEAE (15 events) in the hypertension SMQ [Table 69].

In the EU/NA Long-term Controlled Population, the overall frequency of hypertension TEAE was similar across all treatment groups [Table 70].

Two TEAE in the hypertension SMQ were reported as SAE: 1/812 (0.1%) patient in the mirabegron 50 mg group (hypertension, Patient No. 178-CL-049, 3019-0364) and 1/820 (0.1%) patient in the mirabegron 100 mg group (hypertension, Patient No. 178-CL-049, 1630-7319) [Table 70]:

- Patient No. 178-CL-049, 3019-0364, a 46-year old woman treated with mirabegron 50 mg, experienced an SAE of hypertension on day 3. During the event the patient's blood pressure was

reported as 170/90 mm Hg. Baseline values for blood pressure in the clinical database were reported as 177-180/92-100 mm Hg. The event, which was considered by the investigator to be moderate and not related to treatment, led to discontinuation of study drug on day 2. The event of hypertension was adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a noncardiovascular event (see Section 5.6.1.5.3).

- Patient No. 178-CL-049, 1630-7319, a 77-year old man treated with mirabegron 100 mg, experienced an SAE of hypertension on day 251. The event was considered by the investigator to be moderate and not related to treatment. Blood pressure on admission to the hospital during the event was noted as 248/120 mm Hg. The patient was treated, blood pressure returned to pre-event values and the patient was put back on study drug and completed the study. Blood pressure measurements recorded in the clinical database prior to the event ranged from 108-135/ 49-70 mm Hg. The event of hypertension was adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a non-APTC/MACE cardiovascular event/other nonserious non-MACE cardiovascular event (see Section 5.6.1.5.3).

Table 69 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the Hypertension SMQ, EU/NA OAB 12-week Phase 3 Population

MedDRA v 12.1 Category PT, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Patients with any hypertension TEAE	**117 (8.5%)**	**52 (12.0%)**	**120 (8.7%)**	**58 (6.2%)**	**230 (8.4%)**	**48 (9.7%)**
RR (95% CI) †		1.25 (0.86, 1.80)	1.02 (0.79, 1.32)	0.78 (0.56, 1.08)	0.98 (0.79, 1.23)	
Hypertension	105 (7.6%)	49 (11.3%)	103 (7.5%)	48 (5.2%)	200 (7.3%)	40 (8.1%)
Blood pressure increased	6 (0.4%)	1 (0.2%)	9 (0.7%)	8 (0.9%)	18 (0.7%)	4 (0.8%)
Blood pressure systolic increased	2 (0.1%)	1 (0.2%)	3 (0.2%)	2 (0.2%)	6 (0.2%)	0
Patients with hypertension SAE	**0**	**0**	**1 (0.1%)**	**0**	**1 (< 0.1%)**	**1 (0.2%)**
Hypertensive crisis	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Hypertension	0	0	0	0	0	1 (0.2%)
Patients discontinued study drug due to hypertension TEAE	**3 (0.2%)**	**2 (0.5%)**	**5 (0.4%)**	**4 (0.4%)**	**11 (0.4%)**	**1 (0.2%)**
Hypertension	2 (0.1%)	2 (0.5%)	2 (0.1%)	2 (0.2%)	6 (0.2%)	1 (0.2%)
Blood pressure increased	1 (0.1%)	0	0	2 (0.2%)	2 (0.1%)	0
Hypertensive crisis	0	0	2 (0.1%)	0	2 (0.1%)	0
Blood pressure diastolic increased	0	0	1 (0.1%)	0	1 (< 0.1%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
PTs presented in the table include those ≥ 0.2% for any hypertension TEAE in the total mirabegron group and all PTs for hypertension SAE or TEAE leading to discontinuation of study drug.
ER: extended release; OAB: overactive bladder; PT: preferred term; RR: relative risk; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s); SMQ: Standardized MedDRA Query.
† RR vs placebo. Hazard ratios and 95% CIs from a proportional hazards model stratified by study were used to estimate RRs.

Table 70 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the Hypertension SMQ, EU/NA Long-term Controlled Population

MedDRA v12.1 Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Patients with any hypertension TEAE	**89 (11.0%)**	**83 (10.1%)**	**172 (10.5%)**	**86 (10.6%)**
RR (95% CI) †	1.04 (0.77, 1.39)	0.94 (0.70, 1.27)	0.99 (0.76, 1.28)	
Hypertension	75 (9.2%)	80 (9.8%)	155 (9.5%)	76 (9.4%)

MedDRA v12.1 Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Blood pressure increased	5 (0.6%)	2 (0.2%)	7 (0.4%)	5 (0.6%)
Blood pressure diastolic increased	3 (0.4%)	1 (0.1%)	4 (0.2%)	0
Patients with hypertension SAE	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Hypertension	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Patients discontinued study drug due to hypertension TEAE	**4 (0.5%)**	**2 (0.2%)**	**6 (0.4%)**	**4 (0.5%)**
Hypertension	4 (0.5%)	2 (0.2%)	6 (0.4%)	3 (0.4%)
Blood pressure increased	0	0	0	1 (0.1%)

Study included: 178-CL-049.
PTs presented in the table include those ≥ 0.2% for any hypertension TEAE in the total mirabegron group and all PTs for hypertension SAE or TEAE leading to discontinuation of study drug.
ER: extended release; PT: preferred term; RR: relative risk; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s); SMQ: Standardized MedDRA Query.
† RR vs tolterodine. Hazard ratios and 95% CIs from a proportional hazards model were used to estimate RRs.

5.6.1.5 Findings from Analyses of Cardiovascular TEAE

5.6.1.5.1 Overall AE in the SOC of Cardiac Disorders

TEAE, SAE and TEAE leading to permanent discontinuation of study drug based on the system organ class (SOC) of Cardiac Disorders are summarized for the Global OAB 12-week Phase 2/3 Population and the EU/NA Long-term Controlled Population in Table 71 and Table 72, respectively.

In the Global OAB 12-week Phase 3 Population, the most common TEAE in the total mirabegron group were tachycardia, palpitations, supraventricular extrasystoles and atrial fibrillation [Table 71].

In the EU/NA Long-term Controlled Population, the most common TEAE in the total mirabegron group were tachycardia, angina pectoris and atrioventricular block first degree [Table 72].

Table 71 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the SOC of Cardiac Disorders, Global OAB 12-week Phase 2/3 Population

MedDRA v12.1 Category PT, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolterodine ER 4 mg (n = 958)
Patients with any TEAE in the SOC of Cardiac Disorders	**39 (1.8%)**	**25 (3.1%)**	**55 (2.6%)**	**30 (2.3%)**	**9 (5.4%)**	**119 (2.7%)**	**30 (3.1%)**
Tachycardia	8 (0.4%)	10 (1.2%)	23 (1.1%)	7 (0.5%)	6 (3.6%)	46 (1.0%)	1 (0.1%)
Palpitations	4 (0.2%)	7 (0.9%)	12 (0.6%)	5 (0.4%)	2 (1.2%)	26 (0.6%)	4 (0.4%)
Supraventricular extrasystoles	6 (0.3%)	2 (0.2%)	5 (0.2%)	5 (0.4%)	0	12 (0.3%)	7 (0.7%)
Atrial fibrillation	2 (0.1%)	0	5 (0.2%)	4 (0.3%)	1 (0.6%)	10 (0.2%)	2 (0.2%)
Angina pectoris	1 (< 0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Atrioventricular block first degree	4 (0.2%)	0	4 (0.2%)	1 (0.1%)	0	5 (0.1%)	0
Sinus tachycardia	0	3 (0.4%)	0	1 (0.1%)	0	4 (0.1%)	2 (0.2%)
Ventricular extrasystoles	4 (0.2%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	0	4 (0.1%)	4 (0.4%)
Sinus arrhythmia	1 (< 0.1%)	1 (0.1%)	2 (0.1%)	0	0	3 (0.1%)	1 (0.1%)
Sinus bradycardia	3 (0.1%)	0	3 (0.1%)	0	0	3 (0.1%)	1 (0.1%)
Patients with an SAE in the SOC of Cardiac Disorders	**6 (0.3%)**	**1 (0.1%)**	**5 (0.2%)**	**4 (0.3%)**	**0**	**10 (0.2%)**	**1 (0.1%)**
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
Cardiac failure	0	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
Acute coronary syndrome	1 (< 0.1%)	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Angina pectoris	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Angina unstable	0	1 (0.1%)	0	0	0	1 (< 0.1%)	0

Table continued on next page.

MedDRA v12.1 Category PT, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolterodine ER 4 mg (n = 958)
Cardiac failure acute	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Atrioventricular block first degree	1 (< 0.1%)	0	0	0	0	0	0
Coronary artery disease	2 (0.1%)	0	0	0	0	0	0
Myocardial infarction	1 (< 0.1%)	0	0	0	0	0	0
Patients discontinued study drug due to TEAE in the SOC of Cardiac Disorders	**4 (0.2%)**	**2 (0.2%)**	**8 (0.4%)**	**7 (0.5%)**	**0**	**17 (0.4%)**	**3 (0.3%)**
Palpitations	2 (0.1%)	1 (0.1%)	1 (< 0.1%)	3 (0.2%)	0	5 (0.1%)	1 (0.1%)
Tachycardia	0	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Atrial fibrillation	1 (< 0.1%)	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)	0
Angina pectoris	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Atrioventricular block first degree	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Cardiac failure acute	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Conduction disorder	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Myocardial ischaemia	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (<0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Coronary artery disease	1 (< 0.1%)	0	0	0	0	0	0
Sinus tachycardia	0	0	0	0	0	0	1 (0.1%)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
PTs presented in the table include those ≥ 0.1% for any TEAE in the total mirabegron group and all PTs for SAE or TEAE leading to discontinuation of study drug.
ER: extended release; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s).

Table 72 TEAE, SAE and TEAE Leading to Discontinuation of Study Drug for the SOC of Cardiac Disorders, EU/NA Long-term Controlled Population

MedDRA v12.1 Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Patients with any TEAE in the SOC of Cardiac Disorders	**32 (3.9%)**	**38 (4.6%)**	**70 (4.3%)**	**56 (6.9%)**
Tachycardia	8 (1.0%)	19 (2.3%)	27 (1.7%)	25 (3.1%)
Angina pectoris	3 (0.4%)	3 (0.4%)	6 (0.4%)	6 (0.7%)
Atrioventricular block first degree	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.2%)
Atrial fibrillation	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Arrhythmia	2 (0.2%)	1 (0.1%)	3 (0.2%)	2 (0.2%)
Bundle branch block right	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Coronary artery disease	2 (0.2%)	1 (0.1%)	3 (0.2%)	1 (0.1%)
Patients with an SAE in the SOC of 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%)
Acute myocardial infarction	1 (0.1%)	0	1 (0.1%)	0
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Atrioventricular block first degree	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Cardiac failure	1 (0.1%)	0	1 (0.1%)	0
Coronary artery disease	0	1 (0.1%)	1 (0.1%)	1 (0.1%)

Table continued on next page.

MedDRA v12.1 Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Myocardial infarction	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Myocardial ischaemia	1 (0.1%)	0	1 (0.1%)	0
Sick sinus syndrome	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Angina pectoris	0	0	0	2 (0.2%)
Aortic valve incompetence	0	0	0	1 (0.1%)
Coronary artery stenosis	0	0	0	1 (0.1%)
Patients discontinued study drug due to a TEAE in the SOC of Cardiac Disorders	**4 (0.5%)**	**4 (0.5%)**	**8 (0.5%)**	**7 (0.9%)**
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	0
Cardiac failure	1 (0.1%)	0	1 (0.1%)	0
Coronary artery disease	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Myocardial infarction	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Supraventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Angina pectoris	0	0	0	2 (0.2%)
Aortic valve incompetence	0	0	0	1 (0.1%)
Atrial fibrillation	0	0	0	2 (0.2%)

Study included: 178-CL-049.
PTs presented in the table include those ≥ 0.2% for any TEAE in the total mirabegron group and all PTs for SAE or TEAE leading to discontinuation of study drug.
ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s).

5.6.1.5.2 Congestive Heart Failure

The mirabegron OAB program did not specifically exclude patients with congestive heart failure (CHF). The EU/NA OAB 12-week Phase 3 Population excluded patients with "any clinically significant condition, which in the opinion of the investigator would make the patient unsuitable for the study" and the phase 2/3 studies conducted in Japan and the phase 2 study conducted in the EU (Study 178-CL-044) generally excluded patients with serious or clinically significant cardiac disease. With these criteria in place, 0 to 0.5% of patients in Global OAB 12-week Phase 2/3 Population, 0.2 to 0.8% of patients in EU/NA OAB 12-week Phase 3 Population and 0.4% of subjects in the EU/NA Long-term Controlled Population, respectively, reported a history of cardiac failure at study entry.

In the Global OAB 12-week Phase 2/3 Population, the frequency of TEAE of CHF based on the SMQ of cardiac failure and select PTs was 14/2142 (0.7%), 4/811 (0.5%), 14/2131 (0.7%), 15/1305 (1.1%) and 5/958 (0.5%) for the placebo, mirabegron 25, mirabegron 50 mg, mirabegron 100 mg and tolterodine treatment groups, respectively; no events were observed for mirabegron 200 mg. The majority of cardiac failure TEAE were from the higher level term (HLT) of oedema not elsewhere classified (NEC) (29/33 patients in the total mirabegron group). There were 0/2142 patients treated with placebo, 4/4414 (0.1%) patients treated with mirabegron (1/811 [0.1%] mirabegron 25 mg and 3/1305 [0.2%] mirabegron 100 mg) and 1/958 [0.1%] patient treated with tolterodine who experienced a TEAE in the HLT of heart failures NEC.

In the EU/NA Long-term Controlled Population, the frequency of CHF based on the SMQ of cardiac failure and select PTs was 10/812 (1.2%), 6/820 (0.7%) and 9/812 (1.1%) for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. The majority of cardiac failure TEAE were from the HLT of oedema NEC (12/16 patients in the total mirabegron group). There were 3/1632 (0.2%) patients treated with mirabegron (3/812 [0.4%] patients treated with mirabegron 50 mg, 0/820 patients

treated with mirabegron 100 mg) and 1/812 (0.1%) patient treated with tolterodine who experienced a TEAE in the HLT of heart failures NEC.

A brief summary of the TEAE in the HLTs of heart failures NEC or pulmonary oedema for the EU/NA OAB 12-week Phase 3 Population and EU/NA Long-term Population is presented Table 73. Patients with TEAE in the HLT of oedema NEC are not included in the summary below; while oedema is a symptom of CHF and included in the search strategy for CHF, it is nonspecific, even if due to worsening CHF. Therefore only TEAE in the HLT of heart failures NEC in which the investigator specifically identified CHF, or TEAE in the HLT of pulmonary oedema are summarized below.

Although there were relatively few patients (< 0.8% in any treatment group) with a history of CHF enrolled in these studies and although events falling into the SMQ of cardiac failure were infrequent (< 1.5% in any treatment group), there did not appear to be any evidence that mirabegron treatment exacerbated CHF in this population. Likewise, focusing on the even more infrequent events of TEAE in the HLT of heart failures NEC, there were no discernable imbalances observed between mirabegron treatment arms at different doses or mirabegron treatment arms compared with tolterodine. No TEAE in the HLT of heart failures NEC occurred among patients treated with placebo in the Global OAB 12-week Phase 2/3 Population.

Table 73 Listing of Patients with a TEAE in the HLT of Heart Failures NEC or HLT of Pulmonary Oedema

Study Number Patient No. Age/Race/Gender	Treatment	MedDRA (v12.1) PT / Verbatim Term	Onset/ Stop Day (Last Dose Day)	Outcome	Investigator-assessed Relation-ship to Study Drug	SAE?	Cardiovascular Adjudication Outcome†	Relevant Cardiac History
Global OAB 12-week Phase 2/3 Population								
178-CL-044 303-2101 74/White/Female	Placebo	Pulmonary oedema / Lung oedema	60 / 69 (59)	Recovered	Not related	Yes	Not adjudicated‡	Hypertension, aortic aneurysm, coronary artery disease, mitral insufficiency, atrial fibrillation, stroke
178-CL-044 206-1013 73/White/Female	Mirabegron 25 mg	Cardiac failure / Thoracal pain	82 / 90 (93)	Recovered	Not related	Yes	Non cardiovascular event	Hypertension, coronary disease, diabetes, hyperlipidemia, chronic bronchitis, overweight
178-CL-047 U00021846813 69/White/Female	Mirabegron 100 mg	Cardiac failure congestive / Mild congestive heart failure class III	96 / ongoing (91)	Recovering	Not related	No	Not adjudicated	Hypertension, atherosclerotic cardiovascular disease, coronary bypass graft x 4 vessels, left carotid endartectomy, hyperlipidemia
178-CL-046 3014-2243 90/White/Female	Mirabegron 100 mg	Cardiac failure acute / Acute cardiac insufficiency	80 / 90 (79)	Recovered	Possibly	Yes	Insufficient data	Compensated cardiac insufficiency
178-CL-047 U00020536564 46/Black/Male	Mirabegron 100 mg	Cardiac failure / Congestive heart failure NYHA Class II	72 / 80 (71)	Recovered	Not related	Yes	Non-APTC/MACE (congestive heart failure)	Hypertension, diabetes
178-CL-046 3433-1412 72/White/Female	Tolterodine ER 4 mg	Cardiac failure congestive / CHF progression	7 / 91 (91)	Recovered	Not related	No	Not adjudicated	Chronic heart failure
EU/NA Long-term Controlled Population								
178-CL-049 3433-1273 85/White/Female	Mirabegron 50 mg	Cardiac failure chronic / Chronic heart failure	359 / 363 (359)	Recovered	Possibly	No§	Non-APTC/MACE (congestive heart failure)	Arterial hypertension
178-CL-049 3301-2253 74/White/Male	Mirabegron 50 mg	Cardiac failure congestive / Congestive cardiac failure	223 / ongoing (363)	Not recovered	Not related	No	Not adjudicated	Systolic hypertension
178-CL-049 3034-2380 72/White/Female	Mirabegron 50 mg	Cardiac failure / Cardiac failure	190 / 190 (190)	Fatal	Not related	Yes	APTC/MACE (cardiovascular death)	Diabetes mellitus, hypertension
178-CL-049 3367-2309 78/White/Male	Tolterodine ER 4 mg	Cardiac failure / Cardiac failure	334 / ongoing (363)	Recovering	Possibly	No	Not adjudicated	Hypercholesterolemia, carotid artery surgery, hypertension, ischemic heart disease, atrial fibrillation

Footnotes on next page.

SAE: serious adverse event(s); PT: preferred term; HLT: higher level term; NEC: not elsewhere classified; CHF: congestive heart failure; TEAE: treatment-emergent adverse event(s); ER: extended release; OAB: overactive bladder; APTC: Antiplatelet Trialists' Collaboration; MACE: major adverse cardiovascular events; NYHA: New York Heart Association.
† All deaths and cardiovascular SAE from the mirabegron clinical trials were selected by the Cardiovascular Adjudication Committee for review, therefore, the events for Patient Nos. 178-CL-046, 3433-1412; 178-CL-047, U00021846813; 178-CL-049, 3367-2309; and 178-CL-049, 3301-2253 were not adjudicated by the Cardiovascular Adjudication Committee since they were mild or moderate in severity and were not SAE.
‡ Patient No. 178-CL-044, 303-2101 experienced an SAE of hypertensive crisis that was adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a non-APTC/MACE event of CHF.
§ Patient No. 178-CL-049, 3433-1273 experienced an SAE of atrial flutter that led to permanent discontinuation of study drug.
Source: Studies 178-CL-044; 178-CL-046; 178-CL-047; and 178-CL-049.

5.6.1.5.3 SAE and Deaths Adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron

The Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron included 3 physicians, independent of the Sponsor, with cardiovascular medicine subspecialties in hypertension and/or electrophysiology. Their primary responsibility included blinded evaluation, clinical expert review and independent adjudication of all deaths and cardiovascular SAE reported in the clinical studies of mirabegron. All 41 studies that comprise the NDA dossier were reviewed under the scope of the charter at the time of submission.

The Sponsor had the responsibility for preparing listings by study to be submitted to the Chair of the Committee inclusive of deaths and all SAE. It was the responsibility of the Chair of the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron to make the independent selection of which SAE the Chair judged to be of potential cardiovascular nature to be adjudicated from all SAE; all deaths were adjudicated by the Committee. Throughout the process and the committee evaluation, all data and listings were provided on a blinded basis.

To arrive at an adjudicated diagnosis of a cardiovascular event, the following endpoints were employed:

- APTC/MACE events
  - Nonfatal myocardial infarction
  - Nonfatal stroke
  - Cardiovascular deaths
- Non-APTC/MACE cardiovascular events (includes serious ischemic, heart failure and arrhythmia categories that do not meet the APTC/MACE criteria)
  - Unstable angina
  - Coronary revascularization
  - Transient ischemic attacks
  - Venous and peripheral arterial vascular thrombotic events
  - Congestive heart failure (CHF)
  - Cardiac arrhythmias with no evidence of ischemia
  - Other serious non-MACE cardiovascular events
- Noncardiovascular events

RR and 95% CIs were calculated for the following types of adjudication events: APTC/MACE events, APTC/MACE or Other Ischemic or Thromboembolic-Mediated Cardiovascular Events; and APTC/MACE or Other Ischemic or Thromboembolic-Mediated Cardiovascular Events or CHF. Odds ratios and exact 95% confidence intervals were used to estimate RRs. The RRs comparing mirabegron to placebo for the EU/NA OAB 12-week Phase 3 and Global OAB 12-week Phase 2/3 Populations were presented for each mirabegron dose group and for the total mirabegron group in a given population. The RR comparison for the EU/NA Long-term Controlled Population was

presented for each mirabegron dose group versus tolterodine and for the total mirabegron group versus tolterodine.

Findings from events adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with mirabegron are presented for the Global OAB 12-week Phase 2/3 Population, which includes pooled data from 6 double-blind 12-week phase 2/3 studies conducted globally in Japan, Europe and North America, in patients with OAB. Additionally, a summary of adjudicated events is presented for the EU/NA Long-term Controlled Population.

The number and percent of patients with events selected for adjudication and those with at least one adjudication-confirmed cardiovascular event for the Global OAB 12-week Phase 2/3 Population is presented in Table 74. For this population, the Committee selected 62 events reported in 43 patients for review [Table 74].

Events adjudicated as APTC/MACE cardiovascular events [Table 74] occurred in:

- 4/2142 (0.2%) patients in the placebo group (3 as nonfatal stroke [Patient Nos. 178-CL-047, U00020406833; 178-CL-074, 1974-71984; and 178-CL-074, 2031-70175] and one as cardiovascular death [Patient No. 178-CL-047, U00015976697]),
- 2/811 (0.2%) patients in the mirabegron 25 mg group (both as nonfatal stroke [Patient Nos. 178-CL-045, P02361; and 178-CL-045, P00601]) and
- 1/958 (0.1%) patient in the tolterodine group (cardiovascular death [Patient No. 178-CL-046, 3105-1598]).

Among all mirabegron patients, the RR compared with placebo for the occurrence of APTC/MACE cardiovascular events was 0.24 (95% CI: 0.02, 1.69) [Table 74].

Table 74 Cardiovascular Adjudicated Events, Global OAB 12-week Phase 2/3 Population

Type of CV Event CV Event	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolt ER 4 mg (n = 958)
Number (%) of patients with events requiring adjudication	17 (0.8%)	5 (0.6%)	6 (0.3%)	10 (0.8%)	0	21 (0.5%)	5 (0.5%)
Number (%) of patients with at least one adjudication-confirmed CV event	9 (0.4%)	2 (0.2%)	5 (0.2%)	6 (0.5%)	0	13 (0.3%)	3 (0.3%)
APTC/MACE	**4 (0.2%)**	**2 (0.2%)**	**0**	**0**	**0**	**2 (< 0.1%)**	**1 (0.1%)**
RR		1.32	NE	NE	NE	0.24	
(95% CI) †		(0.12,				(0.02, 1.69)	
Nonfatal MI	0	9.24)	0	0	0	0	0
Nonfatal stroke	3 (0.1%)	0	0	0	0	2 (< 0.1%)	0
CV Death	1 (< 0.1%)	2 (0.2%)	0	0	0	0	1 (0.1%)
		0					
Non-APTC/MACE	**5 (0.2%)**	**0**	**5 (0.2%)**	**6 (0.5%)**	**0**	**11 (0.2%)**	**2 (0.2%)**
Other ischemic or thromboembolic-mediated CV events	3 (0.1%)	0	2 (0.1%)	0	0	2 (< 0.1%)	0
Unstable angina	0	0	1 (<	0	0	1 (<0.1%)	0
Coronary	2 (0.1%)	0	0.1%)	0	0	1 (< 0.1%)	0
revascularization	0	0	1 (<	0	0	0	0
Transient ischemic attack	1 (< 0.1%)	0	0.1%)	0	0	0	0
			0				
Venous and peripheral arterial vascular thrombotic event			0				

Table continued on next page.

Type of CV Event CV Event	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolt ER 4 mg (n = 958)
CHF	1 (< 0.1%)	0	0	1 (0.1%)	0	1 (<0.1%)	0
Arrhythmia, no evidence of ischemia	1 (< 0.1%)	0	3 (0.1%)	5 (0.4%)	0	8 (0.2%)	1 (0.1%)
Atrial arrhythmia	1 (< 0.1%)	0	3 (0.1%)	5 (0.4%)	0	8 (0.2%)	1 (0.1%)
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	4 (0.3%)	0	7 (0.2%)	1 (0.1%)
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Ventricular arrhythmia	0	0	0	0	0	0	0
Ventricular tachycardia‡	0	0	0	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0	0
High grade AV block	0	0	0	0	0	0	0
2nd degree Mobitz II	0	0	0	0	0	0	0
3rd degree	0	0	1 (< 0.1%)	1 (0.1%)	0	2 (< 0.1%)	1 (0.1%)
Other serious non-MACE CV events							
APTC/MACE or other ischemic or thromboembolic-mediated CV events §	7 (0.3%)	2 (0.2%)	2 (0.1%)	0	0	4 (0.1%)	1 (0.1%)
RR (95% CI) †		0.75 (0.08, 3.97)	0.29 (0.03, 1.51)	NE	NE	0.28 (0.06, 1.09)	
APTC/MACE or other ischemic or thromboembolic-mediated CV events or CHF ¶	8 (0.4%)	2 (0.2%)	2 (0.1%)	1 (0.1%)	0	5 (0.1%)	1 (0.1%)
RR (95% CI) †		0.66 (0.07, 3.31)	0.25 (0.03, 1.26)	0.20 (0.00, 1.53)	NE	0.30 (0.08, 1.05)	

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
CV: cardiovascular; APTC: Antiplatelet Trialists' Collaboration; AV: atrioventricular; ER: extended release; MACE: major adverse cardiovascular events; MI: myocardial infarction; OAB: overactive bladder; RR: relative risk; NE: not evaluated due to insufficient data; Tolt: tolterodine; CHF: congestive heart failure.
† Relative risk versus placebo. Odds ratio and exact 95% CI were used to estimate relative risk.
‡ Inclusive of torsade de pointes.
§ The number of patients included in this row have at least one event in the following categories: APTC/MACE + other ischemic or thromboembolic mediated CV events (included under non-APTC/MACE).
¶ The number of patients included in this row have at least one event in the following categories: APTC/MACE + other ischemic or thromboembolic mediated CV events (included under non-APTC/MACE) + CHF (included under non-APTC/MACE).

Overall, for the EU/NA OAB 12-week Phase 3 Population:

- The percentage of mirabegron-treated patients with APTC/MACE and ischemic events was similar or less than the proportion of placebo- or tolterodine-treated patients and was low across all treatment groups.
- There were no events adjudicated to ventricular tachycardia or ventricular fibrillation in any treatment group.

The number and percent of patients with events selected for adjudication and those with at least one adjudication-confirmed cardiovascular event for EU/NA Long-term Controlled Population is presented in Table 75. For this population, the Committee selected 65 events reported in 44 patients for review [Table 75].

Events adjudicated as APTC/MACE events occurred in 6/812 (0.7%) patients in the mirabegron 50 mg group, none in the mirabegron 100 mg group and 4/812 (0.5%) patients in the tolterodine group [Table 75].

- The events in the mirabegron 50 mg patients were nonfatal stroke (3 patients [Patient Nos. 178-CL-049, 1656-7207; 178-CL-049, 3030-1541; and 178-CL-049, 3117-3170]), nonfatal myocardial infarction (2 patients [Patient Nos. 178-CL-049, 1630-6566; and 178-CL-049, 2203-0424]) and cardiovascular death (one patient [Patient No. 178-CL-049, 3034-2380]).
- In the tolterodine patients, the events were cardiovascular death (2 patients [Patient Nos. 178-CL-049, 2190-6983; and 178-CL-049, 1838-6486]), a nonfatal myocardial infarction (one patient [Patient No. 178-CL-049, 3026-1649]) and a nonfatal stroke (one patient [Patient No. 178-CL-049, 3202-2660]).

Overall, for the EU/NA Long-term Controlled Population:

- Among all mirabegron patients, the RR compared with tolterodine for the occurrence of APTC/MACE cardiovascular events was 0.75 (95% CI: 0.18, 3.60) [Table 75].
- The percentage of mirabegron-treated patients with APTC/MACE and ischemic events was similar or less than the proportion of tolterodine-treated patients.
- There were no events adjudicated to ventricular tachycardia or ventricular fibrillation in any treatment group.

Table 75 Cardiovascular Adjudicated Events, EU/NA Long-term Controlled Population

Type of CV Event CV Event	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Number (%) of patients with events requiring adjudication	19 (2.3%)	9 (1.1%)	28 (1.7%)	16 (2.0%)
Number (%) of patients with at least one adjudication-confirmed CV event	**12 (1.5%)**	**3 (0.4%)**	**15 (0.9%)**	**11 (1.4%)**
APTC/MACE	**6 (0.7%)**	**0**	**6 (0.4%)**	**4 (0.5%)**
RR	1.50	NE	0.75	
(95% CI) †	(0.35, 7.27)		(0.18, 3.60)	
Nonfatal MI	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nonfatal stroke	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
CV Death	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Non-APTC/MACE	**6 (0.7%)**	**3 (0.4%)**	**9 (0.6%)**	**7 (0.9%)**
Other ischemic or thromboembolic-mediated CV events	2 (0.2%)	1 (0.1%)	3 (0.2%)	3 (0.4%)
Unstable angina	0	0	0	0
Coronary revascularization	0	0	0	2 (0.2%)
Transient ischemic attack	1 (0.1%)	0	1 (0.1%)	0
Venous and peripheral arterial vascular thrombotic event	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
	2 (0.2%)	0	2 (0.1%)	0
CHF	4 (0.5%)	1 (0.1%)	5 (0.3%)	3 (0.4%)
Arrhythmia, no evidence of ischemia	4 (0.5%)	1 (0.1%)	5 (0.3%)	3 (0.4%)
Atrial arrhythmia	4 (0.5%)	1 (0.1%)	5 (0.3%)	3 (0.4%)
Atrial fibrillation	0	0	0	0
Supraventricular tachycardia	0	0	0	0
Ventricular arrhythmia	0	0	0	0
Ventricular tachycardia ‡	0	0	0	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
High grade AV block	0	0	0	0
2nd degree Mobitz II	1 (0.1%)	0	1 (0.1%)	0
3rd degree	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Other serious non-MACE CV events				
APTC/MACE or other ischemic or thromboembolic-mediated CV events §	8 (1.0%)	1 (0.1%)	9 (0.6%)	7 (0.9%)
RR	1.15	0.14	0.64	
95% CI †	(0.36, 3.73)	(0.00, 1.10)	(0.21, 2.03)	
APTC/MACE or other ischemic or thromboembolic-mediated CV events or CHF ¶	10 (1.2%)	1 (0.1%)	11 (0.7%)	7 (0.9%)
RR	1.43	0.14	0.78	
95% CI †	(0.49, 4.46)	(0.00, 1.10)	(0.28, 2.38)	

Study included: 178-CL-049.

Footnotes continued on next page

CV: cardiovascular; AV: atrioventricular; APTC: Antiplatelet Trialists' Collaboration; ER: extended release; MACE: major adverse cardiovascular events; MI: myocardial infarction; RR: relative risk; NE: not evaluated due to insufficient data; CHF: congestive heart failure.
†Relative risks versus tolterodine. Odds ratio and exact 95% CI were used to estimate relative risk.
‡ Inclusive of torsade de pointes.
§ The number of patients included in this row have at least one event in the following categories: APTC/MACE + other ischemic or thromboembolic mediated CV events (included under non-APTC/MACE).
¶ The number of patients included in this row have at least one event in the following categories: APTC/MACE + other ischemic or thromboembolic mediated CV events (included under non-APTC/MACE) + CHF (included under non-APTC/MACE).

5.6.1.6 Framingham 10-year General Cardiovascular Disease Risk Estimates

The 10-year CVD risk estimates based on the Framingham Study [D'Agostino et al, 2008] were calculated using data from the EU/NA 12-week and long-term phase 3 studies. A summary of these analyses is provided in Appendix 4.

The assessment of CVD risk change associated with pharmacotherapy may be more accurately assessed using data from the 1-year double-blind study 178-CL-049, which included tolterodine ER as an active control, rather than data from the 12-week studies. In the EU/NA Long-term Controlled Population (Study 178-CL-049), median changes from baseline to final visit in CVD risk estimate using mean AM/PM SBP values were the same for mirabegron 50 mg (0.1%) and tolterodine ER 4 mg (0.1%). The percent of patients with increases from baseline to final visit in the 10-year general CVD risk estimate ≥ 5% based on mean AM/PM SBP values was 3.6% for the mirabegron 50 mg group and 4.1% for the tolterodine ER 4 mg group; 1 patient in the mirabegron 50 mg group and 0 patients in the tolterodine ER 4 mg group had a value ≥10%.

5.6.1.7 Summary of Vital Signs Analysis and CV outcomes

- Results of nonclinical and clinical pharmacology studies support the conclusion that modest beta 1-AR agonism occurs at high mirabegron exposures, with the potential for causing increases in pulse rate (Section 3.3.1).
- Mirabegron administered at the proposed therapeutic dose of 50 mg once daily is associated with an increase in pulse rate of approximately 1 bpm (adjusted mean change from baseline) compared to placebo in patients with OAB. A low proportion of patients experience tachycardia AE. The change from baseline in pulse rate following mirabegron at doses of 50 mg was similar to or less than the change from baseline in pulse rate described with several antimuscarinics used in the treatment of OAB including tolterodine, fesoterodine and trospium and tolterodine (measured with as a comparator in the mirabegron database). Consistent with this finding, rates of categorical changes in pulse rate and AE related to rapid pulse rate or tachyarrhythmeas were comparable between 50 mg of mirabegron and tolterodine.
- Mirabegron administered at the proposed therapeutic dose of 50 mg once daily may be associated with an adjusted mean increase of 0.4 to 0.6 mm Hg change from baseline SBP/DBP compared with placebo in patients with OAB. Unlike the change in pulse rate, the 95% CIs for the increase in blood pressure compared to placebo consistently included zero, despite a sample size of 1327 mirabegron 50 mg patients to 1329 placebo patients. Graphical exposure-effect analysis of SBP/DBP in patients with OAB indicated that there was no overall trend for change from baseline in either parameter with increasing mirabegron AUC. Categorical increases from baseline in SBP/DBP for the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations were generally comparable across all treatment groups and there was not an increase in AE rates of hypertension associated with mirabegron treatment compared with either placebo or tolterodine.

- There was no evidence of an increase in cardiovascular outcomes of death, SAE, ventricular arrhythmias or APTC/MACE events associated with mirabegron treatment compared to either placebo or tolterodine.

5.6.1.8 Mirabegron and QT Interval

Results from nonclinical in vitro studies showed that neither mirabegron nor its 5 most abundant human plasma metabolites had an effect on a panel of ion channels present in cardiomyocytes at clinically relevant concentrations [Table 76].

Table 76 Effect of Mirabegron and the 5 Most Abundant Human Metabolites on Myocardial Ion Channels

Analytes	Potassium current			Sodium current	Calcium current
	hERG (I_{Kr})	(I_{Ks})	(I_{to})	($I_{Nav1.5}$)	($I_{Cav1.2}$)
Mirabegron	Inhibition by 14.7% (657-fold)	No Effect (219-fold)	No Effect (219-fold)	Inhibition by 48.5% (219-fold)	Inhibition by 15.3% (219-fold)
M5	IC_{50}: 21 mcmol/L (1955-fold)	No Effect (931-fold)	No Effect (931-fold)	No Effect (931-fold)	No Effect (931-fold)
M11	No Effect (909-fold)	No Effect (303-fold)	No Effect (303-fold)	No Effect (303-fold)	No Effect (303-fold)
M12	No Effect (2142-fold)	No Effect (714-fold)	No Effect (714-fold)	No Effect (714-fold)	No Effect (714-fold)
M14	Inhibition by 17.3% (2553-fold)	No Effect (851-fold)	No Effect (851-fold)	No Effect (851-fold)	No Effect (851-fold)
M16	IC_{50}: 31 mcmol/L (2907-fold)	No Effect (938-fold)	No Effect (938-fold)	Inhibition by 10.5% (938-fold)	Inhibition by 8.8% (938-fold)

No effect was observed up to 30 mcmol/L for hERG and up to 10 mcmol/L for other channels.
Margins between IC_{50}, inhibitory concentrations or the highest treatment concentration and C_{max} /$C_{max,\ u}$ at a dose of 50 mg in elderly females are shown in parentheses. $C_{max,\ u}$ was used for mirabegron, M5 and M16 based on the protein binding rates in Caucasians at the lowest concentration tested. C_{max} was used for M11, M12 and M14.
hERG: human ether-a-go-go related gene; IC_{50}: 50% inhibition concentration; I_{Ca}: calcium current; I_{Kr}: fast component of the delayed rectifier K^+ current; I_{Ks}: slow component of the delayed rectifier K^+ current; I_{Na}: sodium current; I_{to}: transient outward current.

Studies in the dog isolated perfused ventricular wedge model showed that neither the parent compound nor its metabolites prolonged the QT interval or altered the transmural dispersion of repolarization.

Based on these findings, it is concluded that mirabegron has the potential to increase heart rate but the effect on cardiac electrophysiology is limited. The ion channel and isolated perfused ventricular tissue studies showed no discernable indication of ventricular proarrhythmic potential.

Ventricular tachycardia was observed in 3 of 8 monkeys in a 14-day repeated dose oral toxicity study at a 60 mg/kg per day dose of mirabegron. In the female monkey, this finding occurred at systemic exposures that were 29-fold greater than the human systemic exposure measured at the MRHD while in the males, the systemic exposure was 51-fold higher than the human systemic exposure. In the 13-week oral gavage repeated dose monkey study, one of 10 animals administered mirabegron at a dose of 30 mg/kg per day showed, at one of 6 postdose time points, an ECG waveform indicative of ventricular tachycardia. This finding was observed at a systemic exposure that was 13-fold greater than the human systemic exposure at the MRHD. This finding was seen only in this one animal and only at this one time point. Conversely, repeated oral administration of mirabegron at doses up to 30 mg/kg per day for 52 weeks did not result in ventricular tachycardia being observed in any animals.

Taken together, these data show that mirabegron, at the proposed therapeutic dose, has low ventricular arrhythmogenic potential.

Oral administration of mirabegron to conscious cynomolgus monkeys at doses up to 100 mg/kg (38.4-fold higher than the human equivalent dose at the MRHD) did not prolong the QT interval corrected using Bazett's correction formula (QTcB) interval. Heart rate was increased at doses of

≥ 10 mg/kg (3.8-fold higher than the human systemic exposure at the MRHD. In the 52-week repeated dose study in monkeys, oral administration of mirabegron at a dose of 30 mg/kg/day also had no statistically significant effect on the QTcB interval (systemic exposure 12.6-fold higher than the clinical exposure level at the MRHD) but female monkeys at this same dose (7.9-fold higher than the human systemic exposure at the MRHD) did show a significant QTcB interval prolongation only at the day 1 time point. This finding was absent when the QT interval was corrected using the Matsunaga formula [Matsunaga et al, 1998].

In dogs, QT interval corrected using Fridericia's correction formula (QTcF) prolongation was observed in both male and female dogs at a dose of 10 mg/kg (12.7- and 8.9-fold higher than the clinical exposure at the MRHD in males and females, respectively) on day 1 of dosing but not on day 14 (systemic exposure 25.1- and 13.8-fold higher than the human exposure at MRHD for males and females, respectively). Here, too, using the Matsunaga correction, no QT interval prolongation was observed.

5.6.1.8.1 TQT Studies of Mirabegron

Consistent with nonclinical evaluations, a dose-dependent increase in heart rate was reported in early phase 1 clinical studies; however no signal for QTc interval prolongation was detected. Since the nonclinical studies did not suggest a positive signal for proarrhythmic events or QTc prolongation, the formal TQT study, Study 178-CL-037, was conducted after the doses for evaluation in phase 3 studies of patients with OAB were identified. A second TQT study, Study 178-CL-077, was subsequently conducted to characterize the magnitude of effects observed in Study 178-CL-037.

5.6.1.8.1.1 TQT Study 178-CL-037

Study 178-CL-037 was a randomized, double blind, placebo- and active-controlled, crossover study designed to systematically evaluate the effects of 100 mg once daily and 200 mg once daily oral doses of mirabegron OCAS at steady state on the QTcI compared with placebo. A single 400 mg dose of moxifloxacin or matching moxifloxacin placebo was administered as an active control. The design of this study was in accordance with the guidelines established in ICH E14 and was comprised of 48 healthy male and female volunteers.

In the overall study population, mirabegron 100 mg and 200 mg showed no effects on the QT interval. However, a posthoc exploratory subgroup analysis by gender indicated an effect of mirabegron at doses of 100 mg and 200 mg on the QTcI interval, which was above the threshold of regulatory concern for female volunteers. A rigorous remeasurement and reanalysis of QT data successfully reduced data variability and revealed a more pronounced effect of mirabegron on the QTcI interval in the overall population and subgroup analyses. Under the guidelines set by ICH E14 (2005), mirabegron prolonged the QT interval in this study in females at supratherapeutic doses.

While the results from this TQT study suggested that mirabegron caused QTc prolongation in females at the 200 mg dose, the magnitude of this effect could not be determined, as posthoc analysis showed that the original analysis did not adequately correct for drug-induced increases in heart rate. In addition, this study was not adequately powered to detect gender-specific differences. In order to further characterize the effects observed in Study 178-CL-037, an additional Study 178-CL-077 was conducted to determine the magnitude of the effect of mirabegron on the QT interval.

5.6.1.8.1.2 TQT Study 178-CL-077

The second TQT Study 178-CL-077 was performed to assess the effect of mirabegron on QT at the proposed therapeutic dose of 50 mg and the supratherapeutic dose levels of mirabegron 100 and 200 mg. The doses of mirabegron were selected to explore the effect of mirabegron on QTc over a wide exposure range to also allow for accurate concentration-effect modeling. The study was powered separately for male and female volunteers.

Study Design

Study 178-CL-077 was a double-blind, randomized, placebo- and active-controlled, parallel crossover, phase 1 TQT study in which each active treatment was investigated in a separate group crossed over with placebo. Three hundred fifty-two (176 women and 176 men) volunteers were randomized to 1 of 8 treatment sequences and randomization was stratified by gender, with 22 women and 22 men assigned to each sequence.

The study consisted of two 10-day treatment periods (days 1-10). On days 1 to 9, volunteers received once daily dosing of mirabegron, mirabegron placebo or moxifloxacin placebo and on day 10, volunteers received mirabegron, mirabegron placebo, moxifloxacin or moxifloxacin placebo followed by a 1 day post-treatment period (day 11). Each treatment period was separated by a washout period of at least 12 days from day 10 of treatment period 1 to day -4 of treatment period 2.

Moxifloxacin was selected as a positive control since it is known to prolong QT/QTc intervals by between 5 and 10 msec [Couderc et al, 2006].

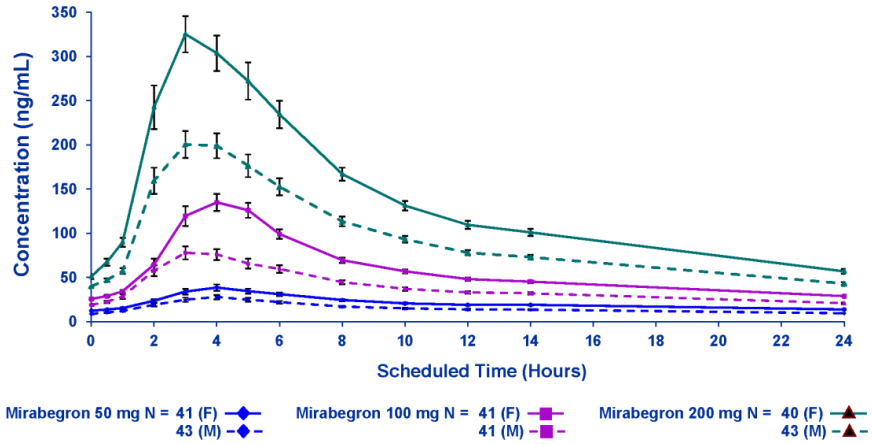
Results

Pharmacokinetic

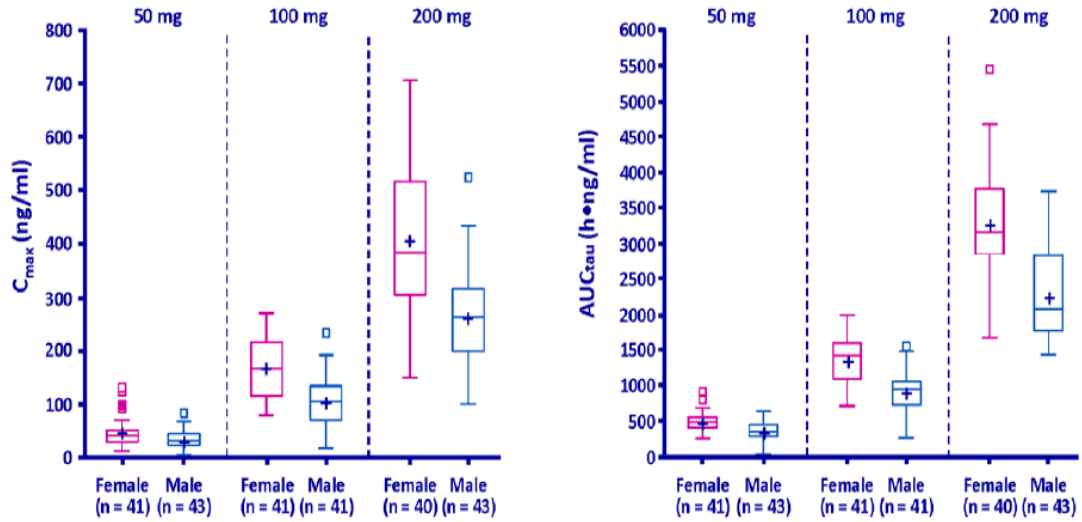
The bioavailability of mirabegron increased with dose, resulting in a more than a dose-proportional increase in C_{max} and AUC_{tau}. In the overall population, a 2-fold increase in dose of mirabegron (from 50 mg to 100 mg) increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a supratherapeutic dose of mirabegron 200 mg increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the proposed therapeutic dose of 50 mg [Figure 38].

Figure 38 **(A) Mean (SE) Steady-State Plasma Concentration-Time Profiles of Mirabegron in Females and Males and (B) Box Plots of C_{max} and AUC_{tau} for Mirabegron at Steady-State in Females and Males**

(A)



(B)



QTcI

To obtain smooth QT interval data and improve the measure of onset and offset, an analysis was performed on superimposed images of individual ECG leads of a representative median beat of each 10-second sample.

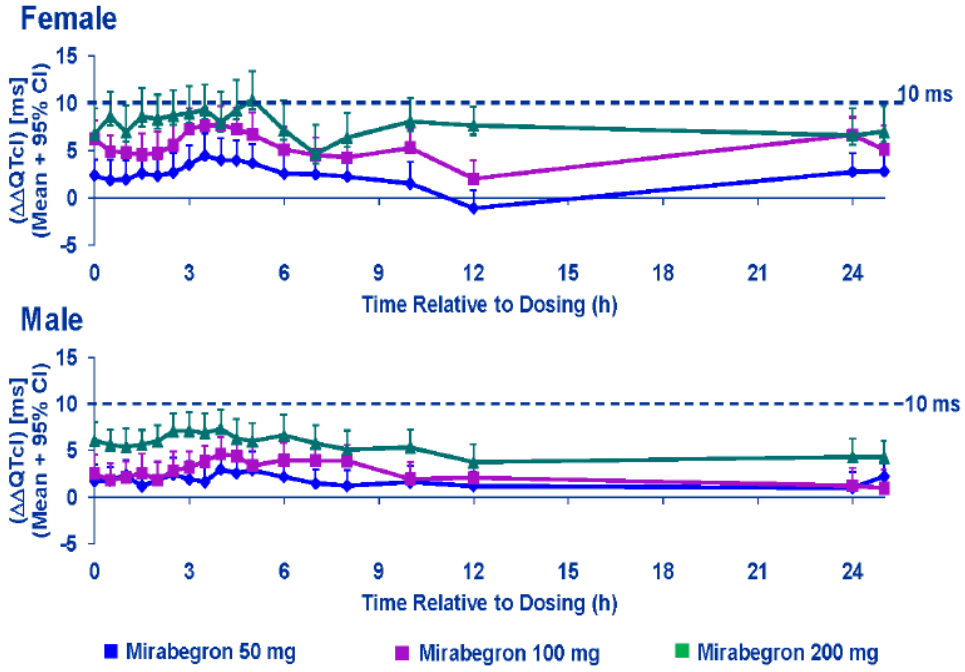
Since previous studies had shown a dose-dependent increase in HR with mirabegron treatment, extra measures were taken to assure that an adequate range of baseline HRs were obtained to cover the range of HRs on treatment. For the individual correction, data from 4 baseline days were used (days -3 and -1 of each treatment period). Five (if 5 were not available no fewer than 3) replicate QTcI measurements were averaged at each time point. In addition the volunteers were asked to perform postural provocative maneuvers (supine, sit or stand at attention) at designated times on the baseline days.

The summary of the primary analysis of ECG variable of time-matched change in the baseline-adjusted QTcI interval between mirabegron and placebo is presented overall and by gender

in Appendix 1, Table 16. Assay sensitivity was confirmed using moxifloxacin. The upper bound of the 1-sided 95% CI is equivalent to the upper bound of the 2-sided 90% CI.

For both males and females at mirabegron 50 mg and 100 mg, the upper bound of the 1-sided 95% CI did not exceed 10 msec at any time point for the largest time-matched mean difference from placebo in the QTcI interval [Figure 39]. In females administered mirabegron at the 50 mg dose, the mean difference with placebo on QTcI interval at 5 hours postdose was 3.67 msec (upper bound of the 1-sided 95% CI: 5.72 msec). In males, the difference was 2.89 msec (upper bound of the 1-sided 95% CI: 4.90 msec). In females administered mirabegron at the 100 mg dose the mean difference with placebo on QTcI interval at 5 hours postdose was 6.71 msec (upper bound of the 1-sided 95% CI: 9.07 msec). In males, the difference was 3.39 msec (upper bound of the 1-sided 95% CI: 5.40 msec). At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 msec at any time point in males, while in females, the upper bound of the one-sided 95% CI did exceed 10 msec between 0.5 to 6 hrs, with maximum difference with placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the 1-sided 95% CI: 13.44 msec).

Figure 39 Mean Change from Placebo, Baseline-Adjusted (+ Upper Bound 1-sided 95% CI) in QTcI Over Time on Days 10 and 11, by Gender



ΔΔQTcI: Difference in baseline-adjusted QTcI from placebo; QTcI: QT interval corrected for heart rate using individual-specific correction formula.

Categorical Changes in QTcI

The number of volunteers with categorical QTcI values and changes from baseline in QTcI using all replicate ECGs across all time points on days 10 and 11 are presented by sex and overall population in Table 77.

Table 77 QTcI Categorical Interval Value on Day 10 and Categorical Changes from Baseline to Day 10 and Day 11

QTcI Interval†, n (%) of volunteers	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Moxifloxacin 400 mg
Female					
n‡	153	41	38	37	37
> 450 msec	7 (4.6%)	2 (4.9%)	1 (2.6%)	5 (13.5%)	5 (13.5%)
> 480 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
n‡	152	41	37	37	36
> 30 msec increases§	0	0	0	2 (5.4%)	1 (2.8%)
> 60 msec increase§	0	0	0	0	0
Male					
n‡	163	42	40	39	42
> 450 msec	0	0	0	0	0
> 480 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
n‡	162	42	40	39	42
> 30 msec increases§	0	0	0	0	0
> 60 msec increase§	0	0	0	0	0
Overall					
n‡	316	83	78	76	79
> 450 msec	7 (2.2%)	2 (2.4%)	1 (1.3%)	5 (6.6%)	5 (6.3%)
> 480 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
n‡	314	83	77	76	78
> 30 msec increases§	0	0	0	2 (2.6%)	1 (1.3%)
> 60 msec increase§	0	0	0	0	0

Volunteers whose valid average ECG readings of QT interval and RR interval history were available for at least 15 (> 80%) of the 18 time points of both study periods during days 10 and 11 (Pharmacodynamic analysis set [PDAS]). Percentages were calculated as the total number of volunteers within each category divided by the total number of volunteers with a nonmissing value.
QTcI: QT interval corrected for heart rate using individual-specific correction formula.
† Using the average of the replicates at each time point.
‡ Number of volunteers with a nonmissing value.
§ Change is time-matched relative to day -1. Baseline results for day -1 at predose and 1 hour were used as the time-matched baseline for 24 and 25 hour postdose on day 10, respectively.

Summary of TQT Studies of Mirabegron

- In TQT Study 178-CL-037 the primary analysis demonstrated that mirabegron administration did not result in QT prolongation. Analysis by gender suggested that mirabegron caused QTc prolongation at a dose of 200 mg in females although the study was not powered for a formal gender evaluation. Posthoc re-analysis using extensive HR and hysteresis correction demonstrated high baseline variability and inadequate HR correction in the original analysis.
- In the TQT Study 178-CL-077, according to ICH E14 criteria, mirabegron did not cause QTcI prolongation at the proposed therapeutic dose of 50 mg or the supratherapeutic dose of 100 mg, a dose which increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold relative to the therapeutic dose of 50 mg. According to ICH E14 criteria, mirabegron prolonged the QTc interval in females at the supratherapeutic dose of 200 mg, a dose which increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the proposed therapeutic dose of 50 mg.

5.6.1.8.2 Summary of QT-Related Data from Clinical Studies

Methods

A program wide evaluation of the proarrythmic potential of mirabegron and the effect on QT/QTc interval was performed. This evaluation focused on AE findings consistent with a proarrythimic

potential event as well as ECG findings collected in the phase 1, 2 and 3 studies. Analyses of these safety data are aligned with those suggested in ICH E14.

This section summarizes the following in regard to the integrated safety data related to potential QTc interval prolongation or its sequelae:

- TEAE suggestive of QTc interval prolongation or its sequelae based on the MedDRA TdP/QT prolongation SMQ.
- A summary of other TEAE of interest including syncope, seizure and cardiac arrhythmias.
- Evaluation of objective centrally-read ECG data from the phase 2/3 studies.
- A summary of the TEAE from the TdP/QT prolongation SMQ and QTcF values where centrally read ECG data were available in phase 1 studies.

Additionally, subgroup analyses of TEAE and ECG findings were performed in accordance with ICH E14, including subgroups of gender, age, patients with and without baseline heart failure, evaluations of patients stratified by baseline potassium status, evaluation of patients stratified by baseline QTc interval status and evaluation of patients based on baseline renal status.

Results

- The frequency of QTc prolongation TEAE based on the MedDRA TdP/QT prolongation SMQ in patients with OAB was ≤ 0.4% and similar across placebo, mirabegron and tolterodine groups.
- In the EU/NA OAB 12-week Phase 3 Population:
  - There was a mean decrease from baseline to final visit in QTcF interval in the mirabegron treatment groups [Table 78].
  - QTcF values categorical changes were low across all treatment groups [Table 79].

Table 78 Summary Statistics of Baseline and Change from Baseline to Final Visit in QTcF on 12-Lead ECG, EU/NA OAB 12-week Phase 3 Population

Parameter	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
QTcF (msec)					
Baseline					
n	1346	432	1350	901	473
Mean (SD)	409.1 (22.64)	412.5 (20.83)	409.4 (22.47)	408.1 (23.56)	402.2 (23.72)
Median	408.0	412.0	408.0	407.0	399.0
Range	333 to 490	347 to 496	337 to 498	346 to 512	344 to 513
Change from Baseline to Final Visit					
n	1232	406	1226	823	421
Mean (SD)	-2.1 (17.49)	-2.3 (16.62)	-1.4 (17.52)	-2.2 (18.56)	1.1 (20.39)
Median	-3.0	-2.0	-2.0	-1.0	1.0
Range	-79 to 69	-44 to 82	-98 to 62	-88 to 73	-54 to 127
95% CI	(-3.1, -1.1)	(-3.9, -0.6)	(-2.4, -0.4)	(-3.4, -0.9)	(-0.8, 3.1)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ECG: electrocardiogram; ER: extended release; OAB: overactive bladder; QTcF: QT interval corrected using Fridericia's correction formula.

Table 79 QTcF Categorical Changes from Baseline, EU/NA OAB 12-week Phase 3 Population

QTcF Category, n (%) of patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
n†	1255	406	1243	843	438
> 450 msec	44 (3.5%)	14 (3.4%)	32 (2.6%)	27 (3.2%)	18 (4.1%)
> 480 msec	3 (0.2%)	0	3 (0.2%)	5 (0.6%)	3 (0.7%)
> 500 msec	1 (0.1%)	0	0	1 (0.1%)	1 (0.2%)
n†	1232	406	1226	823	421
≥ 30 msec to < 60 msec increase	42 (3.4%)	8 (2.0%)	52 (4.2%)	22 (2.7%)	23 (5.5%)
≥ 60 msec increase	2 (0.2%)	1 (0.2%)	1 (0.1%)	2 (0.2%)	2 (0.5%)
Total (≥ 30 msec) increase	44 (3.6%)	9 (2.2%)	53 (4.3%)	24 (2.9%)	25 (5.9%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
Percentages are calculated as the total number of patients within the maximum value or within the change from baseline category divided by the total number of patients with a nonmissing value. For each parameter, the maximum value during the treatment period was used.
ER: extended release; OAB: overactive bladder; QTcF: QT interval corrected using Fridericia's correction formula.
† Number of patients with a nonmissing value.

- In the EU/NA Long-term Controlled Population,
  - Mean QTcF change from baseline to final visit are presented in Table 80.
  - QTcF values categorical changes similar across the mirabegron groups [Table 81].

Table 80 Summary Statistics of Baseline and Change from Baseline to Final Visit in QTcF on 12-Lead ECG, EU/NA Long-term Controlled Population

Parameter	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
QTcF Interval (msec)			
Baseline			
n	804	813	801
Mean (SD)	405.0 (22.01)	404.5 (23.48)	405.4 (24.63)
Median (Range)	405.0 (343 to 514)	404.0 (317 to 507)	404.0 (337 to 550)
Change from Baseline to Final Visit			
n	729	741	724
Mean (SD)	1.0 (18.90)	-0.2 (19.37)	1.5 (19.70)
Median (Range)	1.0 (-66 to 78)	0.0 (-76 to 69)	2.0 (-72 to 60)
95% CI	(-0.4, 2.4)	(-1.6, 1.2)	(0.1, 2.9)

Study included: 178-CL-049.
Baseline was the last value measured on or prior to the first dose of double-blind study drug. Data measured > 10 days after the last dose of double-blind study drug were not included in the summary.
ECG: electrocardiogram; ER: extended release; QTcF: QT interval corrected using Fridericia's correction formula.

Table 81 QTcF Categorical Change from Baseline, EU/NA Long-term Controlled Population

QTcF Category, n (%) of patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
n†	736	747	733
> 450 msec	36 (4.9%)	29 (3.9%)	32 (4.4%)
> 480 msec	5 (0.7%)	2 (0.3%)	6 (0.8%)
> 500 msec	2 (0.3%)	1 (0.1%)	1 (0.1%)
n†	729	741	724
≥ 30 msec to < 60 msec increase	73 (10.0%)	64 (8.6%)	74 (10.2%)
≥ 60 msec increase	3 (0.4%)	3 (0.4%)	3 (0.4%)
Total (≥ 30 msec) increase	76 (10.4%)	67 (9.0%)	77 (10.6%)

Footnotes continued on next page.

Study included: 178-CL-049.
Percentages are calculated as the total number of patients within the maximum value or within change from baseline category divided by the total number of patients with a nonmissing value. For each parameter, the maximum value during the treatment period was used.
ER: extended release; OAB: overactive bladder; QTcF: QT interval corrected using Fridericia's correction formula.
† Number of patients with a nonmissing value.

Analyses of QTcF data revealed:

- Female OAB patients in the EU/NA OAB 12-week Phase 3 Population had a higher frequency of maximum QTcF values > 450 msec compared with males and the frequency of QTcF change from baseline of ≥ 30 msec and < 60 msec was similar in female and male patients.
- In the EU/NA Long-term Controlled Population the frequency of maximum QTcF values > 450 msec was similar in female and male patients and the frequency of QTcF change from baseline of ≥ 30 msec and < 60 msec was higher in female compared with male patients. No trends between females and males were observed in other categorical QTcF analyses;
- Elderly OAB patients ≥ 65 years of age had a higher frequency of maximum QTcF values > 450 msec and change from baseline in QTcF ≥ 30 msec and < 60 msec compared with younger patients with no differences observed across the treatment groups. No trends between patients < 65 and ≥ 65 years of age were observed in other QTcF analyses;
- In OAB patients, no differences were observed in QTcF analyses based on BMI, geographical region and baseline renal status. Limited number of patients within certain subgroup populations preclude definitive conclusions based on race, ethnicity, baseline potassium status and baseline QTc status;
- In the mirabegron phase 1 studies, where ECGs were centrally read, ECG abnormalities of QT prolongation were not reported and volunteers did not report QTc-related TEAE.
- There were no AE of TdP in the development program.

5.6.2 Urinary Tract Events

The data demonstrate that mirabegron is not associated with AUR:

- In the Global OAB 12-week Phase 2/3 Population, few TEAE of urinary retention were reported across the treatment groups with frequency in mirabegron-treated patients less than that observed for placebo- or tolterodine-treated patients; 1/2131 (<0.1%) mirabegron 50 mg patient, 1/167 (0.6%) mirabegron 200 mg patient, 3/958 (0.3%) tolterodine ER 4 mg patients and 7/2142 (0.3%) placebo patients [Appendix 1, Table 26]. AUR was reported as a TEAE for 3/2142 (0.1%) placebo treated patients, 1/2131 (<0.1%) mirabegron 50 mg-treated patient and 3/958 (0.3%) tolterodine-treated patients. The mirabegron 50 mg treated patient had a SAE AUR, a 59-year-old male with significant benign prostate hyperplasia and prostate adenoma who required transurethral resection of the prostate for resolution of BOO.
- In the Global OAB 12-week Phase 2/3 Population, there was no difference in PVR volume mean change from baseline or shift analyses across treatment groups [Table 54; Appendix 1, Table 27].
- In the EU/NA Long-term Controlled Population, 2 TEAE for AUR were reported, one in mirabegron 100 mg (occurred in a 59-year-old female immediate post-op for severe lumbar spinal stenosis) and one patient in tolterodine (65-year-old man with chronic history of LUTS discontinued study drug due to the event) [Appendix 1, Table 26].
- No events of AUR were observed in mirabegron-treated patients in Studies 178-CL-047 and 178-CL-074, where patients at risk for AUR were not specifically excluded.
- In a urodynamic safety study in 200 male patients at risk for AUR (LUTS/BOO), administration of mirabegron at doses of 50 and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate [Table 82]. Two TEAE of

urinary retention were reported, one in a placebo-treated patient requiring catheterization and one in a mirabegron 100 mg-treated patient which resolved without invasive intervention.

Table 82 Mean Change from Baseline in Maximum Flow Rate and Detrusor Pressure at Maximum Flow Rate, Study 178-CL-060

		Placebo (n = 63)	Mirabegron 50 mg (n = 64)	Mirabegron 100 mg (n = 58)
Maximum Flow Rate, Q_{max} (mL/sec)				
Baseline	Actual Mean (SD)	7.37 (3.700)	7.30 (3.215)	7.62 (3.433)
EOT	Actual Mean (SD)	7.06 (3.047)	7.44 (3.907)	7.83 (4.005)
EOT	Adjusted Mean Change from Baseline (SE) †	-0.33 (0.370)	0.07 (0.366)	0.30 (0.388)
Treatment difference compared with placebo (95% CI) ‡			0.40 (**-0.63**, 1.42)	0.62 (**-0.43**, 1.68)
Detrusor Pressure at Maximum Flow Rate, $P_{det}Q_{max}$ (cmH_2O)				
Baseline	Actual Mean (SD)	69.56 (28.468)	70.72 (33.689)	66.95 (20.694)
EOT	n Actual Mean (SD)	63 71.84 (33.879)	64 66.84 (31.912)	57 68.19 (28.051)
EOT	n Adjusted Mean Change from Baseline (SE) †	63 2.92 (2.906)	64 -3.03 (2.872)	57 1.53 (3.086)
Treatment difference compared with placebo (95% CI) §			-5.94 (-13.98, **2.09**)	-1.39 (-9.73, **6.96**)

Study included: 178-CL-060.
All randomized patients who received at least one dose of double-blind study drug and had both urodynamic measurements (cystometry measurement of Q_{max} and $P_{det}Q_{max}$) at baseline and one or both measured at any postbaseline on-treatment visit.
EOT: end of treatment, the last on-treatment assessment (includes patients who did not complete the week 12 visit);
Q_{max}: maximum flow rate; $P_{det}Q_{max}$: detrusor pressure at maximum flow rate.
† Adjusted for pooled centers and baseline values.
‡ Noninferiority was demonstrated if the lower limit of the 95% CI for the treatment difference in change from baseline as compared with placebo was > -3.
§ Noninferiority was demonstrated if the upper limit of the 95% CI for the treatment difference in change from baseline as compared with placebo was < 15.

UTI has been identified as an adverse drug reaction with mirabegron. The frequency of UTI, including severity and treatment relationship, is presented in Table 38 for the EU/NA OAB 12-week Phase 3 Population and in Table 40 for the EU/NA Long-term Population. The majority of UTI TEAE were mild or moderate in severity.

There was no evidence of a mirabegron dose response and the frequency was comparable to tolterodine for the Global OAB 12-week Phase 2/3 Population (mirabegron: 4.3% and tolterodine: 4.4%) and the EU/NA Long-term Populations (mirabegron: 8.8% and tolterodine: 10.0%). Very few of the cases of UTI were serious or resulted in permanent discontinuation of study drug. One case (1/5863, <0.1%) of UTI was serious and 3/5863 (0.1%) mirabegron-treated patients and 1/2142 (<0.1%) placebo-treated patients had a UTI which resulted in permanent discontinuation of study drug.

The frequency of urolithiasis was generally < 0.5%, comparable across the mirabegron, placebo and tolterodine treatment groups, and few events were serious or resulted in permanent discontinuation of study drug. Renal colic was reported in 2 patients in the Global OAB 12-week Phase 2/3 Population (mirabegron 50 mg: 1/2131, <0.1%; and mirabegron 100 mg: 1/1305, 0.1%), 3 patients in the EU/NA Long-term Controlled Population (mirabegron 50 mg: 1/812, 0.1%; mirabegron 100 mg: 1/820, 0.1%; and tolterodine ER 4 mg: 1/812, 0.1%). Renal colic TEAE in these patients were not considered serious and did not result in discontinuation of treatment. One volunteer who received mirabegron 160 mg and metformin 500 mg in a phase 1 study was hospitalized 14 days after study completion with renal colic. A small ureter stone was found. He recovered completely. Results from the urinalysis at the end-of-study visit had been normal.

5.6.3 Neoplasm

5.6.3.1 Results of Nonclinical Genotoxicity Studies and Carcinogenicity Studies with Mirabegron

5.6.3.1.1 Genotoxicity

The genotoxicity of mirabegron was evaluated in vitro by the bacterial reverse mutation assay, the human chromosome aberration assay and rat micronucleus test. The results of these studies showed no nonclinical signal of genotoxicity with mirabegron [Table 83].

Table 83 Summary of Nonclinical Genotoxicity Studies

Assay/Test	Concentration/ Dose	Results	Comments
Bacterial Reverse Mutation Assay	1.6 – 5000 mcg/plate with and without S9 microsomal fraction	Negative	Without S9: Bacterial growth inhibited above 625 mcg/plate With S9: Bacterial growth inhibited above 2500 mcg/plate No genotoxicity observed with any of the test strains of bacteria when compared to vehicle controls.
Chromosome Aberration Assay	655 – 1280 mcg/mL with S9 110 – 215 mcg/mL without S9	Negative	Human peripheral blood lymphocytes treated with mirabegron for 3 hours plus S9: No increase in the number of cells with chromosome aberrations at concentrations up to 1255 mcg/mL Human peripheral blood lymphocytes treated with mirabegron for 20 hours without S9: No increase in the number of cells with chromosomal aberrations was observed at 214.7 mcg/mL.
Rat Micronucleus Test	100 – 400 mg/kg, oral gavage	Negative	Mirabegron did not induce micronuclei in the bone marrow of rats at doses up to 400 mg/kg.

5.6.3.1.2 Carcinogenicity

Carcinogenic potential was determined in mice and rats administered mirabegron daily for 104 weeks [Table 84]. Based on the results, it was concluded that mirabegron showed no discernable carcinogenic potential in mice or rats at systemic exposures listed in Table 85.

Table 84 Summary of Nonclinical Carcinogenicity Studies

Assay/Test	Concentration/ Dose	Results	Comments
Mouse 104 week Carcinogenicity Test	25, 50 and 100 mg/kg, oral gavage	Negative	No treatment related increase in the incidence of tumor compared to vehicle treated controls. All neoplastic findings were typical of those observed in chronic studies with $B6C3F_1$ mice. There were no increases in non-neoplastic findings associated with mirabegron administration.
Rat 104-week Carcinogenicity Test	Males: 12.5, 25 and 50 mg/kg Females: 25, 50 and 100 mg/kg oral gavage	Negative	No treatment related increase in the incidence of tumor compared to vehicle treated controls. All neoplastic findings were typical of those observed in chronic studies with F344 rats. There were no increases in non-neoplastic findings associated with mirabegron administration.

Table 85 Comparison of Exposure at Various Doses in Carcinogenicity Studies and at MRHD

Type of Study	Animal species	Administration period	Dosage† (mg/kg/day)	Exposure ratio‡			
				C_{max}		AUC	
				Male	Female	Male	Female
Carcinogenicity	Mice	104 weeks	25	15.0	18.2	5.8	4.7
			50	30.3	14.2	13.9	9.1
			100	43.4	28.7	37.8	20.9
	Rats	104 weeks	12.5/25	22.8	17.1	10.3	11.6
			25/50	24.6	29.5	18.1	23.9
			50/100	50.3	56.9	38.1	45.0

MRHD: maximum recommended human dose.
† Dosage in rats was different for males and females, table presents dose for males/females.
‡ Comparison with values in elderly males and females at MRHD (50 mg).

In addition to the rodent chronic repeated dose rat studies (26-week) and the 2 rodent carcinogenicity studies, nonrodents were also chronically administered mirabegron. Cynomolgus monkeys (4 males and 4 females per group) were administered mirabegron by oral gavage daily for 52 weeks at a dose of 0, 3, 10 or 30 mg/kg. Toxicokinetics were determined on day 1, as well as on weeks 13, 27 and 52. At the end of the dosing period, the animals were terminated. Histolopathologic evaluation showed no neoplastic or hyperplastic findings in any of the organs.

This data supports that mirabegron and its metabolites do not induce a proliferative response in vivo. This absence of hyperplastic findings also supports that mirabegron would not act to induce tumor growth.

5.6.3.2 Clinical Evaluation of Potential Neoplasm Events in the Mirabegron Clinical Development Program

SAE within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) in the Global 12-week Phase 2/3 Population, consisting of 6 studies, were observed to be nominally higher in total mirabegron group compared with placebo group in one of these studies, Study 178-CL-047. In the EU/NA Long-term Controlled Population (Study 178-CL-049), SAE within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) were nominally higher in the mirabegron 100 mg treatment group compared with mirabegron 50 mg and tolterodine treatment groups. The reported SAE within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) were heterogeneous and represented benign as well as malignant events, generally reflecting the most prevalent malignancies in US and Europe [US Cancer Statistics Working Group, 2010;EUROCARE Working Group, 2011].

Patients with previous or current malignant disease of the pelvic organs were excluded from the phase 2/3 clinical trials conducted in EU/NA. Studies conducted in Japan excluded patients with previous history of bladder or prostate tumors, and patients with malignant tumors (except those who have not received treatment for malignant tumors for at least 5 years before initiation of the pretreatment period and were not considered to have a recurrence).

A program-wide evaluation was completed to compare the frequency of neoplasms, with particular focus upon new malignant events, across total mirabegron, placebo and active control treatment groups. Through application of broad search criteria, both serious and nonserious potential neoplasm events were identified.

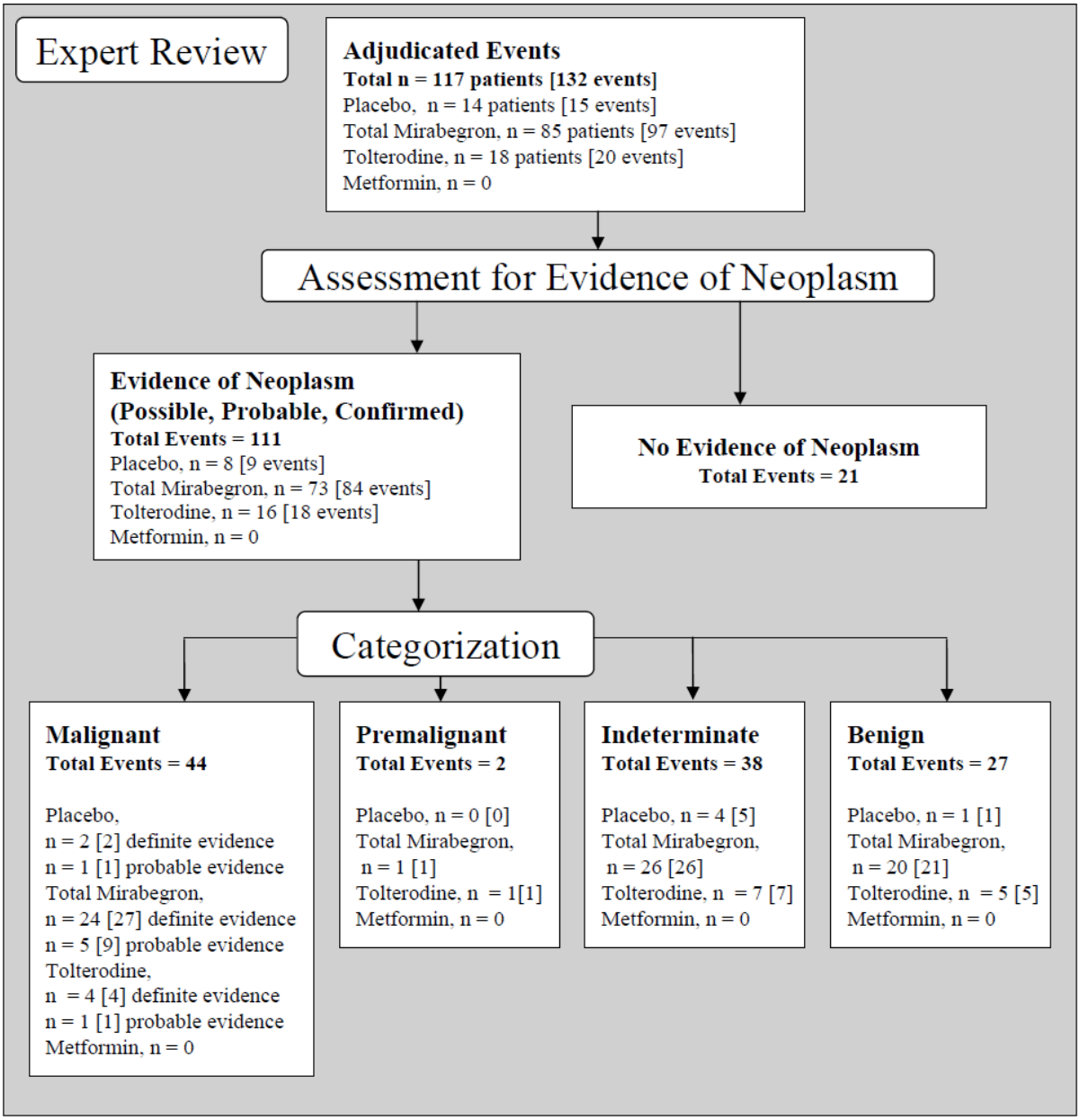
This evaluation was supported by an Independent Adjudication Committee comprised of oncology specialists. The primary objective of the Adjudication Committee was to conduct blinded review of available clinical information for individual subjects with reported potential neoplasm events. The Adjudication Committee assessed the malignancy status of the neoplasm for events that were

identified as having evidence of neoplasm and categorized them as: malignant neoplasm, premalignant neoplasm, indeterminate or benign neoplasm.

5.6.3.3 Adjudication Committee Assessment of Evidence of Neoplasm

An overview of the assessment by the adjudication committee of the 132 potential neoplasm events reported in 117 patients in the Global Phase 2/3 Population is presented in Figure 40.

Figure 40 Summary of Adjudicated Potential Neoplasm Events in the Global Phase 2/3 Population by Treatment Group



Number of patients with at least one event (n) and [number of events] are presented. A patient may have more than one adjudicated event.

5.6.3.4 Analysis of Adjudicated Malignant Events

Overall, across the entire global phase 2/3 program, a total of 44 events in 37 patients were adjudicated as malignant [Table 86].

Table 86 Adjudication Summary of Malignant Events, Global Phase 2/3 Population

Adjudication Outcome	Treatment Group					
	Placebo		Total Mirabegron		Tolterodine ER 4 mg	
	Patients	Events	Patients	Events	Patients	Events
All Events	**3**	**3**	**29**	**36**	**5**	**5**
New Event	2	2	21	27	4	4
Pre-existing Event with Evidence of Worsening	0	0	3	4	0	0
Pre-existing Event with No Evidence of Worsening	1	1	5	5	1	1

ER: extended release.

All patients with adjudicated new malignant events are summarized in this document for the following populations:

- Global OAB 12-week Phase 2/3 Population (placebo-controlled) and
- EU/NA Long-term Controlled Population (12-months active-controlled)
- Global Phase 2/3 Population

5.6.3.4.1 Global OAB 12-Week Phase 2/3 Population Analysis of New Malignant Events

A total of 10 new malignant events were reported in 9 patients in the Global OAB 12-week Phase 2/3 Population [Table 87]. New malignant events reported in Study 178-CL-047 accounted for the majority of new malignant events (7 of 8 events reported in the total mirabegron group) in the Global OAB 12-week Phase 2/3 Population.

Table 87 Summary of New Malignant AE by Study, Global OAB 12-week Phase 2/3 Population

MedDRA(v12.1) PT† n (%) of Patients	Placebo		Total Mirabegron		Tolterodine ER 4 mg		Combined Comparator‡	
	N	E	N	E	N	E	N	E
Overall pooled population	**(n = 2142)**		**(n = 4414)**		**(n = 958)**		**(n = 3100)**	
Overall	2 (0.09%)	2	7 (0.16%)	8	0		2 (0.06%)	2
RR (95% CI) § - placebo			1.70 (0.32, 16.78)					
RR (95% CI) ¶ - comparator			2.46 (0.47, 24.29)					
Individual Study Analyses								
178-CL-044	**(n = 169)**		**(n = 673)**		**(n = 85)**		**(n = 254)**	
Overall	0	0	0	0	0	0	0	0
178-CL-045	**(n = 213)**		**(n = 626)**		**(n = 0)**		**(n = 213)**	
Overall	0	0	0	0	0	0	0	0
178-CL-046	**(n = 494)**		**(n = 989)**		**(n = 495)**		**(n = 989)**	
Overall	1 (0.20%)	1	0	0	0	0	1 (0.10%)	1
Skin neoplasm excision	1 (0.20%)	1	0	0	0	0	1 (0.10%)	1
178-CL-047	**(n = 453)**		**(n = 875)**		**(n = 0)**		**(n = 453)**	
Overall	0	0	6 (0.69%)	7	0	0	0	0
Basal cell carcinoma	0	0	2 (0.23%)	2	0	0	0	0
Prostate cancer	0	0	2 (0.23%)	2	0	0	0	0
Lung carcinoma cell type unspecified recurrent	0	0	1 (0.11%)	1	0	0	0	0
Malignant melanoma	0	0	1 (0.11%)	1	0	0	0	0
Malignant melanoma with metastases to lymph nodes	0	0	1 (0.11%)	1	0	0	0	0
178-CL-048	**(n = 380)**		**(n = 379)**		**(n = 378)**		**(n = 758)**	
Overall	0	0	0	0	0	0	0	0
178-CL-074	**(n = 433)**		**(n = 872)**		**(n = 0)**		**(n = 433)**	
Overall	1 (0.23%)	1	1 (0.11%)	1	0	0	1 (0.23%)	1
Basal cell carcinoma	1 (0.23%)	1	1 (0.11%)	1	0	0	1 (0.23%)	1

Footnotes on the following page.

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
AE: adverse event(s); ER: extended release; OAB: overactive bladder; PT: preferred term; RR: relative risk.
† N was the number of patients with a response, E was the number of events. Sorting order: decreasing percentage by PT.
‡ The combined comparator group included placebo and tolterodine.
§ RR was the relative risk versus placebo. Odds ratios and exact 95% CIs were used to estimate relative risks.
¶ RR was the relative risk versus combined comparator group, using the same analysis as described in § above.

Sensitivity Analysis for Dose

The results of a sensitivity analysis based on dose of mirabegron are presented in Table 88. The new malignant events were heterogeneous with ≤ 2 events reported by tumor organ of origin in any treatment group.

Table 88 Summary of New Malignant AE, Sensitivity Analysis by Dose Group, Global OAB 12-week Phase 2/3 Population

MedDRA(v12.1) Tumor Organ of Origin † PT n (%) of Patients	Mirabegron 25 mg (n = 811)	E	Mirabegron 50 mg (n = 2131)	E	Mirabegron 100 mg (n = 1305)	E	Mirabegron 200 mg (n = 167)	E
Overall	0	0	5 (0.23%)	6	2 (0.15%)	2	0	0
Skin (NonMelanoma)	0	0	2 (0.09%)	2	1 (0.08%)	1	0	0
Basal cell carcinoma	0	0	2 (0.09%)	2	1 (0.08%)	1	0	0
Prostate	0	0	2 (0.40%)	2	0	0	0	0
Prostate cancer	0	0	2 (0.40%)	2	0	0	0	0
Skin (Melanoma)	0	0	1 (0.05%)	2	0	0	0	0
Malignant melanoma	0	0	1 (0.05%)	1	0	0	0	0
Malignant melanoma with metastases to lymph nodes	0	0	1 (0.05%)	1	0	0	0	0
Lung	0	0	0	0	1 (0.08%)	1	0	0
Lung carcinoma cell type unspecified recurrent	0	0	0	0	1 (0.08%)	1	0	0

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
AE: adverse event(s); OAB: overactive bladder; PT: preferred term.
† N was the number of patients with a response, E was the number of events. Sorting order: decreasing percentage by tumor organ of origin and decreasing percentage by PT.

5.6.3.4.2 EU/NA Long-Term Controlled Population Analysis of New Malignant Events

Of the 2444 patients in Study 178-CL-049, 1389 patients had been previously treated in Study 178-CL-046, 599 patients had been previously treated in Study 178-CL-047 and the remaining 456 patients were not enrolled from a previous mirabegron study. Patients who participated in 2 sequential studies may have been randomized to the same or different treatment groups. Therefore, analyses herein are presented by treatment groups for each study.

In the EU/NA Long-term Controlled Population, a total of 21 events were reported in 16 patients Table 90.

Blinded assessment by the Adjudication Committee determined that 11/21 new malignant events reported for patients in the EU/NA Long-term Controlled Population were possibly related to the study drug (total mirabegron: 8/17 events [transition cell carcinoma, lung neoplasm malignant, pancreatic carcinoma, basal cell carcinoma (3 patients) and endometrial cancer (2 patients)]; total tolterodine: 3/4 events [breast cancer (2 patients) and endometrial cancer])

Sensitivity Analysis by Dose

There were no notable differences across the dose groups by tumor organ of origin [Table 89].

Table 89 Summary of New Malignant AE, Sensitivity Analysis for Tertiary Treatment Groups, EU/NA Long-term Controlled Population

MedDRA(v12.1) Tumor Organ of Origin † PT† n (%) of Patients	Mirabegron 50 mg (n = 812)	E	Mirabegron 100 mg (n = 820)	E	Total Tolterodine (n = 812)	E
Overall	3 (0.37%)	7	9 (1.10%)	10	4 (0.49%)	4
Skin (NonMelanoma)	3 (0.37%)	7	2 (0.24%)	2	1 (0.12%)	1
Basal cell carcinoma	3 (0.37%)	7	2 (0.24%)	2	0	0
Squamous cell carcinoma	0	0	0	0	1 (0.12%)	1
Breast	0	0	2 (0.33%)	2	2 (0.33%)	2
Breast cancer	0	0	2 (0.33%)	2	2 (0.33%)	2
Prostate	0	0	1 (0.47%)	2	0	0
Prostate cancer	0	0	1 (0.47%)	1	0	0
Prostatic specific antigen increased	0	0	1 (0.47%)	1	0	0
Uterus	0	0	1 (0.16%)	1	1 (0.17%)	1
Endometrial cancer	0	0	1 (0.16%)	1	1 (0.17%)	1
Bladder	0	0	1 (0.12%)	1	0	0
Transition cell carcinoma	0	0	1 (0.12%)	1	0	0
Lung	0	0	1 (0.12%)	1	0	0
Lung neoplasm malignant	0	0	1 (0.12%)	1	0	0
Pancreas	0	0	1 (0.12%)	1	0	0
Pancreatic carcinoma	0	0	1 (0.12%)	1	0	0

Study included: 178-CL-049.
AE: adverse event(s); PT: preferred term.
† N was the number of patients with a response, E was the number of events. Sorting Order: Decreasing percentage by tumor organ of origin and decreasing percentage by PT.

Table 90 Summary of New Malignant AE, EU/NA Long-term Controlled Population

MedDRA(v12.1) Tumor Organ of Origin † PT	Mirabegron Only (n = 1395)		Tolterodine (12 week) → Mirabegron (12 month) (n = 237)		Tolterodine Only (n = 444)		Mirabegron (12 week) → Tolterodine (12 month) (n = 368)		Total Mirabegron (n = 1632)		Total Tolterodine (n = 812)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Overall	11 (0.79%)	16	1 (0.42%)	1	3 (0.68%)	3	1 (0.27%)	1	12 (0.74%)	17	4 (0.49%)	4
RR (95% CI) ‡	1.17 (0.31, 6.55)											
RR (95% CI) §									1.50 (0.45, 6.38)			
Skin (NonMelanoma)	5 (0.36%)	9	0	0	0	0	1 (0.27%)	1	5 (0.31%)	9	1 (0.12%)	1
Basal cell carcinoma	5 (0.36%)	9	0	0	0	0	0	0	5 (0.31%)	9	0	0
Squamous cell carcinoma	0	0	0	0	0	0	1 (0.27%)	1	0	0	1 (0.12%)	1
Prostate	1 (0.28%)	2	0	0	0	0	0	0	1 (0.24%)	2	0	0
Prostate cancer	1 (0.28%)	1	0	0	0	0	0	0	1 (0.24%)	1	0	0
Prostatic specific antigen increased	1 (0.28%)	1	0	0	0	0	0	0	1 (0.24%)	1	0	0
Breast	2 (0.19%)	2	0	0	2 (0.59%)	2	0	0	2 (0.17%)	2	2 (0.33%)	2
Breast cancer	2 (0.19%)	2	0	0	2 (0.59%)	2	0	0	2 (0.17%)	2	2 (0.33%)	2
Uterus	1 (0.10%)	1	0	0	1 (0.30%)	1	0	0	1 (0.08%)	1	1 (0.17%)	1
Endometrial cancer	1 (0.10%)	1	0	0	1 (0.30%)	1	0	0	1 (0.08%)	1	1 (0.17%)	1
Bladder	1 (0.07%)	1	0	0	0	0	0	0	1 (0.06%)	1	0	0
Transition cell carcinoma	1 (0.07%)	1	0	0	0	0	0	0	1 (0.06%)	1	0	0

Table continued on next page.

MedDRA(v12.1) Tumor Organ of Origin †	Mirabegron Only (n = 1395)		Tolterodine (12 week) → Mirabegron (12 month) (n = 237)		Tolterodine Only (n = 444)		Mirabegron (12 week) → Tolterodine (12 month) (n = 368)		Total Mirabegron (n = 1632)		Total Tolterodine (n = 812)	
PT	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Lung	1 (0.07%)	1	0	0	0	0	0	0	1 (0.06%)	1	0	0
Lung neoplasm malignant	1 (0.07%)	1	0	0	0	0	0	0	1 (0.06%)	1	0	0
Pancreas	0	0	1 (0.42%)	1	0	0	0	0	1 (0.06%)	1	0	0
Pancreatic carcinoma	0	0	1 (0.42%)	1	0	0	0	0	1 (0.06%)	1	0	0

Study included: 178-CL-049.
AE: adverse event(s); PT: preferred term; RR: relative risk.
† N was the number of patients with a response, E was the number of events. Sorting order: decreasing percentage by tumor organ of origin and decreasing percentage by PT.
‡ RR was the relative risk versus tolterodine only. Odds ratios and exact 95% CIs were used to estimate relative risks.
§ RR was the relative risk versus total tolterodine using the same analysis as described in ‡.

5.6.3.4.3 Global Phase 2/3 Population

Sensitivity Analysis for Dose

A sensitivity analysis, based on dose, demonstrated that the incidence rate per patient years at risk for new malignant events was 0.0101 (1.01 per 100 patient years at risk) in the mirabegron dose interval of ≥ 100 mg to < 200 mg compared with 0.0051 (0.51 per 100 patient years at risk) in the mirabegron dose interval of ≥ 50 mg to < 100 mg; no new malignant events were reported in the lower mirabegron dose intervals (< 25 mg or ≥ 25 mg to < 50 mg) or at the highest mirabegron dose interval (≥ 200 mg) [Table 91].

New malignant events were heterogeneous with no notable differences across the dose groups by tumor organ of origin [Table 91].

Table 91 New Malignant AE per Patient Years at Risk, Sensitivity Dose-range Analysis of Secondary Treatment Groups, Global Phase 2/3 Population

MedDRA(v12.1) Tumor Organ of Origin PT †	Mirabegron < 25 mg	Mirabegron ≥ 25 mg to < 50 mg	Mirabegron ≥ 50 mg to < 100 mg	Mirabegron ≥ 100 mg to < 200 mg	Mirabegron ≥ 200 mg	Mirabegron Dose Titration
Patient-years at Risk	0	244.77	1566.20	1186.87	71.74	75.58
Overall ‡	0	0/244.77 (0)	8/1563.87 (0.0051)	12/1183.53 (0.0101)	0/71.74 (0)	1/75.44 (0.0133)
Prostate‡	0	0/61.08 (0)	2/393.10 (0.0051)	1/306.61 (0.0033)	0/6.07 (0)	0/ 25.79 (0)
Prostate cancer	0	0	2	1	0	
Prostatic specific antigen increased	0	0	0	1	0	
Uterus‡	0	0/183.68 (0)	0/1172.97 (0)	1/879.94 (0.0011)	0/65.67 (0)	0/49.79 (0)
Endometrial cancer	0	0	0	1	0	
Breast ‡	0	0/183.68 (0)	0/1172.97 (0)	2/878.62 (0.0023)	0/65.67 (0)	0/49.79 (0)
Breast cancer	0	0	0	2	0	
Skin (Melanoma) ‡	0	0/244.77 (0)	1/1565.94 (0.0006)	0/1186.87 (0)	0/71.74 (0)	0/75.58 (0)
Malignant melanoma	0	0	1	0	0	
Metastases to lymph nodes	0	0	1	0	0	
Skin (Nonmelanoma) ‡	0	0/244.77 (0)	5/1564.26 (0.0032)	4/1185.77 (0.0034)	0/71.74 (0)	1/75.44 (0.0133)
Basal cell carcinoma	0	0	5	4	0	1

Table continued on next page.

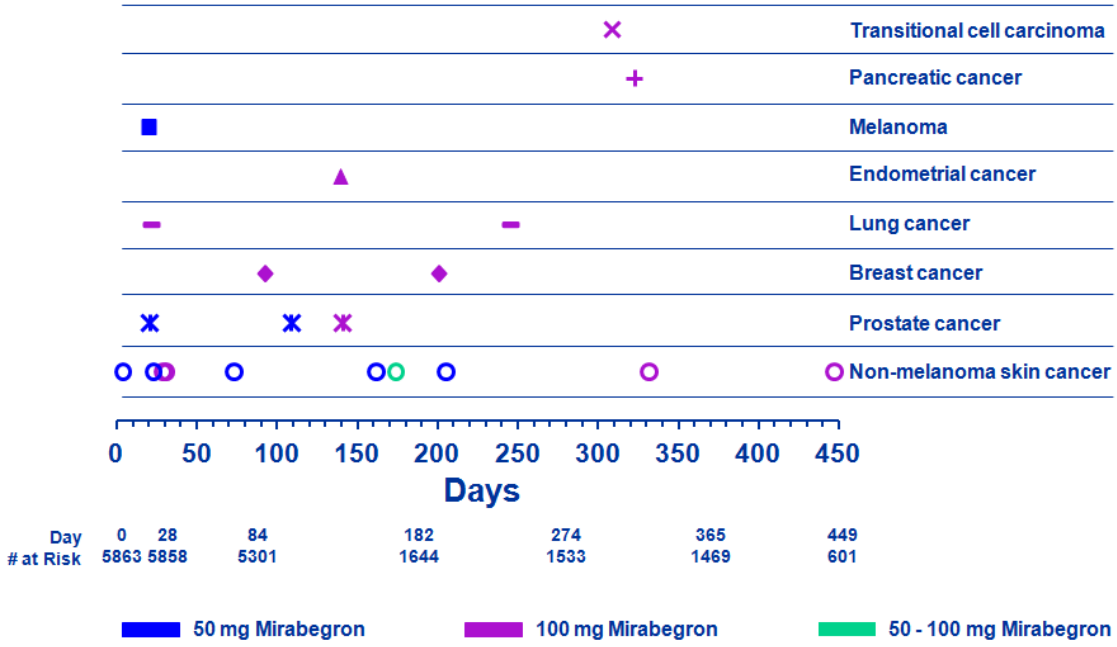
MedDRA(v12.1) Tumor Organ of Origin PT †	Mirabegron < 25 mg	Mirabegron ≥ 25 mg to < 50 mg	Mirabegron ≥ 50 mg to < 100 mg	Mirabegron ≥ 100 mg to < 200 mg	Mirabegron ≥ 200 mg	Mirabegron Dose Titration
Bladder‡	0	0/244.77 (0)	0/1566.20 (0)	1/1186.79 (0.0008)	0/71.74 (0)	0/75.58 (0)
Transition cell carcinoma	0	0	0	1	0	
Lung‡	0	0/244.77 (0)	0/1566.20 (0)	2/1186.59 (0.0017)	0/71.74 (0)	0/75.58 (0)
Lung carcinoma cell type unspecified recurrent	0	0	0	1	0	
Lung neoplasm malignant	0	0	0	1	0	
Pancreas‡	0	0/244.77 (0)	0/1566.20 (0)	1/1186.79 (0.0008)	0/71.74 (0)	0/75.58 (0)
Pancreatic carcinoma	0	0	0	1	0	

Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060 and 178-CL-074. AE: adverse event(s); PT: preferred term.
† Sorting order: decreasing incidence rate by tumor organ of origin and decreasing number by PT.
‡ Incidence Rate was the number of patients with event per patient-years at risk.

Time to Event Analysis

In the total mirabegron group, 15/21 new malignant events were reported within the first 150 days of treatment initiation, 9 of which were identified within the first 3 months of treatment initiation [Figure 41].

Figure 41 Time to Onset of Adjudicated New Malignant Events in the Total Mirabegron Group, Global Phase 2/3 Population



Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060 and 178-CL-074.For subjects who experienced a new malignant event during Study 178-CL-049 and received mirabegron in both 178-CL-049 and either 178-CL-046 or 178-CL-047, time to onset is calculated as the total days at risk on mirabegron. The treatment group displayed above refers to the treatment received at the time of the malignant event.

5.6.3.5 Comparison of Malignancy Rates in The Mirabegron Development Program to External Cancer Databases

An epidemiological evaluation was conducted to compare the malignancy rates of the cancers identified in the mirabegron development program to external rates reported in available databases reflecting the general population, using indirect standardization on International Agency for Research on Cancer annual incidence data [Curado et al, 2007].

Comparisons of observed rates for new malignancies reported more than once on mirabegron (across the program) to expected rates in the general population using indirect standardization are provided below.

Table 92 Neoplasm Epidemiologic Data: Observed vs Expected New Malignancies

	Observed	Expected†	Standardized Morbidity Rate‡ (95% CI) §
Prostate (Male only)	3	2.69	1.113 (0.230, 3.253)
Breast (Female only)	2	4.51	0.443 (0.054, 1.601)
Lung	2	3.66	0.547 (0.066, 1.976)

†The expected number of patients with an event was computed using the database found at the International Agency for the Research on Cancer.
‡ Standardized Morbidity Ratio is the observed number of patients with an event / expected number of patients with an event.
§ 95% CIs were computed from the exact Poisson distribution for the number of observed patients divided by the number of expected.

5.6.3.6 Neoplasm Summary

Overall, the available nonclinical and clinical data do not support an association of mirabegron exposure with the observed imbalance of new malignant events in the Global Phase 2/3 clinical program. This conclusion is based upon the following:

- The absence of genotoxicity and carcinogenicity as demonstrated in nonclinical experiments conducted across the lifespan in mice and rats;
- The attribution of the observed numerical imbalance of new malignant events in the Global Phase 2/3 Population, in large part, to events reported in the EU/NA OAB 12-week Phase 3 Population. Review of the individual 12-week study data revealed an imbalance of adjudicated new malignancies in a single study (Study 178-CL-047: 4/442, 0.9% mirabegron 50 mg; 2/433. 0.46% mirabegron 100 mg; 0/453, 0% placebo), which was not replicated in the other 5 studies included in the pooled Global OAB 12-week Population;
- The lack of evidence of increased risk of new malignant events with longer exposure to mirabegron;
- The biological implausibility for mirabegron to a) influence the growth of a wide array of malignancies given that the imbalance was not dominated by a specific malignancy or collection of similar malignancies b) result in the development of tumors (particularly slow growing tumors) in humans during the short-term treatment period observed in the mirabegron clinical program and c) a lower RR for malignancy in the one year study than in the 12 week studies.
- The demonstration, in an epidemiologic analysis, that the observed rates of the most frequent malignancies reported in mirabegron-treated patients are not larger than expected rates in an age-adjusted population.

5.6.4 Hypersensitivity

During the mirabegron clinical development program, 2 events with findings suggestive of drug hypersensitivity reactions reported in 2 subjects (PTs of Stevens-Johnson syndrome [SJS] and leukocytoclastic vasculitis) prompted a program-wide evaluation. These cases prompted a comprehensive, retrospective, program-wide evaluation of potential hypersensitivity events. To provide a comprehensive and standardized evaluation of potential hypersensitivity events, the sponsor

established an independent hypersensitivity Expert Committee consisting of experts in drug hypersensitivity (2 dermatologists and one allergist).

SJS (Urticaria) Case

The investigator for Patient No. 178-CL-045, P00244 (74 year-old woman assigned to mirabegron 100 mg) initially reported drug-induced urticaria (not SJS) based on the clinical manifestations observed on day 26. The initial cutaneous lesions were reported as urticaria, without severe mucosal lesions, blisters or skin erosions. This patient also experienced a nonserious event of white blood cell count decreased, concurrent with urticaria, with white blood cell count 2900 cells/mcL on day 28 (5700 cells/mcL at baseline). Study drug was withdrawn on day 30 and white blood cell count increased to 10890 cells/mcL by day 37.

This patient also experienced elevated liver chemistry tests concurrent with the urticaria and leukopenia; laboratory results on day 28 revealed elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma-glutamyl transferase. Liver function tests continued to be elevated during hospitalization and peaked on day 39 and returned to within normal limits on day 56 and no liver biopsy was performed.

The investigator reported the event of SJS based on evaluations completed during hospitalization (day 39 to day 47). However, the patient did not consent to allow the investigator access to the medical records detailing the skin manifestations during hospitalization. On day 102 (72 days after stopping study drug), the patient once again developed urticaria which resolved spontaneously without medical treatment.

The Expert Committee's blinded review identified the event as a definite hypersensitivity reaction, but characterized the cutaneous manifestations as urticaria and not SJS. The Expert Committee also identified the leukopenia as a plausible, but not definite, hypersensitivity reaction.

The Expert Committee assessed urticaria and leukopenia as possibly related to study drug (mirabegron) with an alternative explanation of hypersensitivity reaction to expired Kyufu Gold herbal medication that was taken on day 24 to day 26 just prior to reaction onset on day 26. Kyufu Gold has been associated with rare cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis [Kyufu Gold package insert, 2009]. Furthermore, on day 102 (72 days after stopping study drug), the patient once again developed urticaria which resolved spontaneously without treatment suggesting an underlying alternative cause that was not related to mirabegron.

Leukocytoclastic Vasculitis Case

Volunteer No. 178-CL-076, U00022981217 (treated with mirabegron 100 mg) had definite hypersensitivity reactions characterized as cutaneous vasculitis and polyarthritis that occurred concurrently on day 35 (last study drug dose was on day 31). On day 30 and day 35, the volunteer had liver function tests and serum chemistries that were within normal limits and urinalysis that was negative for protein with 0-2 urine erythrocytes/high power field. The event resolved following treatment with methylprednisolone and diphenhydramine on day 45.

Due to the occurrences of these 2 index cases, a broad and sensitive search strategy using prespecified SMQs (v12.1) was employed to capture potential hypersensitivity events in the mirabegron clinical database. All TEAE, from all treatment groups and regardless of assigned causality, that met the prespecified search terms and were: a) SAE or b) nonserious AE with investigator-graded severity of moderate or severe, were considered potential hypersensitivity events and were further evaluated by the Expert Committee blinded to treatment allocation.

The Expert Committee identified plausible hypersensitivity reactions by reviewing subject data packages (blinded to treatment group) for subjects who experienced potential hypersensitivity events. Plausible hypersensitivity reactions were categorized by type of hypersensitivity reaction (immediate,

nonimmediate-primarly cutaneous, nonimmediate-primarly noncutaneous or undetermined) and were further characterized.

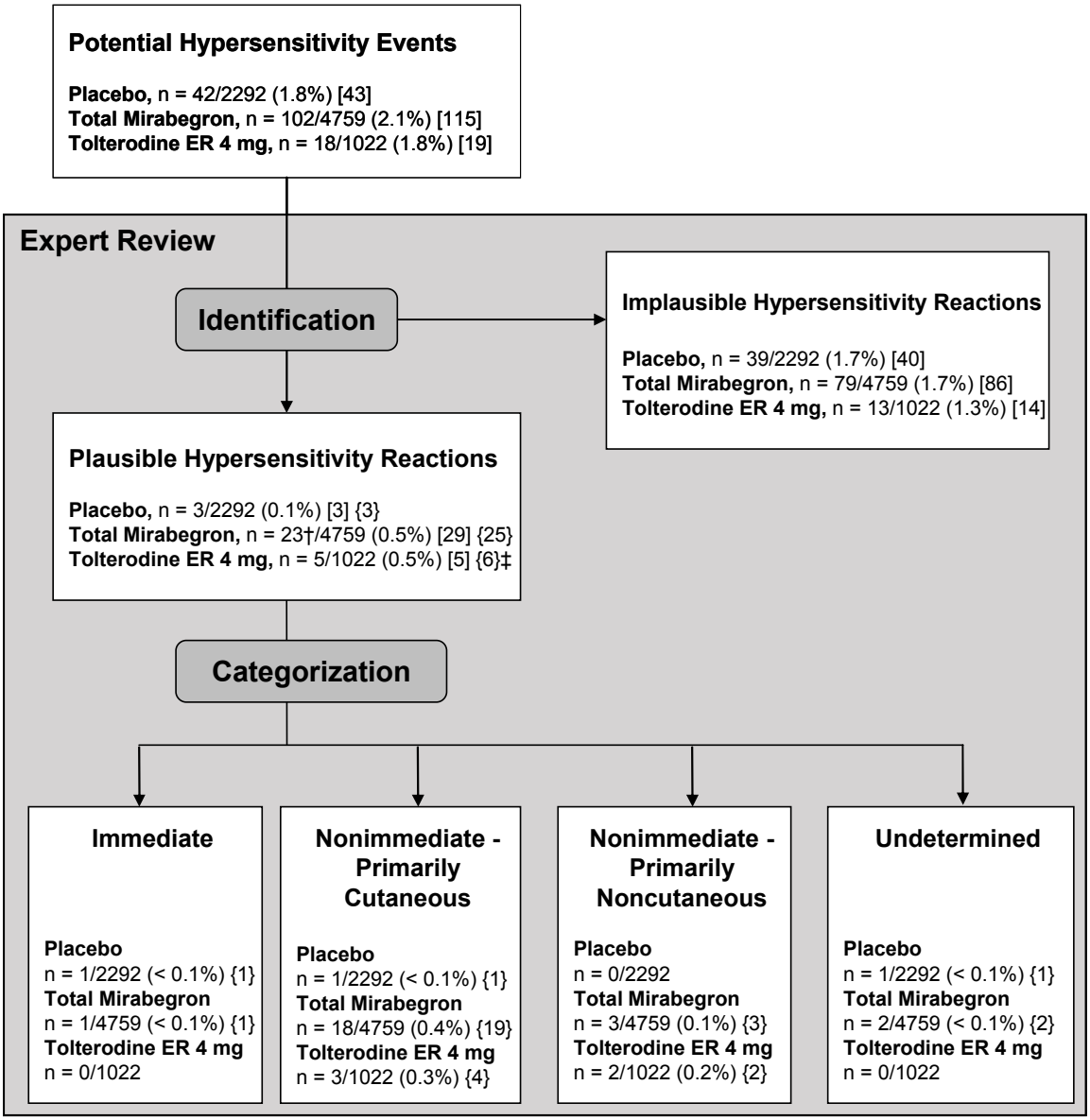
5.6.4.1 Results of Expert Review Committee

5.6.4.1.1 Identification and Categorization of Plausible Hypersensitivity Reactions

Global 12-week Phase 2/3 Population

Figure 42 summarizes the identification and categorization of the plausible hypersensitivity reactions by the Expert Committee for the Global 12-week Phase 2/3 Population by treatment group.

Figure 42 Identification and Categorization of Plausible Hypersensitivity Reactions in the Global 12-week Phase 2/3 Population



Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-060 and 178-CL-074.
Number of patients (%), number of potential hypersensitivity events [n] and number of plausible hypersensitivity reactions {n} are presented. A patient can have > 1 retrieved event, > 1 potential hypersensitivity event and/or > 1 plausible hypersensitivity reaction. *Footnotes continued on next page.*

ER: extended release.
† One mirabegron-treated patient (Patient No. 178-CL-045, P00244) was assessed as having plausible hypersensitivity reactions of 2 different types and is counted in both the nonimmediate – primarily cutaneous and in the nonimmediate-primarily noncutaneous reaction categories.
‡ One tolterodine-treated patient (Patient No. 178-CL-046, 3431-1836) had a potential hypersensitivity event assessed as 2 plausible hypersensitivity reactions; therefore, the number of plausible hypersensitivity reactions exceeds the number of potential hypersensitivity events among tolterodine-treated patients with plausible hypersensitivity reactions.

Plausible hypersensitivity cases are summarized by mirabegron dose group in Table 93.

Table 93 Plausible Hypersensitivity Cases by Assessed Hypersensitivity Reaction Category and Mirabegron Dose Group, Global 12-week Phase 2/3 Population

Hypersensitivity Reaction Category, n (%) of Patients	≥ 25 mg to < 50 mg (n = 811)	≥ 50 mg to < 100 mg (n = 2201)	≥ 100 mg to < 200 mg (n = 1370)	≥ 200 mg (n = 297)
Plausible hypersensitivity cases	3 (0.4%)	6 (0.3%)	10 (0.7%)	4 (1.3%)
Immediate	0	0	1 (0.1%)	0
Nonimmediate – primarily cutaneous	3 (0.4%)	6 (0.3%)	6 (0.4%)	3 (1.0%)
Nonimmediate – primarily noncutaneous	0	0	3 (0.2%)	0
Undetermined type	0	0	1 (0.1%)	1 (0.3%)

Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-060 and 178-CL-074. Note: Study 178-CL-008 was 4 weeks in duration.
A patient assessed as a plausible hypersensitivity case may have experienced more than one hypersensitivity reaction category.

EU/NA Long-term Controlled Population

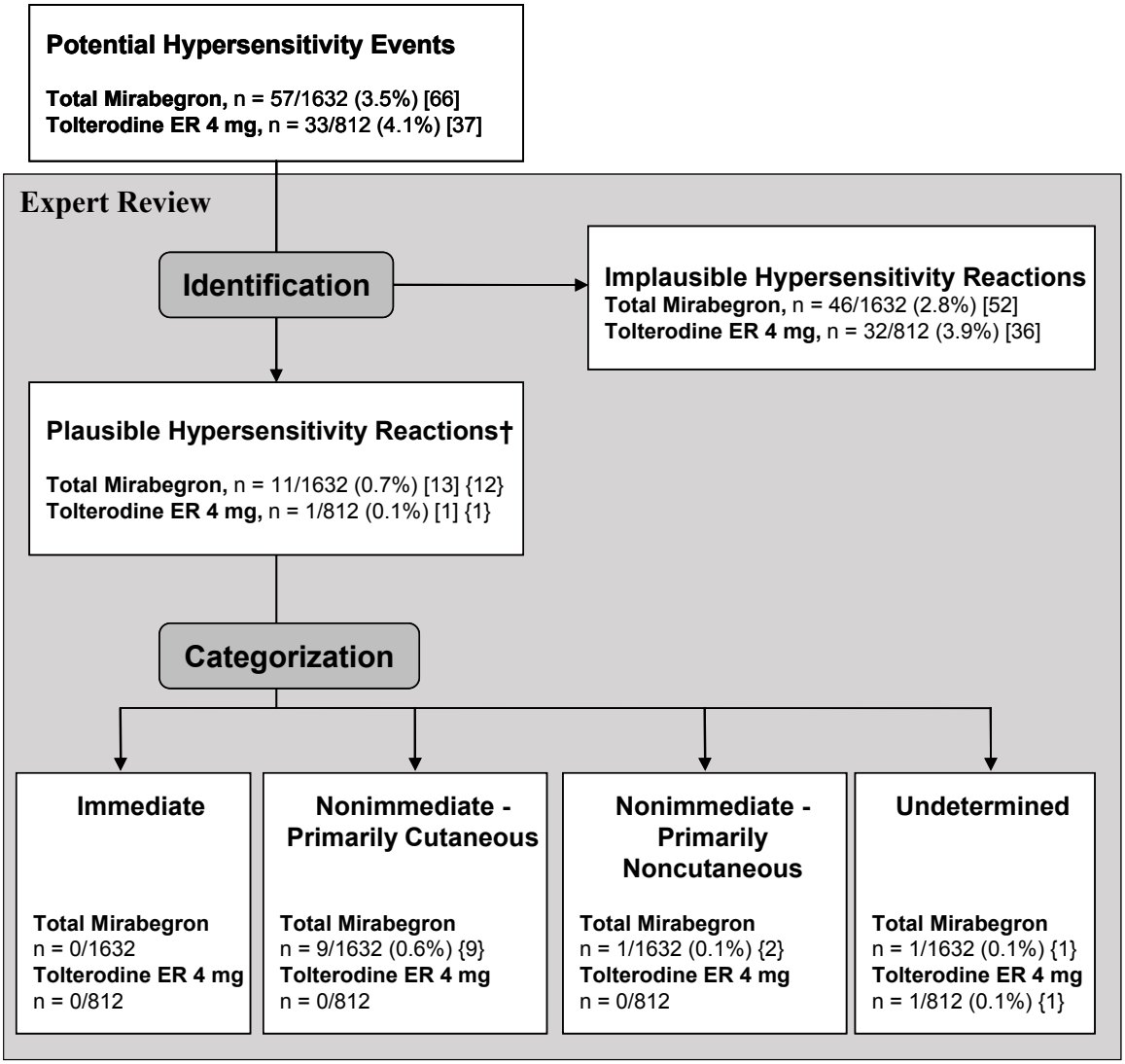
Figure 43 summarizes the identification and categorization of the plausible hypersensitivity reactions by the Expert Committee for the EU/NA Long-term Controlled Population.

The Expert Committee most frequently categorized the plausible hypersensitivity reactions as nonimmediate-primarily cutaneous: 2/812 (0.2%) mirabegron 50 mg- and 7/820 (0.9%) mirabegron 100 mg-treated patients.

Global Phase 1 Population

In the Global Phase 1 Population, the Expert Committee identified plausible hypersensitivity reactions in 2/1000 (0.2%) mirabegron-treated volunteers: one mirabegron 100 mg- (OCAS formulation multiple doses) and one mirabegron 100 mg- (IR/OCAS formulation single dose) treated volunteers. The Expert Committee further identified both plausible reactions as definite hypersensitivity reactions, and assessed both as possibly related to study drug.

Figure 43 Identification and Categorization of Plausible Hypersensitivity Reactions in the EU/NA Long-term Controlled Population



Study included: 178-CL-049
Number of patients (%), number of potential hypersensitivity events [n] and number of plausible hypersensitivity reactions {n} are presented. A patient can have > 1 retrieved event, > 1 potential hypersensitivity event and/or > 1 plausible hypersensitivity reaction.
ER: extended release; EU: Europe; NA: North America.
† A mirabegron-treated patient (Patient No. 178-CL-049, U00018157696) had a potential hypersensitivity event that was assessed as not part of a hypersensitivity reaction. Therefore, in the total mirabegron group, the number of events in subjects with implausible hypersensitivity reactions plus the number of events in subjects with plausible hypersensitivity reactions is less than the total number of potential hypersensitivity events.

5.6.4.1.2 Characterization of Plausible Hypersensitivity Reactions

As presented in Section 5.6.4.1.1 the Expert Committee identified 44 subjects with plausible hypersensitivity reactions: 31 patients from Global 12-week Phase 2/3 Population, 12 patients from EU/NA Long-term Controlled Population and 2 volunteers from Global Phase 1 Population. The 44 subjects with plausible hypersensitivity reactions, including 35 mirabegron-treated subjects, are summarized in Table 94. The Expert Committee designated medical term(s) that best described each plausible hypersensitivity reaction; these medical terms were coded in MedDRA (v12.1).

Table 94 Listing of Subjects with Plausible Hypersensitivity Reactions by Assessed Hypersensitivity Reaction Category

Study No.	Subject No.	Daily Dose	Expert Committee Assessments		
			Reaction PT(s) MedDRA(v12.1)	Definite Hypersensitivity Reaction	Causality Assessment
Immediate					
Placebo					
178-CL-047	U00022517637	NA	urticaria	Yes	not related
Mirabegron					
178-CL-047	U00016568017	100 mg	pruritus generalised	Yes	not related
Nonimmediate – primarily cutaneous					
Placebo					
178-CL-047	U00022058056	NA	urticaria	Yes	possibly related
Mirabegron					
178-CL-008	55-395	300 mg	urticaria	Yes	possibly related
178-CL-008	53-348	200 mg	urticaria	Yes	possibly related
178-CL-045	P00244†	100 mg	urticaria	Yes	possibly related
178-CL-046	3225-2900	100 mg	urticaria	Yes	possibly related
178-CL-047	U00020277080	100 mg	rash macular	Yes	possibly related
178-CL-059	2027	100 mg	urticaria	Yes	possibly related
178-CL-076	U00022981217	30 mg IV/ 100 mg oral	polyarthritis, cutaneous vasculitis	Yes	possibly related
178-CL-047	U00018156541	50 mg	leukocytoclastic vasculitis	Yes	possibly related
178-CL-074	1630-71016	25 mg	skin reaction	Yes	possibly related
178-CL-049	3115-2941	100 mg	urticaria	Yes	not related
178-CL-044	804-1166	25 mg	urticaria	Yes	not related
178-CL-008	50-360	300 mg	rash	No	possibly related
178-CL-047	U00016516844	100 mg	pruritus, rash	No	possibly related
178-CL-047	U00020538287	100 mg	urticaria	No	possibly related
178-CL-047	U00022236756	100 mg	purpura	No	possibly related
178-CL-049	3115-3115‡	100 mg	pruritus	No	possibly related
178-CL-049	3171-0549	100 mg	urticaria	No	possibly related
178-CL-049	3304-0541	100 mg	rash	No	possibly related
178-CL-049	U00022056678	100 mg	pruritus	No	possibly related
178-CL-046	3061-2405	50 mg	urticaria	No	possibly related
178-CL-047	U00015347969	50 mg	urticaria	No	possibly related
178-CL-049	3101-2272	50 mg	urticaria	No	possibly related
178-CL-074	2050-71735	50 mg	pruritus	No	possibly related
178-CL-049	2199-0585	100 mg	rash	No	not related
178-CL-049	U00018157696	100 mg	urticaria	No	not related
178-CL-049	U00016646149	50 mg	eyelid oedema	No	not related
178-CL-048	P06705	50 mg	urticaria	No	not related
178-CL-044	503-1362	50 mg	rash	No	not related
178-CL-044	312-1911	25 mg	rash	No	not related
Tolterodine ER					
178-CL-008	11-110	4 mg	rash papular	Yes	possibly related
178-CL-046	3431-1836	4 mg	rash, pruritus	Yes	possibly related
178-CL-046	3082-3125	4 mg	rash	No	not related
Nonimmediate – primarily noncutaneous					
Mirabegron					
178-CL-046	3301-3010	100 mg	oedema	Yes	possibly related
178-CL-044	608-1570	100 mg	neutropenia	No	possibly related
178-CL-045	P00244†	100 mg	leukopenia	No	possibly related
178-CL-049	2037-0516	100 mg	hemolytic anemia, thrombocytopenia	No	possibly related

Table continued on next page.

Study No.	Subject No.	Daily Dose	Expert Committee Assessments		
			Reaction PT(s) MedDRA(v12.1)	Definite Hypersensitivity Reaction	Causality Assessment
Tolterodine ER					
178-CL-046	3203-2240	4 mg	stomatitis	No	possibly related
178-CL-046	3314-2727	4 mg	stomatitis	No	possibly related
Undetermined type					
Placebo					
178-CL-046	3441-1475	NA	unevaluable event	No	not related
Mirabegron					
178-CL-044	121-1739	200 mg	hypersensitivity	No	possibly related
178-CL-046	3115-3115‡	100 mg	hypersensitivity	No	possibly related
178-CL-049	U00016676102	100 mg	hypersensitivity	No	not related
Tolterodine ER					
178-CL-049	3330-2138	4 mg	hypersensitivity	No	possibly related

Within each hypersensitivity category and treatment group the subjects are arranged by definite hypersensitivity reaction (definite hypersensitivity reactions listed first), then by causality assessment (hypersensitivity reactions that were possibly related listed first), then by mirabegron daily dose (for mirabegron-treated subjects) and lastly by study and subject number.
PT: preferred term; ER: extended release.
† Patient No. 178-CL-045, P00244 had hypersensitivity reactions in 2 categories and is featured twice.
‡ Patient No. 178-CL-046, 3115-3115 is the same as Patient No. 178-CL-049, 3115-3115; this patient had hypersensitivity reactions in both studies (2 different populations) and is featured twice.

5.6.4.2 Summary of Mirabegron and Hypersensitivity

- Overall, the available clinical data do not support an association of mirabegron exposure with immediate-type hypersensitivity reactions.
- Hypersensitivity reactions of hemolytic anemia and thrombocytopenia (1 patient) and neutropenia (1 patient) occurred in mirabegron-treated subjects, but there was not a consistent pattern to establish an association of mirabegron with nonimmediate, primarily noncutaneous hypersensitivity reactions.
- Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura and lip and eyelid edema, occurred in mirabegron-treated subjects during the clinical development program, including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses ≥ 100 mg, with nonimmediate, primarily cutaneous hypersensitivity reactions cannot be ruled out.

5.6.5 Glaucoma

As requested by the FDA Division of Reproductive and Urologic Products following the report of 2 SAE of glaucoma, the Sponsor conducted a systematic evaluation of AE representing glaucoma during the mirabegron clinical program. Subsequently, the FDA Division requested a dedicated study to assess the effect of mirabegron on IOP.

A systematic evaluation of glaucoma-type AE in all completed clinical studies was conducted within the global mirabegron clinical development program which included 8752 patients (5863 mirabegron-treated patients) and 1000 mirabegron-treated healthy volunteers. For subjects with a TEAE in the glaucoma SMQ (narrow search), a Targeted Glaucoma Questionnaire was sent to the investigators to elicit consistent information on the reported event as well as any additional ocular history available for these subjects. An external expert panel established case definitions and reviewed subject data packages on all available data, including treatment assignment, to classify the reported events.

Twelve cases were retrieved using the glaucoma SMQ (narrow search) in the mirabegron clinical development program. The external expert panel assessed the cases as follows:

- 5 cases were classified within the category of glaucoma (4 of these cases had sufficient documentation to confirm an event of glaucoma):
  - 1 patient with acute narrow angle glaucoma
  - 1 patient with open angle glaucoma
  - 1 patient with glaucoma suspect
  - 1 patient with chronic narrow angle glaucoma
  - 1 patient had insufficient information to confirm or refute glaucoma and is included conservatively as glaucoma
- 1 case was classified as nonglaucoma, ocular hypertension (ocular hypertension, by definition, is not glaucoma):
- 6 patients were classified as not having a TEAE since additional data ascertainment revealed a medical history of a preexisting condition with no evidence of worsening of the underlying condition while on study treatment.

Eleven of the 12 retrieved cases were in patients who received mirabegron. The case of chronic narrow angle glaucoma occurred in a patient who received tolterodine.

Additional eye assessments in other phase 1 studies as well as a program-wide evaluation of reported ocular events throughout the clinical program do not suggest an association of mirabegron and glaucoma or other ocular safety issues.

Further, the effect of mirabegron on IOP was formally examined in a PD and safety study to characterize the potential effect of a beta 3-AR agonist on this ocular safety parameter. In a phase 1b study to assess the effect of mirabegron on IOP (Study 178-CL-081), a supratherapeutic dose of mirabegron 100 mg administered orally once daily for 8 weeks in healthy research subjects was non-inferior to placebo for the primary endpoint of change from baseline to day 56 in subject-average IOP as measured by Goldmann applanation tonometry, based on the non-inferiority limit of 1.5 mm Hg. The upper bound of the 2-sided 95% CI for the difference in mean change from baseline to day 56 in subject-average IOP between mirabegron 100 and placebo was 0.3 mm Hg, and the mean change itself was -0.1 mm Hg. IOP data from day 10 are concordant with day 56 [Table 95]. No subject discontinued the study due to an increased IOP. Clinically significant increases from baseline IOP measurements occurred rarely and only in placebo-treated subjects. The results from this study support the ocular safety of mirabegron.

Table 95 Change from Baseline to Day 56 in Subject-Average IOP (mm Hg), Study 178-CL-081

	Study Treatment	
Statistic	**Placebo n = 156**	**Mirabegron 100 mg n = 154**
Baseline, mean (SE)	15.4 (0.16)	15.3 (0.16)
Mean change from Baseline (SE)	-0.2 (0.13)	-0.2 (0.12)
Adjusted mean (SE) change from baseline	-0.2 (0.12)	-0.3 (0.12)
Mean (SE) difference vs. placebo	--	**-0.1 (0.17)**
95% 2-sided CI for difference †	--	**(-0.4, 0.3)**
Achieve noninferiority criteria (yes or no)?	--	yes

All subjects who received study drug, provided a baseline and postbaseline subject-average IOP and met one of the following criteria: completed the study and had a day 56 subject-average IOP measurement; or did not complete the study, but had a subject-average IOP measurement taken within the window for the day 56 visit specified in the schedule of assessments (day 53 to day 59); or, discontinued study drug because of an elevated IOP (full analysis set [FAS]).
For subjects who discontinued due to elevated intraocular pressure the day 56 values were values taken at time of discontinuation. Descriptive statistics for adjusted change from baseline were generated from an ANCOVA model with treatment group as a fixed factor and baseline as a covariate.
Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment group.
-- not applicable; ANCOVA: analysis of covariance; IOP: intraocular pressure
† If the upper limit was less than 1.5 mm Hg, then noninferiority was demonstrated.

Collectively, data do not support an association between mirabegron and glaucoma. Mirabegron at a supratherapeutic dose of 100 mg did not increase IOP in healthy subjects after 56 days of treatment. Therefore, the available nonclinical and clinical data do not support an association between mirabegron and the observed events of glaucoma.

5.6.6 Other

5.6.6.1 Syncope, Postural Hypotension and Falls

For syncope, postural hypotension and falls, there were no events with a PT of syncope and one event of loss of consciousness in a mirabegron-treated patient that was not considered serious in the EU/NA Long-term Controlled Population. Most of the events in this overall category were related to falls.

5.6.6.2 Seizure

One case of a brief tonic-clonic spasm was reported in a healthy volunteer receiving mirabegron in a phase 1 study. In the phase 2/3 studies, no seizures were reported in mirabegron-treated patients but cases of seizures occurred in the placebo (2 patients) and active comparator (1 patient) treatment arms in phase 3 studies. There is no evidence to suggest that mirabegron is associated with seizures.

5.7 Safety in Special Populations

5.7.1 Intrinsic Factors

5.7.1.1 Age Group 1 (< 65 years, ≥ 65 years)

Although TEAE were generally reported more frequently in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups, the difference from placebo or from tolterodine was generally similar in each age group in the EU/NA OAB 12-week Phase 3 Population [Table 96 and Appendix 1, Table 17] and the EU/NA Long-term Controlled Population [Table 97 and Appendix 1, Table 18].

The frequency of SAE and TEAE leading to permanent discontinuation of study drug was lower in patients < 65 years of age compared with patients ≥ 65 years of age across treatment groups.

Table 96 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA OAB 12-week Phase 3 Population, by Age

		Mirabegron				
n (%) of Patients	**Placebo**	**25 mg**	**50 mg**	**100 mg**	**Total Mirabegron**	**Tolterodine ER 4 mg**
Age < 65	**n = 859**	**n = 278**	**n = 861**	**n = 566**	**n = 1705**	**n = 303**
SAE	14 (1.6%)	5 (1.8%)	15 (1.7%)	9 (1.6%)	29 (1.7%)	3 (1.0%)
TEAE	404 (47.0%)	126 (45.3%)	389 (45.2%)	244 (43.1%)	759 (44.5%)	136 (44.9%)
TEAE leading to permanent d/c of study drug	20 (2.3%)	10 (3.6%)	24 (2.8%)	14 (2.5%)	48 (2.8%)	8 (2.6%)
Age ≥ 65	**n = 521**	**n = 154**	**n = 514**	**n = 363**	**n = 1031**	**n = 192**
SAE	15 (2.9%)	2 (1.3%)	14 (2.7%)	17 (4.7%)	33 (3.2%)	8 (4.2%)
TEAE	254 (48.8%)	84 (54.5%)	258 (50.2%)	158 (43.5%)	500 (48.5%)	95 (49.5%)
TEAE leading to permanent d/c of study drug	26 (5.0%)	7 (4.5%)	29 (5.6%)	20 (5.5%)	56 (5.4%)	14 (7.3%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
d/c: discontinued; ER: extended release; OAB: overactive bladder; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

Table 97 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA Long-term Controlled Population, by Age

n (%) of Patients	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mirabegron	Tolterodine ER 4 mg
Age <65	**n = 523**	**n = 504**	**n = 1027**	**n = 509**
SAE	24 (4.6%)	22 (4.4%)	46 (4.5%)	22 (4.3%)
TEAE	297 (56.8%)	303 (60.1%)	600 (58.4%)	313 (61.5%)
TEAE leading to permanent d/c of study drug	28 (5.4%)	30 (6.0%)	58 (5.6%)	23 (4.5%)
Age ≥65	**n = 289**	**n = 316**	**n = 605**	**n = 303**
SAE	18 (6.2%)	29 (9.2%)	47 (7.8%)	22 (7.3%)
TEAE	188 (65.1%)	200 (63.3%)	388 (64.1%)	195 (64.4%)
TEAE leading to permanent d/c of study drug	20 (6.9%)	20 (6.3%)	40 (6.6%)	23 (7.6%)

Study included: 178-CL-049.
d/c: discontinued; ER; extended release; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

5.7.1.2 Age Group 2 (< 75 years, ≥ 75 years)

In the Global OAB 12-week Phase 2/3 Population, the frequency of TEAE was similar in patients < 75 years of age and patients ≥ 75 years of age for the total mirabegron treatment group, but was numerically higher for patients ≥ 75 years in the tolterodine group. In the EU/NA Long-term Controlled Population, the frequency of TEAE was numerically higher in patients ≥ 75 years of age compared with patients < 75 years of age across treatment groups.

In the EU/NA OAB 12-week Phase 3 and EU/NA Long-term Populations, the frequency of SAE and TEAE leading to permanent discontinuation of study drug was generally higher in patients ≥ 75 years of age compared with patients < 75 years of age for the total mirabegron group.

5.7.1.3 Gender

The overview of SAE, TEAE and TEAE leading to permanent discontinuation of study drug by gender are presented in Table 98 and [Appendix 1, Table 19] for the EU/NA OAB 12-week Phase 3 Population and in Table 99 and [Appendix 1, Table 20] for the EU/NA Long-term Controlled Population.

In the EU/NA OAB 12-week Phase 2/3 Population and the EU/NA Long-term Controlled Population, although TEAE were generally reported more frequently in female patients compared with male patients across treatment groups, the difference from placebo or from tolterodine was generally similar between genders [Table 98 and Table 99].

The frequency of SAE and TEAE leading to permanent discontinuation of study drug was similar in male and female patients across treatment groups. No dose adjustment is necessary based on gender.

Table 98 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA OAB 12-week Phase 3 Population, by Gender

n (%) of Patients	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mirabegron	Tolterodine ER 4 mg
Female	**n = 1002**	**n = 293**	**n = 982**	**n = 675**	**n = 1950**	**n = 361**
SAE	19 (1.9%)	3 (1.0%)	17 (1.7%)	19 (2.8%)	39 (2.0%)	9 (2.5%)
TEAE	487 (48.6%)	147 (50.2%)	466 (47.5%)	303 (44.9%)	916 (47.0%)	166 (46.0%)
TEAE leading to permanent d/c of study drug	31 (3.1%)	11 (3.8%)	36 (3.7%)	25 (3.7%)	72 (3.7%)	15 (4.2%)
Male	**n = 378**	**n = 139**	**n = 393**	**n = 254**	**n = 786**	**n = 134**
SAE	10 (2.6%)	4 (2.9%)	12 (3.1%)	7 (2.8%)	23 (2.9%)	2 (1.5%)
TEAE	171 (45.2%)	63 (45.3%)	181 (46.1%)	99 (39.0%)	343 (43.6%)	65 (48.5%)
TEAE leading to permanent d/c of study drug	15 (4.0%)	6 (4.3%)	17 (4.3%)	9 (3.5%)	32 (4.1%)	7 (5.2%)

Footnotes appear on next page

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
d/c: discontinued; ER: extended release; OAB: overactive bladder; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

Table 99 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug, EU/NA Long-term Controlled Population, by Gender

n (%) of Patients	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mirabegron	Tolterodine ER 4 mg
Female	**n = 602**	**n = 608**	**n = 1210**	**n = 600**
SAE	30 (5.0%)	38 (6.3%)	68 (5.6%)	36 (6.0%)
TEAE	359 (59.6%)	382 (62.8%)	741 (61.2%)	376 (62.7%)
TEAE leading to permanent d/c of study drug	34 (5.6%)	38 (6.3%)	72 (6.0%)	27 (4.5%)
Male	**n = 210**	**n = 212**	**n = 422**	**n = 212**
SAE	12 (5.7%)	13 (6.1%)	25 (5.9%)	8 (3.8%)
TEAE	126 (60.0%)	121 (57.1%)	247 (58.5%)	132 (62.3%)
TEAE leading to permanent d/c of study drug	14 (6.7%)	12 (5.7%)	26 (6.2%)	19 (9.0%)

Study included: 178-CL-049.
d/c: discontinued; ER: extended release; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

5.7.1.4 Race

No apparent differences by race were observed; however, due to small numbers of non-White patients in phase 3 studies and non-White, non-Asian patients in phase 2/3 studies [Table 34 and Table 35], conclusions regarding TEAE according to race cannot be drawn.

5.7.1.5 Ethnicity

Populations consisted of mostly non-Hispanic or non-Latino patients (95.4% of patients in the Global Phase 2/3 Population and 94.3% of patients in the Global OAB 12-week Phase 2/3 Population) [Table 34 and Table 35]; thus, there were too few Hispanic or Latino patients to effectively evaluate comparisons based on ethnicity.

5.7.1.6 BMI

In the EU/NA OAB 12-week Phase 3 Population and the EU/NA Long-term Controlled Population, the overall frequency of TEAE generally increased with increasing BMI.

5.7.1.7 History of BPH (Males Only)

Subgroup analysis based on presence or absence of history of BPH for male patients was performed because patients with BPH are at high risk for urinary retention and UTI. Although the rates of UTI were generally higher in male patients with BPH history compared with males without BPH, the pattern of treatment comparisons between treatment groups was similar to that observed in the overall population, indicating that these patients are not at increased risk of UTI with mirabegron treatment.

5.7.2 Extrinsic Factors

5.7.2.1 Geographic Region

In the EU/NA OAB 12-week Phase 3 Population and the EU/NA Long-term Controlled Population, the frequency of TEAE was generally higher in North America compared with Europe across treatment groups.

5.7.2.2 Prior OAB Medication History

Evaluation of safety by history of prior OAB medication use was performed.

In the EU/NA OAB 12-week Phase 3 Population and EU/NA Long-term Controlled Population, the overall frequency of TEAE was higher in patients with prior OAB medication history (Yes category) compared with patients with no prior OAB medication history (No category); the overall

discontinuation frequency (due to insufficient effect) was also higher in patients with prior OAB medication history (Yes category) compared with patients with no prior OAB medication history (No category).

5.7.2.3 Baseline Use of Alpha 1-AR Antagonists

For EU/NA OAB 12-week Phase 3 Population and EU/NA Long-term Controlled Population, the overall frequency of TEAE was generally lower for patients with baseline use of alpha 1-AR antagonists (Yes category) compared with patients without baseline use of alpha 1-AR antagonists (No category) in the total mirabegron and placebo groups, while the opposite was true in the tolterodine group. The Yes category was considerably smaller than the No category.

The frequency of SAE and TEAE leading to permanent discontinuation of study drug was generally higher with baseline use of alpha 1-AR antagonists in all groups in the 12-week phase 3 [Table 100; Appendix 1, Table 21; and Appendix 1, Table 22] and long-term controlled studies than without baseline use [Table 101; Appendix 1, Table 23; and Appendix 1, Table 24].

Table 100 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug by Baseline Use of Alpha 1-AR Antagonists, EU/NA OAB 12-week Phase 3 Population

Baseline use of Alpha 1-AR Antagonists, n (%) of Patients	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total Mirabegron	
YES	**n = 82**	**n = 32**	**n = 92**	**n = 68**	**n = 192**	**n = 34**
SAE	3 (3.7%)	0	3 (3.3%)	5 (7.4%)	8 (4.2%)	1 (2.9%)
TEAE	36 (43.9%)	15 (46.9%)	43 (46.7%)	29 (42.6%)	87 (45.3%)	17 (50.0%)
TEAE leading to permanent d/c of study drug	3 (3.7%)	4 (12.5%)	4 (4.3%)	3 (4.4%)	11 (5.7%)	4 (11.8%)
NO	**n = 1298**	**n = 400**	**n = 1283**	**n = 861**	**n = 2544**	**n = 461**
SAE	26 (2.0%)	7 (1.8%)	26 (2.0%)	21 (2.4%)	54 (2.1%)	10 (2.2%)
TEAE	622 (47.9%)	195 (48.8%)	604 (47.1%)	373 (43.3%)	1172 (46.1%)	214 (46.4%)
TEAE leading to permanent d/c of study drug	43 (3.3%)	13 (3.3%)	49 (3.8%)	31 (3.6%)	93 (3.7%)	18 (3.9%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
d/c: discontinued; ER: extended release; OAB: overactive bladder; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

Table 101 SAE, TEAE and TEAE Leading to Permanent Discontinuation of Study Drug by Baseline Use of Alpha 1-AR Antagonists, EU/NA Long-term Controlled Population

Baseline Use of Alpha 1-AR Antagonists, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
YES	**n = 47**	**n = 49**	**n = 96**	**n = 48**
SAE	5 (10.6%)	5 (10.2%)	10 (10.4%)	3 (6.3%)
TEAE	32 (68.1%)	24 (49.0%)	56 (58.3%)	29 (60.4%)
TEAE leading to permanent d/c of study drug	4 (8.5%)	1 (2.0%)	5 (5.2%)	3 (6.3%)
NO	**n = 765**	**n = 771**	**n = 1536**	**n = 764**
SAE	37 (4.8%)	46 (6.0%)	83 (5.4%)	41 (5.4%)
TEAE	453 (59.2%)	479 (62.1%)	932 (60.7%)	479 (62.7%)
TEAE leading to permanent d/c of study drug	44 (5.8%)	49 (6.4%)	93 (6.1%)	43 (5.6%)

Study included: 178-CL-049.
d/c: discontinued; ER: extended release; SAE: severe adverse event(s); TEAE: treatment-emergent adverse event(s).

5.7.2.4 Food Status

An evaluation of safety parameters by food status (fed, fasted or mixed) for patients in the EU/NA OAB 12-week Phase 3 Studies was performed as discussed in Section 3.2.8.2.

Overall safety findings for TEAE, pulse rate, blood pressure, ECGs and PVR volume provide evidence that mirabegron is safe across food statuses (fed or fasted).

Pulse rate changes showed greater increases in the fed compared with the fasted status across dose groups, SBP changes showed greater increases in the fasted compared with the fed status across dose groups, and DBP changes were similar in both the fed and fasted status across dose groups [Appendix 2, Figure 2 (pulse) and Appendix 2, Figure 3 (blood pressure)]. Overall, there is no consistent pattern in these cardiovascular pharmacodynamic parameters, providing support for the absence of a clinically meaningful difference in vital sign assessments in the fed and fasted mirabegron groups. Across the mirabegron development program, pulse rate is the most consistently affected cardiovascular pharmacodynamic parameter and it does not show an increased response in the fasted dose groups.

No clinically relevant differences were observed for ECG parameters or PVR based on food status in the phase 3 studies.

5.8 Mirabegron Safety Comparison to Antimuscarinic OAB Drugs

The tolerability and safety of mirabegron were compared with antimuscarinic OAB drugs that were presented by Chapple et al [2008] in the updated systematic meta-analysis [Table 102; and Appendix 1, Table 25]. The tolerability and safety profile of mirabegron appeared favorable in comparison with other OAB agents, most specifically for the occurrence of the sentinel antimuscarinic side effect of dry mouth.

5.9 Overdose, Dependence, Rebound and Abuse

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, AE reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 bpm (3 of 6 subjects). Multiple doses of mirabegron administered to healthy volunteers at doses up to 300 mg daily for 10 days resulted in increases in pulse rate and SBP. Treatment for overdose should be symptomatic and supportive. In the event of overdose, heart rate, blood pressure and ECG monitoring are recommended.

There were no AE with the PT that included the word "overdose" reported among the 5863 patients who received at least one dose of mirabegron in phase 2/3 studies.

In both the preclinical and clinical mirabegron studies, there is no evidence of withdrawal or rebound.

5.10 Pregnancy

There have been 9 pregnancies during the clinical development program (7 in mirabegron-treated patients, 1 in a placebo-treated volunteer and 1 in a patient whose treatment assignment remains blinded). Of the 7 mirabegron-treated cases, 3 pregnancies were completed with outcome of full-term live born males, 1 of these males was born with cryptorchism which resolved within his first 6 months of life with no intervention; 1 pregnancy resulted in spontaneous abortion; 2 pregnancies resulted in elective abortions; and there was 1 completed suicide in which pregnancy was discovered on autopsy. A spontaneous complete abortion of 1 of 2 gestational sacs was reported in the placebo-treated healthy volunteer; no additional information is available. A spontaneous abortion was reported for a patient whose treatment remains blinded.

Table 102 Adverse Event Reporting of Antimuscarinics and Mirabegron Compared to Placebo

	Mirabegron 50 mg/day†	Darifenacin 7.5 mg/day	Darifenacin 7.5 mg/day titrated	Darifenacin 15 mg/day	Fesoterodine 4 mg/day	Fesoterodine 8 mg/day	Oxybutynin IR 5 mg/day	Oxybutynin IR 7.5 - 10 mg/day	Oxybutynin IR 15 mg/day	Oxybutynin IR 20 mg/day
Any AE										
RR	1.00 [0.99]	1.26	2.0	1.32	1.31	1.54	--	1.72	1.29	--
95% CI	0.95 - 1.05	1.10 - 1.44	1.38 - 2.91	1.18 - 1.48	1.08 - 1.59	1.29 - 1.84	--	1.38 - 2.14	1.19 - 1.40	--
P value	0.956	< 0.01	< 0.01	< 0.01	0.01	< 0.01	--	< 0.01	< 0.01	--
n	4273 [2755]	938	395	1262	555	570	--	289	748	--
Any SAE										
RR	0.90 [1.00]	2.62	0.59	0.60	--	--	--	15.00	0.74	--
95% CI	0.57 - 1.42	0.91 - 7.56	0.16 - 2.17	0.19 - 1.84	--	--	--	0.86 - 261.2	0.29 - 1.91	--
P value	0.652	0.08	0.43	0.37	--	--	--	0.06	0.53	--
n	4273 [2755]	938	395	1262	--	--	--	488	568	--
Dry mouth (any severity)										
RR	0.89 [0.79]	2.57	2.15	4.40	3.01	3.95	1.08	2.96	4.42	2.9
95% CI	0.58 - 1.36	1.79 - 3.68	1.16 - 3.99	3.34 - 5.79	2.17 - 4.20	2.87 - 5.44	0.90 - 1.29	2.46 - 3.55	3.53 - 5.53	1.73 - 4.87
P value	0.586	< 0.01	0.01	< 0.01	< 0.01	< 0.01	0.41	< 0.01	< 0.01	< 0.01
n	4273 [2755]	938	395	1611	1010	1016	57	923	1006	62
	Oxybutynin TDS 3.9 - 4.0 mg/day	**Propiverine IR 45 mg/day**	**Propiverine ER 20 mg/day**	**Propiverine ER 30 mg/day**	**Solifenacin 5 mg/day**	**Solifenacin 10 mg/day**	**Tolterodine ER 4 mg/day**	**Tolterodine IR 2 mg/day**	**Tolterodine IR 4 mg/day**	**Trospium chloride 40 mg/day**
Any AE										
RR	1.59	1.42	1.58	1.69	1.23	1.32	1.19	1.00	1.13	1.30
95% CI	0.96 - 2.63	1.17 - 1.74	1.02 - 2.43	1.24 - 2.29	1.10 - 1.37	1.06 - 1.66	1.06 - 1.32	0.89 - 1.12	1.05 - 1.21	1.15 - 1.45
P value	0.07	< 0.01	0.04	< 0.01	< 0.01	0.02	< 0.01	0.97	< 0.01	< 0.01
n	355	457	62	593	1230	488	2634	851	2119	1409
Any SAE										
RR	--	--	--	11.91	--	--	0.88	2.06	0.82	2.24
95% CI	--	--	--	0.71 - 201.1	--	--	0.58 - 1.33	0.60 - 7.03	0.50 - 1.36	0.49 - 10.25
P value	--	--	--	0.09	--	--	0.53	0.25	0.45	0.3
n	--	--	--	593	--	--	3199	398	2335	517
Dry mouth (any severity)										
RR	1.41	3.13	4.10	3.38	3.32	5.90	3.00	2.41	3.44	3.17
95% CI	0.73 - 2.73	1.27 - 7.71	2.76 - 6.07	1.93 - 5.90	2.55 - 4.32	4.59 - 7.59	2.47 - 3.64	1.67 - 3.49	2.92 - 4.04	2.37 - 4.24
P value	0.31	0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
n	612	164	867	593	3691	2951	4129	838	4071	1389

†The values for mirabegron 50 mg/day are for the Global OAB 12 Week Phase 2/3 population. The values between brackets [xx] are for the EU/NA OAB 12 week Phase 3 population. Relative risk versus placebo for mirabegron 50 mg/day was estimated using Cochran Mantel Haenszel stratified by study. This methodology is consistent with the methodology used to estimate the relative risk for the antimuscarinics in Chapple et al [2008]. n represents the number of patients who contrinuted to the meta-analysis (placebo+mirabegron 50 mg).
--: not applicable; AE: adverse event(s); OAB: overactive bladder; RR: relative risk; SAE: severe adverse event(s); ER: extended release; IR: immediate release; TDS: transdermal system.

5.11 Safety Summary

Mirabegron at the proposed therapeutic dose of 50 mg is well tolerated in the OAB population studied, inclusive of patients with multiple comorbidities and concomitant medications. Participants in the mirabegron clinical development program closely match the demographics and disease characteristics of the general OAB population. The safety data from the clinical program are therefore generalizable to the population of patients intended for the use of mirabegron in the treatment of OAB. Nonclinical and clinical safety data, including AE of interest, support the safety and tolerability of mirabegron 50 mg in the treatment of patients with OAB.

6 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The mirabegron phase 2/3 OAB development program examined doses from 25 to 200 mg, with the 25, 50 and 100 mg doses included in the primary phase 3 studies (Study 178-CL-046, 178-CL-047 and 178-CL-074). Based on the efficacy response modeled from the phase 2b results (178-PK-009), the 50 mg dose of mirabegron was included in all three primary phase 3 studies, mirabegron 100 mg was included in 2 primary studies (Study 178-CL-046 and 178-CL-047) and mirabegron 25 mg was included in one primary study (Study 178-CL-074).

An overview of the coprimary and key secondary efficacy endpoint results from these primary studies is provided in [Table 103]. For the coprimary efficacy endpoints, the mirabegron 25, 50 and 100 mg groups had similar adjusted mean change from baseline to final visit versus placebo in mean number of incontinence episodes and micturitions per 24 hours. A meaningful incremental efficacy benefit for mirabegron 100 mg compared with mirabegron 50 mg was not demonstrated. The mirabegron 50 mg group in Study 178-CL-074 alone had results similar to the mirabegron 50 and 100 mg groups in the pooled primary studies analysis.

For the key secondary efficacy endpoints, the mirabegron 25 mg group had a noticeably lesser effect compared with the 50 mg group in Study 178-CL-074 and the mirabegron 50 and 100 mg groups in the pooled primary studies analysis. The magnitude of improvement was similar across the mirabegron 50 and 100 mg groups for the key secondary efficacy endpoints. The mirabegron 25 mg group in Study 178-CL-074 did not statistically separate from placebo in the important key secondary endpoint of mean volume voided per micturition while the mirabegron 50 mg group in Study 178-CL-074 showed statistically significant improvement versus placebo. At the first measured time point of week 4 in Study 178-CL-074, the mirabegron 25 mg group had a numerically smaller effect compared with the mirabegron 50 mg group in mean number of incontinence episodes and micturitions per 24 hours. While the magnitude of effect was similar between the mirabegron 25 mg and mirabegron 50 mg group for mean number of urgency incontinence episodes per 24 hours in Study 178-CL-074, the mirabegron 25 mg group had a numerically smaller effect as compared with the mirabegron 50 mg group for mean level of urgency and mean number of urgency episodes (Grade 3 or 4) per 24 hours.

These key secondary endpoints are particularly relevant to the dose selection of an OAB treatment as the condition itself is a composite of symptoms characterized by urgency, with or without urge incontinence, usually with frequency and nocturia [Wein & Rovner, 2002]. Mitigation of the composite of symptoms collectively is important in the selection of the therapeutic dose. Management of the composite of symptoms comprising OAB is essential for effective outcomes, patient satisfaction and patient adherence. The clinical impact of mitigating key secondary endpoints of urgency as well as its impact on QoL and patient's perception of effective management of the condition is well characterized [Cardozo et al, 2009; Chapple et al, 2005; Wagner et al, 2002].

The key secondary endpoints characterizing urgency, a core symptom of OAB management, and mean volume voided are more consistently and effectively treated with mirabegron 50 mg than

mirabegron 25 mg. Similarly, efficacy was consistently observed after 4 weeks of treatment with mirabegron 50 mg but not with mirabegron 25 mg; the speed of improvement in symptoms of OAB could affect adherence to therapy.

The quality of life assessments support that patients treated with mirabegron 50 and 100 mg experienced a meaningful effect [Table 20, Table 21, Table 22]. Results from quality of life endpoints provide strong evidence that the patients not only obtained objective evidence of improvement but also clinically meaningful benefits from mirabegron 50 mg in the treatment of their disease. The directional parallelism between the subjective and objective measures substantially supports the clinical significance of the effect of mirabegron 50 mg.

Table 103 Overview of Coprimary and Key Secondary Efficacy Results

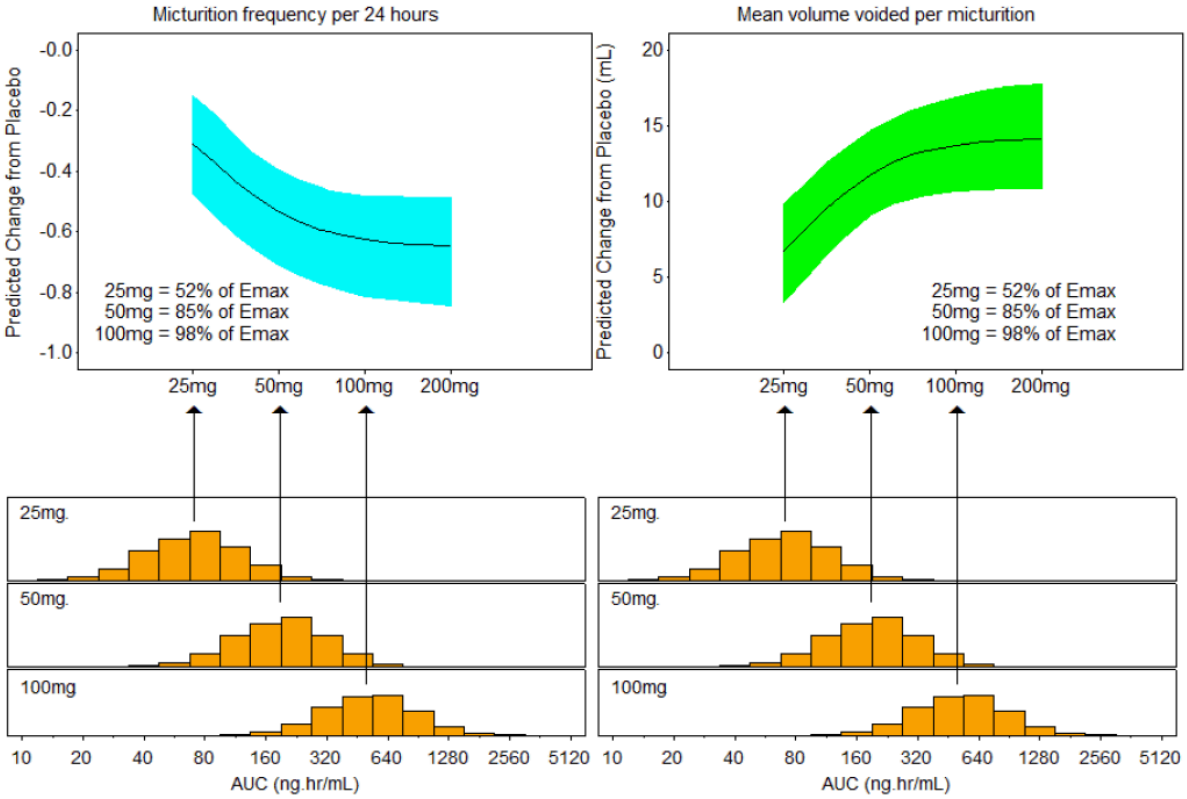
	Study 178-CL-074		Pooled Primary Studies	
	Mirabegron 25 mg	**Mirabegron 50 mg**	**Mirabegron 50 mg**	**Mirabegron 100 mg**
Coprimary Efficacy Results				
Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours (FAS-I)				
n	254	257	862	577
Adjusted mean difference vs placebo (SE)	-0.40 (0.17)	-0.42 (0.17)	-0.40 (0.09)	-0.41 (0.11)
95% 2-sided CI	(-0.74, -0.06)	(-0.76, -0.08)	(-0.58, -0.21)	(-0.62, -0.19)
P value†	0.005#	0.001#	< 0.001#	< 0.001#
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours (FAS)				
n	410	426	1324	890
Adjusted mean difference vs placebo (SE)	-0.47 (0.18)	-0.42 (0.17)	-0.55 (0.10)	-0.54 (0.12)
95% 2-sided CI	(-0.82, -0.13)	(-0.76, -0.08)	(-0.75, -0.36)	(-0.77, -0.31)
P value‡	0.007#	0.015#	< 0.001#	< 0.001#
Key Secondary Efficacy Results				
Change from Baseline to Final Visit in Mean Volume Voided per Micturition (FAS)				
n	410	426	1322	890
Adjusted mean difference vs placebo (SE)	4.6 (3.16)	12.4 (3.13)	11.9 (1.82)	12.3 (2.12)
95% 2-sided CI	(-1.6, 10.8)	(6.3, 18.6)	(8.3, 15.5)	(8.1, 16.5)
P value‡	0.15	< 0.001#	< 0.001#	< 0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours (FAS-I)				
n	254	255	857	574
Adjusted mean difference vs placebo (SE)	-0.34 (0.17)	-0.51 (0.17)	-0.45 (0.10)	-0.42 (0.12)
95% 2-sided CI	(-0.68, -0.01)	(-0.85, -0.17)	(-0.64, -0.26)	(-0.65, -0.20)
P value†	0.039§	< 0.001#§	< 0.001#	< 0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours (FAS)				
n	410	424	1317	886
Adjusted mean difference vs placebo (SE)	-0.18 (0.18))	-0.37 (0.17)	-0.40 (0.09)	-0.56 (0.11)
95% 2-sided CI	(-0.53, 0.16)	(-0.71, -0.03)	(-0.59,-0.22)	(-0.78, -0.35)
P value‡	0.30§	0.035§	< 0.001#	< 0.001#
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)				
n	410	426	1323	886
Adjusted mean difference vs placebo (SE)	-0.07 (0.04)	-0.14 (0.04)	-0.11 (0.02)	-0.11 (0.03)
95% 2-sided CI	(-0.15, 0.01)	(-0.22, -0.06)	(-0.16, -0.07)	(-0.16, -0.06)
P value‡	0.083§	< 0.001§	< 0.001#	< 0.001#
Change from Baseline to Final Visit in Mean Number of Urgency Incontinent Episodes per 24 hours (FAS-I)				
n	247	251	834	567
Adjusted mean difference vs placebo (SE)	-0.36 (0.16)	-0.39 (0.16)	-0.40 (0.09)	-0.40 (0.10)
95% 2-sided CI	(-0.67, -0.05)	(-0.69, -0.08)	(-0.57, -0.23)	(-0.60, -0.20)
P value†	0.004	0.002§	< 0.001#	< 0.001#
Change from Baseline to Final Visit in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 hours (FAS)				
n	410	426	1320	885
Adjusted mean difference vs placebo (SE)	-0.33 (0.22)	-0.59 (0.22)	-0.64 (0.13)	-0.60 (0.15)
95% 2-sided CI	(-0.76, 0.10)	(-1.01, -0.16)	(-0.89, -0.39)	(-0.89, -0.31)
P value‡	0.13	0.007§	< 0.001#	< 0.001#

Footnotes appear on next page.

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode recorded in the baseline 3-day micturition diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).
ANCOVA: analysis of covariance.
For the pooled primary studies and Study 178-CL-074, a stepwise parallel gate keeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary and key secondary efficacy endpoints. Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was used to adjust for multiplicity within each stage.
In the pooled primary studies, the adjusted mean difference versus placebo for change from baseline and corresponding 95% CI were generated from an ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate. In Study 178-CL-074, the adjusted mean difference versus placebo for change from baseline and corresponding 95% CI were generated from an ANCOVA model with treatment group, gender and geographical region as fixed factors and baseline as a covariate.
Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups.
† Nominal P values are from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis.
‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis.
# Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.
§ Study 178-CL-074 only: Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided (P = 0.15), subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Mean volume voided per micturition and subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level. Since the mirabegron 50 mg group did not meet statistical significance with multiplicity adjustment for change from baseline to week 4 in mean number of micturitions per 24 hours (P = 0.035), subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Nominal P values are provided in the table.

Exposure-efficacy response modeling using data from phase 2b study 178-CL-044 and the primary phase 3 studies 178-CL-046, 178-CL-047 and 178-CL-074, supports the dose selection of mirabegron 50 mg once daily in the treatment of patients with OAB. Three endpoints were examined: micturition frequency per 24 hours and mean volume voided per micturition in a joint model (consistent with the high correlation in these endpoints) as well as incontinence episodes per 24 hours. For micturition frequency and mean volume voided, there was dose separation across the dose range examined with doses of mirabegron 25 mg, 50 mg and 100 mg achieving 52%, 85% and 98% of E_{max}, respectively [Figure 44]. Mirabegron exposure-efficacy response modeling for incontinence episodes per 24 hours is flat across the 25 to 100 mg dose range with all mirabegron exposures being associated with a reduction in the rate of incontinence of 26.5% (95% CI: 18.0% to 34.2%) versus placebo. This modeling supports the dose selection of 50 mg since the median relative increase in efficacy for micturition frequency is 65% higher for mirabegron 50 mg relative to efficacy with mirabegron 25 mg whereas the relative increase is 15% going from mirabegron 50 to 100 mg.

Figure 44 Mirabegron Exposure-Efficacy Response Model, Micturition Frequency per 24 Hours and Mean Volume Voided per Micturition



Mirabegron at the proposed dose of 50 mg once daily was well tolerated in OAB patients and in the various sub-populations with multiple comorbidities and concomitant medications. An overview of the safety of mirabegron is summarized in Table 104. The overall frequency of AE was low, generally comparable to placebo, and generally not treatment limiting. Results were generally similar across the mirabegron treatment groups with no clinically meaningful differences in the safety profile of mirabegron 25 mg compared to mirabegron 50 mg while mirabegron 100 mg demonstrated a somewhat higher frequency of events related to pulse rate changes and hypersensitivity.

AE reported in the mirabegron group at a higher frequency than placebo in the EU/NA OAB 12-week Phase 3 Population included tachycardia and UTI; a dose response was not observed among the mirabegron 25, 50 and 100 mg dose groups for these events.

Mirabegron 50 mg once daily increased pulse rate by approximately 1 bpm compared with placebo; changes were reversible upon discontinuation of treatment, and pulse rate changes were comparable in magnitude to those observed with tolterodine and mirabegron 25 mg. Rates of categorical changes in pulse and AE related to rapid pulse or tachyarrhythmias were comparable between mirabegron 25 mg and mirabegron 50 mg and were higher for mirabegron 100 mg.

Mirabegron 50 mg was associated with a mean 0.4 to 0.6 mm Hg change from baseline SBP/DBP compared with placebo in patients with OAB. Mean blood pressure changes were less for mirabegron 25 mg, however categorical increases from baseline in SBP/DBP were generally comparable across all treatment groups, including placebo, and there was not an increase in AE rates of hypertension compared with placebo for the mirabegron treatment groups.

APTC/MACE events were not increased in the mirabegron population for any dose and were comparable to placebo.

Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura and lip and eyelid edema, occurred in mirabegron-treated subjects during the clinical development program, including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses ≥ 100 mg, with nonimmediate, primarily cutaneous hypersensitivity reactions cannot be ruled out; the frequency of these events was similar between mirabegron 25 and 50 mg.

Table 104 Key Safety Assessments for the Placebo and Mirabegron 25, 50 and 100 mg, EU/NA OAB 12-week Phase 3 Population

	Placebo n=1380	Mirabegron 25 mg n=432	Mirabegron 50 mg n=1375	Mirabegron 100 mg n=929
Adverse Events				
SAE	2.1%	1.6%	2.1%	2.8%
TEAE	47.7%	48.6%	47.1%	43.3%
TEAE leading to permanent d/c of study drug	3.3%	3.9%	3.9%	3.7%
UTI	1.8%	4.2%	2.9%	2.7%
Tachycardia	0.6%	1.6%	1.2%	0.4%
Cardiovascular Parameters - Pulse				
Change from Baseline to Final Visit in Pulse Rate, Mean Difference from Placebo	--	AM: 0.9 PM: 0.6	AM: 1.0 PM: 1.0	AM: 1.9 PM: 2.3
Change from baseline ≥ 2 bpm in pulse rate at 3 consecutive postbaseline visits	AM: 14.3% PM: 14.0%	AM: 15.8% PM: 13.4%	AM: 20.5% PM: 19.5%	AM: 32.3% PM: 27.4%
Any occurrence of tachycardia	3.1%	4.9%	3.8%	4.6%
Cardiovascular Parameters – Blood Pressure				
Change from Baseline to Final Visit in Blood Pressure, Mean Difference from Placebo, SBP/DBP	--	AM: -0.5/-0.1 PM: -1.0/-0.3	AM: 0.6/0.4 PM: 0.5/0.4	AM: 0.4/0.2 PM: 0.9/0.5
Change from baseline ≥ 2 mm Hg in SBP at 3 consecutive postbaseline visits	AM: 21.1% PM: 20.4%	AM: 18.3% PM: 16.5%	AM: 21.2% PM: 21.0%	AM: 22.4% PM: 27.4%
Change from baseline ≥ 2 mm Hg in DBP at 3 consecutive postbaseline visits	AM: 14.2% PM: 15.8%	AM: 12.7% PM: 13.4%	AM: 18.2% PM: 18.5%	AM: 18.2% PM: 21.3%
Patients With AM or PM SBP Increase > 5 mm Hg and > 140 mm Hg on 3 consecutive postbaseline visits	AM: 5.3% PM: 1.2%	AM: 6.8% PM: 1.3%	AM: 6.9% PM: 1.2%	AM: 5.8% PM: 1.5%
Patients with any hypertension TEAE	8.5%	12.0%	8.7%	6.2%
Cardiovascular Parameters – Adjudication†				
n	2142	811	2131	1305
Number (%) of patients with at least one adjudication-confirmed CV event	0.4%	0.2%	0.2%	0.5%
Number of patients with an APTC/MACE event	0.2%	0.2%	0	0
Hypersensitivity‡				
n	2292	811	2201	1370
Plausible hypersensitivity cases	0.1%	0.4%	0.3%	0.7%

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
† Data presented are for the Global OAB 12-week Phase 2/3 Population which include 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
‡ Data presented are for the Global 12-week Phase 2/3 Studies which include 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-060 and 178-CL-074.

Data for the efficacy endpoints evaluated in the primary phase 3 studies, including endpoints to evaluate objective measures of micturition frequency and urgency along with the clinically meaningful benefits as assessed by the patient, support mirabegron 50 mg orally once daily for

effective treatment of patients with OAB. The safety of mirabegron 50 mg is also supported by these data with no clinically meaningful differences in the safety profile of mirabegron 25 mg compared with mirabegron 50 mg while mirabegron 100 mg demonstrated a somewhat higher frequency of events related to pulse rate changes and hypersensitivity.

Collectively, the efficacy and safety data support the proposed therapeutic dose of mirabegron 50 mg for the treatment of patients with OAB.

7 BENEFITS AND RISKS DISCUSSION

7.1 Benefits

OAB is a disturbance of filling/storage and has been defined by the International Continence Society as a "symptom syndrome consisting of urgency with or without urge urinary incontinence, often associated with urinary frequency and nocturia" [Abrams et al, 2002]. OAB has a significant impact on HRQL, particularly emotional symptoms, sexual health and overall well-being [Rogers et al, 2009; Resnick & Yalla, 1992]. The problematic and unpredictable symptoms of OAB can have damaging effects on an individual's daily routine [Milsom et al, 2001]. Antimuscarinics are the current standard therapeutic agents for the treatment of OAB. Antimuscarinics are associated with AE such as dry mouth, constipation and blurred vision at therapeutic doses, which may limit patient adherence to the therapy [Chapple et al, 2008; Hegde, 2006].

Mirabegron has a distinct mechanism of action (beta 3-AR agonist) compared with the current standard therapeutic agents, primarily antimuscarinics, for the treatment of symptoms of OAB.

The global clinical development program of mirabegron consisted of 41 studies conducted over 10 years and included 10,552 subjects. Of these, 29 phase 1 studies in 1800 volunteers provide a thorough characterization of the clinical pharmacology of mirabegron. The safety of mirabegron is further supported by 12 phase 2/3 studies involving 8752 patients (8433 patients with OAB) of which, 5863 (5648 patients with OAB) received mirabegron. The efficacy of mirabegron in the treatment of symptoms of OAB is supported by 6 global, 12-week phase 2b/3 studies.

The population evaluated in the mirabegron development program for OAB is representative of the population that would receive the product after market approval and similar to the population evaluated with other OAB compounds. Inclusion and exclusion criteria in the phase 3 studies were broad and allowed inclusion of patients who were antimuscarinic treatment naive and patients who received prior OAB antimuscarinic therapy.

The clinical efficacy of mirabegron 50 mg was established in 3 placebo-controlled primary studies. The effect of mirabegron 50 mg has been consistently shown to be superior to placebo in reducing mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. Mirabegron 50 mg, the recommended therapeutic dose, demonstrated superiority compared with placebo for key secondary endpoints as defined in the phase 3 program, including change from baseline to final visit in mean volume voided per micturition, change from baseline to week 4 in mean number of incontinence episodes and micturitions per 24 hours and change from baseline to final visit in measurements of urgency. The magnitude of improvement was similar across the mirabegron 50 and 100 mg groups for the majority of efficacy endpoints. The mirabegron 25 mg group in Study 178-CL-074 did not significantly separate from placebo in the important key secondary endpoints.

Standard and clinically established instruments to assess quality of life measures were utilized in these studies to assess the impact of mirabegron on the patient's experience of symptoms and changes in HRQL. Mirabegron 50 mg led to significant changes in HRQL measures in parallel with the improvements in objective measures of OAB.

Results from quality of life endpoints provide strong evidence that the patients not only obtained objective evidence of improvement but also clinically meaningful benefits from mirabegron 50 mg in

the treatment of their disease. The directional parallelism between the subjective and objective measures substantially supports the clinical significance of the effect of mirabegron 50 mg.

Time to onset of action in the primary phase 3 studies was at the first measured time point of week 4 while phase 2b studies demonstrated improvement over placebo as early as the first measured time point of week 1. The odds ratio for responders with a ≥ 50% reduction in incontinence episodes from baseline to final visit was 1.54 (95% CI: 1.26, 1.89) for the mirabegron 50 mg group.

Subpopulation analyses demonstrate the efficacy of mirabegron regardless of demographic characteristics, OAB characteristics, intrinsic/extrinsic factors comprised of comorbid conditions or concomitant medications that might affect the coprimary efficacy endpoints or when administered with or without food. In addition, these analyses demonstrate that mirabegron is effective in patients who are antimuscarinic treatment naive and in patients who failed previous OAB antimuscarinic treatment representing an unmet medical need.

Mirabegron demonstrated an early and durable effect on the coprimary and key secondary endpoints in the 52-week clinical safety study.

The range of responses for mirabegron 50 mg in the mean difference from placebo for incontinence episodes and micturition frequency is within the range of values observed with approved OAB treatments [Chapple et al, 2008]. These results are also consistent with the range observed in individual studies reported in package inserts for other OAB agents.

Taken together, the objective, subjective, responder analyses, and persistence of effect data support the efficacy of mirabegron at the proposed therapeutic dose of 50 mg once daily.

7.2 Unfavorable Effects

Mirabegron at the proposed dose of 50 mg once daily is well tolerated in OAB patients and in the various sub-populations with multiple comorbidities and concomitant medications. The frequency of AE was low, generally comparable to placebo, and generally not treatment limiting. Results were similar across the mirabegron treatment groups. Common adverse drug reactions (AE reported in the mirabegron 50 mg group at a frequency > 1%, higher than placebo and with a plausible causative link to mirabegron) in the EU/NA OAB 12-week Phase 3 Population include tachycardia (1.0% mirabegron, 0.6% placebo) and UTI (3.0% mirabegron, 1.8% placebo).

Mirabegron 50 mg once daily increased pulse rate by approximately 1 bpm compared to placebo; changes were reversible upon discontinuation of treatment, and pulse changes were comparable in magnitude to those observed with tolterodine. Rates of categorical changes in pulse and AE related to rapid pulse or tachyarrhythmias were comparable between mirabegron 50 mg and tolterodine. Mirabegron 50 mg was associated with a mean 0.4 to 0.6 mm Hg change from baseline SBP/DBP compared with placebo in patients with OAB. Categorical increases from baseline in SBP/DBP for the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations were generally comparable across all treatment groups, including placebo, and there was not an increase in AE rates of hypertension compared with placebo for mirabegron treatment groups. APTC/MACE events were not increased in the mirabegron population, either compared with placebo or active comparator.

In TQT testing, QTc prolongation using ICH criteria (95% CI of QTc > 10 msec) was seen only in females at a dose of 200 mg, which had 6.5-times greater exposure (AUC) than the proposed 50 mg dose.

UTI has been identified as an adverse drug reaction with mirabegron. The frequency of UTI was higher in mirabegron 50 mg patients (2.9%) compared with placebo patients (1.8%) in the 12-week studies. There was no evidence of a mirabegron dose response and the frequency was comparable to tolterodine for the Global OAB 12-week Phase 2/3 Population (mirabegron: 4.3% and tolterodine: 4.4%) and the EU/NA Long-term Populations (mirabegron: 8.8% and tolterodine: 10.0%).

Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, and lip and eyelid edema, occurred in mirabegron-treated subjects during the clinical development program including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses ≥ 100 mg, with nonimmediate, primarily cutaneous reactions cannot be ruled out. These cutaneous reactions were generally reversible with discontinuation of mirabegron and symptomatic treatment as clinically indicated.

The safety of mirabegron has been thoroughly evaluated, generally does not represent product related safety concerns, and where appropriate, can be addressed in product labeling.

7.3 Benefit Risk Balance

Antimuscarinics are the current standard therapeutic agents used for the treatment of OAB. Typical antimuscarinic side effects limit their use. Adverse effects associated with antimuscarinic therapy, such as dry mouth were observed with mirabegron at a frequency similar to or lower than placebo and lower than antimuscarinics in both the mirabegron clinical studies and in the OAB literature. The heart rate effect of mirabegron 50 mg is within or below the range observed with other OAB products.

Consistent with its distinct mechanism, mirabegron offers an additional pharmacologic treatment option for patients with OAB. The effect of mirabegron 50 mg has been consistently shown to be superior to placebo for the co-primary, key secondary and quality of life endpoints and within range of the effects observed with other OAB products. Mirabegron addresses an unmet medical need for patients with OAB who are not candidates for antimuscarinic therapy, who are intolerant to antimuscarinic therapy or those who have an inadequate response to prior antimuscarinic therapy.

Mirabegron has not been evaluated in patients with end-stage renal disease, severe hepatic impairment, severe uncontrolled hypertension, pregnancy and pediatric patients, therefore, mirabegron is not recommended for use in these patient populations.

In conclusion, mirabegron at a proposed therapeutic dose of 50 mg once daily represents a new approach for the treatment of OAB which is safe, well tolerated and effective for the treatment of patients with OAB under the conditions in the proposed labeling. The benefits of treatment exceed any risk associated with the use of the product.

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APPENDIX 1 SUPPLEMENTARY TABLES 4

Appendix 1 Supplementary Tables

Appendix 1, Table 1 Overview of the Clinical Development Program for Mirabegron

Phase	IR Formulation		OCAS Formulation	
	Single Dose	**Multiple Dose**	**Single Dose**	**Multiple Dose**
Phase 1	SAD 178-CL-001 MB 178-CL-007 †	MAD 178-CL-002 DDI 178-CL-005§ 178-CL-006	BA 178-CL-033 ¶ DDI 178-CL-036 178-CL-070 Renal 178-CL-038 Hepatic 178-CL-039 FE 178-CL-041 178-CL-064‡ 178-CL-078 ‡ CI 178-CL-053 DP 178-CL-066‡ PK 178-CL-076¶	PK 178-CL-030† 178-CL-031 178-CL-034‡§ TQT 178-CL-037 178-CL-077 DDI 178-CL-040 178-CL-058 178-CL-059 178-CL-068 178-CL-069§ 178-CL-080§ A/G 178-CL-072 IOP 178-CL-081
Phase 2 (Other)		POC DM 12-weeks 178-CL-003 178-CL-004		Urodynamics LUTS/BOO 178-CL-060
Phase 2 (OAB)		POC 4-weeks 178-CL-008		DF 12-weeks 178-CL-044 178-CL-045‡
Phase 3 (OAB)				E/S, 12-weeks 178-CL-046 178-CL-047 178-CL-074 178-CL-048‡ E/S, 52 weeks 178-CL-049 178-CL-051‡

A/G: age and gender; BA: bioavailability; CI: cardiac impedance; DDI: drug-drug interaction; DF: dose finding; DM: Type 2 diabetes mellitus; DP: dose proportionality; E/S: efficacy and safety; FE: food effect; IOP: intraocular pressure; IR: immediate release; LUTS/BOO: lower urinary tract symptoms/bladder outlet obstruction;
MB: mass balance; MAD: multiple ascending dose; OAB: overactive bladder; OCAS: oral controlled absorption system; PK: pharmacokinetics; POC: proof of concept; SAD: single ascending dose; TQT: thorough QT.
† Study 178-CL-030 also included the IR formulation and Study 178-CL-007 used an oral solution of radiolabeled mirabegron.
‡ Studies conducted in Japan.
§ Studies 178-CL-005, 178-CL-034, 178-CL-069 and 178-CL-080 also included single doses.
¶ Used an intravenous formulation.

Appendix 1, Table 2 Summary of Adjusted Plasma Pharmacokinetic Parameters on Day 10, by Sex, Study 178-CL-077

Parameter	Study Treatment					
	Mirabegron 50 mg (n = 84)		Mirabegron 100 mg (n = 82)		Mirabegron 200 mg (n = 83)	
	Female	Male	Female	Male	Female	Male
n	41	43	41	41	40	43
AUC_{tau}/(dose/wt) ([ng·hr/mL]/[mg/kg])						
Mean	664.8	563.5	942.1	711.5	1087.7	909.0
(SD)	(166.16)	(185.88)	(258.54)	(238.15)	(284.23)	(247.50)
Min-Max	369.6-964.2	83.9-957.3	391.4-1743.1	197.9-1254.6	610.7-1712.2	466.2-1492.8
AUC_{tau} /Dose ([ng·hr/mL]/mg)						
Mean	10.07	7.22	13.87	9.17	16.37	11.18
(SD)	(2.768)	(2.536)	(3.425)	(2.967)	(4.183)	(2.935)
Min-Max	5.29-18.54	0.92-12.94	7.25-20.13	2.92-15.59	8.48-27.23	7.17-18.70
C_{max}/(dose/wt) ([ng/mL]/[mg/kg])						
Mean	63.572	56.712	115.219	81.503	136.482	108.442
(SD)	(35.6210)	(27.1644)	(34.6492)	(35.1069)	(49.9264)	(38.2835)
Min-Max	20.982-217.010	7.145-127.669	57.893-211.139	19.158-156.649	57.817-258.586	40.274-195.220
C_{max}/Dose (ng/mL/mg)						
Mean	0.958	0.726	1.717	1.056	2.046	1.333
(SD)	(0.5120)	(0.3584)	(0.5393)	(0.4627)	(0.6969)	(0.4721)
Min-Max	0.301-2.646	0.078-1.721	0.813-2.705	0.197-2.354	0.767-3.529	0.509-2.636
CL/F/wt ([L/hr]/kg)						
Mean	1.607	2.155	1.154	1.627	0.988	1.180
(SD)	(0.4335)	(1.6603)	(0.3822)	(0.8004)	(0.2801)	(0.3159)
Min-Max	1.037-2.706	1.045-11.913	0.574-2.555	0.797-5.053	0.584-1.637	0.670-2.145

All randomized volunteers who received at least one dose of randomized study drug and had pharmacokinetic data adequate for calculating pharmacokinetic parameters (Pharmacokinetic Analysis Set [PKAS]).
Study 178-CL-077 was conducted in healthy female and male volunteers.

Appendix 1, Table 3 Common TEAE ≥ 2% of Patients in Any Treatment Group, by Food Status Group 1, EU/NA OAB 12-week Phase 3 Population

MedDRA (v12.1) Preferred Term, n (%) of Patients	Treatment	n	Food Status			
			Overall†	Fed (≥ 90%)	Mixed (> 10% to < 90%)	Fasted (≤ 10%)
Hypertension	Placebo	1380	105/1380 (7.6%)	37/449 (8.2%)	40/522 (7.7%)	27/406 (6.7%)
	Mirabegron 50 mg	1375	103/1375 (7.5%)	42/460 (9.1%)	37/518 (7.1%)	24/395 (6.1%)
	Mirabegron 100 mg	929	48/929 (5.2%)	15/317 (4.7%)	14/302 (4.6%)	19/306 (6.2%)
Nasopharyngitis	Placebo	1380	35/1380 (2.5%)	7/449 (1.6%)	17/522 (3.3%)	11/406 (2.7%)
	Mirabegron 50 mg	1375	54/1375 (3.9%)	20/460 (4.3%)	23/518 (4.4%)	11/395 (2.8%)
	Mirabegron 100 mg	929	25/929 (2.7%)	11/317 (3.5%)	5/302 (1.7%)	9/306 (2.9%)
Urinary tract infection	Placebo	1380	25/1380 (1.8%)	7/449 (1.6%)	13/522 (2.5%)	5/406 (1.2%)
	Mirabegron 50 mg	1375	40/1375 (2.9%)	11/460 (2.4%)	20/518 (3.9%)	9/395 (2.3%)
	Mirabegron 100 mg	929	25/929 (2.7%)	13/317 (4.1%)	7/302 (2.3%)	5/306 (1.6%)
Headache	Placebo	1380	42/1380 (3.0%)	15/449 (3.3%)	18/522 (3.4%)	9/406 (2.2%)
	Mirabegron 50 mg	1375	44/1375 (3.2%)	14/460 (3.0%)	19/518 (3.7%)	11/395 (2.8%)
	Mirabegron 100 mg	929	22/929 (2.4%)	6/317 (1.9%)	7/302 (2.3%)	9/306 (2.9%)
Dry mouth	Placebo	1380	29/1380 (2.1%)	8/449 (1.8%)	14/522 (2.7%)	7/406 (1.7%)
	Mirabegron 50 mg	1375	23/1375 (1.7%)	11/460 (2.4%)	5/518 (1.0%)	7/395 (1.8%)
	Mirabegron 100 mg	929	23/929 (2.5%)	8/317 (2.5%)	7/302 (2.3%)	8/306 (2.6%)
Constipation	Placebo	1380	20/1380 (1.4%)	5/449 (1.1%)	9/522 (1.7%)	6/406 (1.5%)
	Mirabegron 50 mg	1375	22/1375 (1.6%)	5/460 (1.1%)	11/518 (2.1%)	6/395 (1.5%)
	Mirabegron 100 mg	929	15/929 (1.6%)	4/317 (1.3%)	6/302 (2.0%)	5/306 (1.6%)
Upper respiratory tract infection	Placebo	1380	23/1380 (1.7%)	6/449 (1.3%)	7/522 (1.3%)	10/406 (2.5%)
	Mirabegron 50 mg	1375	20/1375 (1.5%)	4/460 (0.9%)	5/518 (1.0%)	11/395 (2.8%)
	Mirabegron 100 mg	929	11/929 (1.2%)	7/317 (2.2%)	4/302 (1.3%)	0/306
Dizziness	Placebo	1380	12/1380 (0.9%)	3/449 (0.7%)	5/522 (1.0%)	4/406 (1.0%)
	Mirabegron 50 mg	1375	13/1375 (0.9%)	5/460 (1.1%)	4/518 (0.8%)	4/395 (1.0%)
	Mirabegron 100 mg	929	6/929 (0.6%)	1/317 (0.3%)	2/302 (0.7%)	3/306 (1.0%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug (Safety Analysis Set [SAF]). TEAE 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 one or more TEAE within a level of the MedDRA term were counted only once in that level.
OAB: overactive bladder; TEAE: treatment-emergent adverse event(s).
† Patients were excluded from food status categorization if > 50% of the diary days collected did not have either the fed or fasted checkbox marked; therefore the number of patients in fed + mixed + fasted may not add up to the overall n value.

Appendix 1, Table 4 Baseline OAB Characteristics of Patients Included in Clinical Trials

Drug	Study Number	Treatment Total Daily Dose	Mean Number of Micturitions per 24 Hours	Mean Number of Incontinence Episodes per 24 Hours	Mean Volume Voided per Micturition (mL)
Mirabegron	Pooled Primary Phase 3 Studies	Placebo Mirabegron 50 mg Mirabegron 100 mg	11.6 11.7 11.6	1.8 1.8 1.8	159.2 158.9 157.9
	Pooled Primary Phase 3 Studies - Incontinence Subset	Placebo Mirabegron 50 mg Mirabegron 100 mg	11.6 11.7 11.6	2.7 2.7 2.8	159.1 158.4 158.6
Fesoterodine	SP-583	Placebo Fesoterodine 4 mg Fesoterodine 8 mg	12.0 11.6 11.9	3.7 3.8 3.7	150.2 160.0 153.9
	SP-584	Placebo Fesoterodine 4 mg Fesoterodine 8 mg	12.2 12.9 12.0	3.7 3.9 3.9	159.4 152.0 155.9
Solifenacin	905-CL-013	Placebo Solifenacin 10 mg	11.5 11.7	3.0 3.1	190.3 183.5
	905-CL-014	Placebo Solifenacin 10 mg	11.8 11.5	2.9 2.9	175.7 174.2
	905-CL-015	Placebo Solifenacin 5 mg Solifenacin 10 mg	12.2 12.1 12.3	2.7 2.6 2.6	143.8 149.6 147.2
	905-CL-018	Placebo Solifenacin 5 mg Solifenacin 10 mg	12.3 12.1 12.1	3.2 2.7 2.8	147.2 148.5 145.9
Trospium†	IP631-003	Placebo Trospium 20 mg	12.93 12.74	4.77 4.37	156.6 155.1
	IP631-005	Placebo Trospium 20 mg	13.17 12.94	3.90 3.84	154.6 154.8
Trospium XR	IP631-018	Placebo Trospium XR 60 mg	12.74 12.77	--	156.0 151.0
	IP631-022	Placebo Trospium XR 60 mg	12.94 12.84	--	151.80 149.60
Darifenacin§	A1371001	Placebo Darifenacin 15 mg	10.4 10.5	15.5‡ 16.2‡	147.1 155.0
	A1371002	Placebo Darifenacin 7.5 mg Darifenacin 15 mg	10.1 10.3 11.0	16.1‡ 14.0‡ 17.3‡	162.2 161.7 157.3
	A1371041	Placebo Darifenacin 7.5 mg Darifenacin 15 mg	10.1 10.1 10.1	16.6‡ 16.3‡ 17.0‡	162.4 160.2 151.8
Tolterodine	CTN 94-OATA-008	Placebo Tolterodine 2 mg Oxybutynin 5 mg	11.7 11.5 10.7	3.3 2.9 2.6	157 166 176
	CTN 94-OATA-009	Placebo Tolterodine 1 mg Tolterodine 2 mg	11.3 11.5 11.2	3.5 3.9 3.6	158 151 155
	CTN 94-OATA-010	Placebo Tolterodine 2 mg Oxybutynin 5 mg	11.6 11.6 11.5	3.5 3.7 3.4	160 155 149
Tolterodine ER	98-TOCR-007	Placebo Tolterodine ER 4 mg Tolterodine IR 2 mg	--	22.1-23.3‡	--
Oxybutynin XL	C-95-031	Placebo Oxybutynin XL	--	--	--
	C-95-049-05	Oxybutynin XL Oxybutynin IR	--	--	--

--: not applicable or no data provided; ER: extended release; IR: immediate release; OAB: overactive bladder; XL: extended release; XR: extended release.
† In Studies IP631-003 and IP631-005, the data was collected using a 4-point severity scale
‡ Number of incontinence episodes per week. For tolterodine ER, this number was only presented as a range across all treatment groups and not separately for each treatment group.
§ Median values are presented.
Source FDA Documents: Medical Review(s) Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Statistical Review(s) Application Number 21-518 (VESIcare, Solifenacin Succinate) 2004, Statistical Review Application Number 21-595 (Sanctura, Trospium Chloride). Medical Review(s) (Parts 1, 2, and 3) 2004, Statistical Review Application Number 22-103 (Sanctura XR, Trospium Chloride) 2007, Medical and Statistical Review(s) Application Number 21-513 (Enablex, Darifenacin Hydrobromide) 2004, Statistical Review(s) (Parts 1 and 2) Application Number 20-771 (Detrol, Tolterodine L-tartrate) 1998, Medical Review(s) (Parts 1 and 2) Application Number 21-228 (Detrol LA, Tolterodine) 2000 and Medical and Statistical Review(s) Application Number 20-897 (Ditropan XL, Oxybutynin Chloride) 1998. Toviaz EPAR, Scientific Discussion. European Medicines Agency, London, UK and Emselex EPAR and Scientific Discussion European Medicines Agency, London, UK. Enablex (darifenacin) package insert, 2011.

Appendix 1, Table 5 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, Study 178-CL-049, FAS-I

	Mirabegron 50 mg (n = 479)	Mirabegron 100 mg (n = 483)	Tolterodine ER 4 mg (n = 488)
Baseline			
Mean (SE) Median Min to Max	2.66 (0.120) 1.67 0.3 to 16.3	2.49 (0.113) 1.67 0.3 to 16.3	2.42 (0.107) 1.67 0.3 to 17.0
Final Visit			
Mean (SE) Median Min to Max	1.61 (0.130) 0.33 0.0 to 18.3	1.26 (0.104) 0.33 0.0 to 23.3	1.19 (0.094) 0.33 0.0 to 15.3
Change from Baseline			
Mean (SE) Median Min to Max	-1.05 (0.102) -1.00 -10.3 to 8.7	-1.24 (0.105) -1.00 -13.0 to 17.0	-1.23 (0.084) -1.00 -11.7 to 5.0
Adjusted Change from Baseline†			
Mean (SE) 95% 2-sided CI	-1.01 (0.087) (-1.18, -0.84)	-1.24 (0.086) (-1.41, -1.07)	-1.26 (0.086) (-1.43, -1.10)

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).
Min: minimum; Max: maximum; ER: extended release.
† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, previous study history, gender and geographical regions as fixed factors and baseline as a covariate.

Appendix 1, Table 6 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, Study 178-CL-049, FAS

	Mirabegron 50 mg (n = 789)	Mirabegron 100 mg (n = 802)	Tolterodine ER 4 mg (n = 791)
Baseline			
Mean (SE)	11.13 (0.100)	11.16 (0.102)	10.94 (0.093)
Median	10.67	10.33	10.33
Min to Max	6.3 to 31.7	5.7 to 29.3	4.7 to 25.3
Final Visit			
Mean (SE)	9.85 (0.110)	9.73 (0.113)	9.58 (0.109)
Median	9.33	9.33	9.00
Min to Max	2.0 to 28.7	3.0 to 28.0	4.0 to 29.7
Change from Baseline			
Mean (SE)	-1.28 (0.087)	-1.43 (0.085)	-1.36 (0.087)
Median	-1.33	-1.33	-1.33
Min to Max	-11.7 to 12.0	-13.0 to 12.3	-11.5 to 13.2
Adjusted Change from Baseline†			
Mean (SE)	-1.27 (0.083)	-1.41 (0.082)	-1.39 (0.083)
95% 2-sided CI	(-1.44, -1.11)	(-1.57, -1.25)	(-1.56, -1.23)

All randomized patients who took at least one 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]).
Min: minimum; Max: maximum; ER: extended release.
† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, previous study history, gender and geographical regions as fixed factors and baseline as a covariate.

Appendix 1, Table 7 Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition, Study 178-CL-049, FAS

	Mirabegron 50 mg (n = 789)	Mirabegron 100 mg (n = 802)	Tolterodine ER 4 mg (n = 791)
Baseline			
Mean (SE)	160.1 (2.09)	164.9 (2.06)	160.1 (2.01)
Median	154.7	160.3	156.2
Min to Max	28 to 346	28 to 350	36 to 354
Final Visit			
Mean (SE)	177.5 (2.60)	186.3 (2.62)	178.3 (2.41)
Median	171.7	178.6	171.9
Min to Max	33 to 729	21 to 493	38 to 433
Change from Baseline			
Mean (SE)	17.5 (1.67)	21.4 (1.63)	18.1 (1.67)
Median	12.4	15.7	12.1
Min to Max	-152 to 386	-175 to 251	-149 to 272
Adjusted Change from Baseline†			
Mean (SE)	17.5 (1.65)	21.5 (1.63)	18.1 (1.64)
95% 2-sided CI	(14.3, 20.7)	(18.3, 24.7)	(14.8, 21.3)

All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Min: minimum; Max: maximum; ER: extended release.
† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, previous study history, gender and geographical regions as fixed factors and baseline as a covariate.

Appendix 1, Table 8 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Demographics, Pooled Primary Phase 3 Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Gender	Male	n		154	168	94	362	382	241
		Baseline	Mean (SE)	2.12 (0.223)	2.25 (0.189)	2.01 (0.189)	11.68 (0.179)	12.04 (0.173)	11.50 (0.204)
		Adjusted Diff. from Baseline	Mean (SE)	-1.41 (0.159)	-1.48 (0.152)	-1.52 (0.205)	-0.92 (0.135)	-1.29 (0.131)	-1.62 (0.166)
			95% 2-sided CI	(-1.72, -1.10)	(-1.78, -1.18)	(-1.92, -1.12)	(-1.18, -0.66)	(-1.55, -1.04)	(-1.95, -1.29)
		Adjusted Diff. vs Placebo	Mean	--	-0.07	-0.11	--	-0.37	-0.70
			95% 2-sided CI		(-0.50, 0.36)	(-0.62, 0.40)		(-0.74, -0.01)	(-1.12, -0.28)
	Female	n		724	694	483	966	942	649
		Baseline	Mean (SE)	2.86 (0.098)	2.83 (0.101)	2.94 (0.115)	11.54 (0.096)	11.56 (0.102)	11.60 (0.117)
		Adjusted Diff from Baseline	Mean (SE)	-1.03 (0.074)	-1.50 (0.075)	-1.50 (0.093)	-1.31 (0.082)	-1.93 (0.084)	-1.79 (0.103)
			95% 2-sided CI	(-1.17, -0.89)	(-1.65, -1.35)	(-1.68, -1.32)	(-1.47, -1.15)	(-2.09, -1.77)	(-1.99, -1.59)
		Adjusted Diff. vs Placebo	Mean		-0.47	-0.47	--	-0.62	-0.48
			95% 2-sided CI	--	(-0.67, -0.26)	(-0.70, -0.23)		(-0.85, -0.39)	(-0.74, -0.22)
	Interaction P value:				**0.22**			**0.16**	
Age Group	< 65 years	n		533	507	342	824	825	550
		Baseline	Mean (SE)	2.73 (0.120)	2.68 (0.117)	2.74 (0.127)	11.70 (0.116)	11.92 (0.120)	11.65 (0.134)
		Adjusted Diff. from Baseline	Mean (SE)	-1.19 (0.086)	-1.41 (0.088)	-1.41 (0.109)	-1.29 (0.089)	-1.80 (0.089)	-1.70 (0.112)
			95% 2-sided CI	(-1.36, -1.02)	(-1.58, -1.24)	(-1.63, -1.20)	(-1.47, -1.11)	(-1.97, -1.62)	(-1.92, -1.48)
		Adjusted Diff. vs Placebo	Mean	--	-0.22	-0.22	--	-0.51	-0.41
			95% 2-sided CI		(-0.46, 0.02)	(-0.50, 0.05)		(-0.75, -0.26)	(-0.69, -0.12)
	≥ 65 years	n		345	355	235	504	499	340
		Baseline	Mean (SE)	2.72 (0.135)	2.76 (0.139)	2.86 (0.170)	11.37 (0.120)	11.33 (0.124)	11.45 (0.156)
		Adjusted Diff. from Baseline	Mean (SE)	-0.96 (0.106)	-1.61 (0.105)	-1.63 (0.131)	-1.05 (0.114)	-1.68 (0.115)	-1.81 (0.141)
			95% 2-sided CI	(-1.16, -0.75)	(-1.82, -1.41)	(-1.89, -1.38)	(-1.28, -0.83)	(-1.90, -1.45)	(-2.08, -1.53)
		Adjusted Diff. vs Placebo	Mean	--	-0.66	-0.68	--	-0.62	-0.75
			95% 2-sided CI		(-0.95, -0.37)	(-1.01, -0.35)		(-0.94, -0.30)	(-1.11, -0.40)
	Interaction P value:				**0.036**			**0.31**	
	< 75 years	n		766	751	493	1174	1175	780
		Baseline	Mean (SE)	2.68 (0.095)	2.67 (0.094)	2.71 (0.108)	11.64 (0.092)	11.77 (0.095)	11.61 (0.108)
		Adjusted Diff. from Baseline	Mean (SE)	-1.13 (0.072)	-1.49 (0.072)	-1.47 (0.092)	-1.18 (0.075)	-1.72 (0.075)	-1.69 (0.095)
			95% 2-sided CI	(-1.27, -0.99)	(-1.63, -1.35)	(-1.65, -1.29)	(-1.32, -1.03)	(-1.87, -1.58)	(-1.87, -1.50)
		Adjusted Diff. vs Placebo	Mean	--	-0.36	-0.34	--	-0.55	-0.51
			95% 2-sided CI		(-0.56, -0.16)	(-0.57, -0.11)		(-0.75, -0.34)	(-0.75, -0.27)
	≥ 75 years	n		112	111	84	154	149	110
		Baseline	Mean (SE)	3.06 (0.266)	3.02 (0.283)	3.25 (0.298)	11.06 (0.206)	11.16 (0.229)	11.31 (0.308)
		Adjusted Diff. from Baseline	Mean (SE)	-0.87 (0.187)	-1.51 (0.187)	-1.67 (0.217)	-1.37 (0.206)	-1.96 (0.210)	-2.11 (0.245)
			95% 2-sided CI	(-1.23, -0.50)	(-1.88, -1.15)	(-2.10, -1.25)	(-1.78, -0.97)	(-2.38, -1.55)	(-2.59, -1.63)
		Adjusted Diff. vs Placebo	Mean	--	-0.65	-0.81	--	-0.59	-0.73
			95% 2-sided CI		(-1.17, -0.13)	(-1.37, -0.25)		(-1.17, -0.02)	(-1.36, -0.11)
	Interaction P value:				**0.30**			**0.79**	

Table continued on next page.

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Race	White	n		806	804	541	1227	1235	838
		Baseline	Mean (SE)	2.74 (0.092)	2.72 (0.093)	2.78 (0.104)	11.57 (0.085)	11.71 (0.092)	11.47 (0.101)
		Adjusted Diff. from Baseline	Mean (SE)	-1.06 (0.070)	-1.50 (0.070)	-1.49 (0.088)	-1.15 (0.073)	-1.76 (0.073)	-1.76 (0.092)
			95% 2-sided CI	(-1.19, -0.92)	(-1.64, -1.37)	(-1.66, -1.32)	(-1.30, -1.01)	(-1.90, -1.61)	(-1.94, -1.58)
		Adjusted Diff. vs Placebo	Mean	--	-0.45	-0.43	--	-0.60	-0.61
			95% 2-sided CI		(-0.64, -0.25)	(-0.66, -0.21)		(-0.81, -0.40)	(-0.84, -0.37)
	Black or African American	n		58	41	28	80	61	36
		Baseline	Mean (SE)	2.83 (0.473)	2.34 (0.307)	2.96 (0.511)	11.64 (0.511)	11.53 (0.390)	12.70 (0.725)
		Adjusted Diff. from Baseline	Mean (SE)	-1.54 (0.261)	-1.44 (0.310)	-1.60 (0.376)	-1.74 (0.287)	-1.66 (0.329)	-1.21 (0.429)
			95% 2-sided CI	(-2.05, -1.03)	(-2.04, -0.83)	(-2.34, -0.87)	(-2.31, -1.18)	(-2.31, -1.02)	(-2.06, -0.37)
		Adjusted Diff. vs Placebo	Mean	--	0.10	-0.06	--	0.08	0.53
			95% 2-sided CI		(-0.68, 0.89)	(-0.96, 0.83)		(-0.77, 0.93)	(-0.48, 1.54)
	Asian	n		8	11	2	13	17	8
		Baseline	Mean (SE)	2.13 (0.504)	2.91 (1.031)	0.67 (0.333)	11.38 (0.798)	11.33 (0.414)	15.33 (1.366)
		Adjusted Diff. from Baseline	Mean (SE)	-1.60 (0.698)	-0.81 (0.595)	-1.14 (1.394)	-2.29 (0.709)	-2.25 (0.620)	-1.28 (0.905)
			95% 2-sided CI	(-2.97, -0.23)	(-1.97, 0.36)	(-3.87, 1.59)	(-3.68, -0.90)	(-3.46, -1.03)	(-3.05, 0.50)
		Adjusted Diff. vs Placebo	Mean	--	0.79	0.46	--	0.04	1.02
			95% 2-sided CI		(-1.01, 2.59)	(-2.60, 3.52)		(-1.80, 1.89)	(-1.24, 3.27)
	Other	n		6	6	6	8	11	8
		Baseline	Mean (SE)	1.39 (0.315)	4.28 (1.337)	3.50 (1.460)	12.04 (1.462)	11.85 (0.738)	14.08 (1.473)
		Adjusted Diff. from Baseline	Mean (SE)	-1.83 (0.805)	-1.82 (0.806)	-1.89 (0.807)	-1.61 (0.903)	-1.06 (0.770)	-2.32 (0.905)
			95% 2-sided CI	(-3.41, -0.25)	(-3.40, -0.24)	(-3.48, -0.31)	(-3.38, 0.16)	(-2.57, 0.45)	(-4.09, -0.55)
		Adjusted Diff. vs Placebo	Mean	--	0.01	-0.07	--	0.55	-0.71
			95% 2-sided CI		(-2.23, 2.24)	(-2.30, 2.17)		(-1.78, 2.87)	(-3.22, 1.79)
	Interaction P value:				**0.38**			**0.070**	
Ethnicity	Non-Hispanic or Latino	n		559	534	276	804	808	381
		Baseline	Mean (SE)	2.77 (0.120)	2.65 (0.110)	2.73 (0.149)	11.51 (0.110)	11.70 (0.115)	11.64 (0.177)
		Adjusted Diff. from Baseline	Mean (SE)	-1.04 (0.086)	-1.43 (0.088)	-1.60 (0.129)	-1.08 (0.096)	-1.65 (0.096)	-1.76 (0.148)
			95% 2-sided CI	(-1.21, -0.87)	(-1.60, -1.26)	(-1.85, -1.34)	(-1.27, -0.90)	(-1.83, -1.46)	(-2.05, -1.47)
		Adjusted Diff. vs Placebo	Mean	--	-0.39	-0.55	--	-0.56	-0.67
			95% 2-sided CI		(-0.63, -0.15)	(-0.86, -0.24)		(-0.82, -0.30)	(-1.02, -0.32)
	Hispanic or Latino	n		28	35	20	44	43	31
		Baseline	Mean (SE)	2.56 (0.362)	2.64 (0.358)	2.26 (0.398)	11.19 (0.401)	12.33 (0.700)	11.82 (0.470)
		Adjusted Diff. from Baseline	Mean (SE)	-0.97 (0.383)	-1.46 (0.343)	-1.23 (0.455)	-1.53 (0.407)	-1.29 (0.412)	-1.80 (0.487)
			95% 2-sided CI	(-1.73, -0.22)	(-2.14, -0.79)	(-2.12, -0.34)	(-2.33, -0.73)	(-2.10, -0.49)	(-2.75, -0.84)
		Adjusted Diff. vs Placebo	Mean	--	-0.49	-0.25	--	0.24	-0.26
			95% 2-sided CI		(-1.50, 0.52)	(-1.42, 0.91)		(-0.90, 1.38)	(-1.51, 0.98)
	Interaction P value:				**0.79**			**0.40**	
BMI Group	< 25 kg/m^2	n		223	234	143	373	370	236
		Baseline	Mean (SE)	2.53 (0.158)	2.46 (0.155)	2.83 (0.203)	11.69 (0.164)	11.90 (0.166)	11.69 (0.228)
		Adjusted Diff. from Baseline	Mean (SE)	-1.18 (0.132)	-1.64 (0.129)	-1.48 (0.166)	-1.36 (0.132)	-2.04 (0.133)	-1.81 (0.168)
			95% 2-sided CI	(-1.43, -0.92)	(-1.89, -1.39)	(-1.81, -1.16)	(-1.61, -1.10)	(-2.30, -1.78)	(-2.14, -1.48)
		Adjusted Diff. vs Placebo	Mean	--	-0.47	-0.31	--	-0.68	-0.46
			95% 2-sided CI		(-0.83, -0.10)	(-0.73, 0.11)		(-1.05, -0.32)	(-0.88, -0.04)

Table continued on next page.

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
BMI Group	25 to < 30 kg/m^2	n		304	306	193	461	499	326
		Baseline	Mean (SE)	2.47 (0.159)	2.75 (0.157)	2.60 (0.182)	11.68 (0.153)	11.62 (0.141)	11.54 (0.145)
		Adjusted Diff. from Baseline	Mean (SE)	-1.21 (0.113)	-1.47 (0.113)	-1.72 (0.144)	-1.15 (0.119)	-1.85 (0.115)	-2.02 (0.144)
			95% 2-sided CI	(-1.44, -0.99)	(-1.69, -1.25)	(-2.00, -1.44)	(-1.38, -0.91)	(-2.07, -1.63)	(-2.31, -1.74)
		Adjusted Diff. vs Placebo	Mean	--	-0.25	-0.51	--	-0.70	-0.88
			95% 2-sided CI		(-0.57, 0.06)	(-0.87, -0.14)		(-1.03, -0.38)	(-1.24, -0.51)
	≥ 30 kg/m^2	n		351	322	241	493	455	327
		Baseline	Mean (SE)	3.08 (0.145)	2.87 (0.150)	2.91 (0.154)	11.40 (0.130)	11.63 (0.154)	11.54 (0.170)
		Adjusted Diff. from Baseline	Mean (SE)	-0.95 (0.106)	-1.41 (0.110)	-1.34 (0.129)	-1.13 (0.115)	-1.41 (0.120)	-1.41 (0.143)
			95% 2-sided CI	(-1.15, -0.74)	(-1.63, -1.19)	(-1.60, -1.09)	(-1.35, -0.90)	(-1.64, -1.17)	(-1.69, -1.13)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.39	--	-0.28	-0.28
			95% 2-sided CI		(-0.76, -0.16)	(-0.72, -0.07)		(-0.61, 0.04)	(-0.65, 0.08)
	Interaction P value:				**0.59**			**0.11**	
Geographical Region	Europe	n		405	405	281	676	666	478
		Baseline	Mean (SE)	2.55 (0.119)	2.80 (0.137)	2.89 (0.147)	11.70 (0.115)	11.69 (0.114)	11.51 (0.124)
		Adjusted Diff. from Baseline	Mean (SE)	-1.11 (0.096)	-1.57 (0.096)	-1.42 (0.119)	-1.37 (0.089)	-1.90 (0.090)	-1.78 (0.109)
			95% 2-sided CI	(-1.29, -0.92)	(-1.76, -1.38)	(-1.65, -1.18)	(-1.54, -1.19)	(-2.08, -1.73)	(-2.00, -1.57)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.31	--	-0.53	-0.42
			95% 2-sided CI		(-0.73, -0.20)	(-0.62, -0.01)		(-0.78, -0.29)	(-0.70, -0.13)
	North America	n		473	457	296	652	658	412
		Baseline	Mean (SE)	2.88 (0.132)	2.64 (0.117)	2.69 (0.142)	11.44 (0.126)	11.71 (0.135)	11.66 (0.167)
		Adjusted Diff. from Baseline	Mean (SE)	-1.09 (0.093)	-1.43 (0.095)	-1.59 (0.122)	-1.02 (0.110)	-1.59 (0.110)	-1.70 (0.144)
			95% 2-sided CI	(-1.27, -0.90)	(-1.62, -1.24)	(-1.83, -1.35)	(-1.24, -0.81)	(-1.81, -1.38)	(-1.98, -1.42)
		Adjusted Diff. vs Placebo	Mean	--	-0.34	-0.51	--	-0.57	-0.68
			95% 2-sided CI		(-0.60, -0.08)	(-0.81, -0.20)		(-0.87, -0.27)	(-1.04, -0.32)
	Interaction P value:				**Not applicable†**			**Not applicable†**	

Pooled studies included: 178-CL-046, 178-CL-04, and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All patients in the FAS who had least one incontinence episode in the baseline diary (Full Analysis Set-Incontinence [FAS-I]).
Descriptive statistics for adjusted changes from baseline are generated from the analysis of covariance (ANCOVA) model with treatment group, gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. For the subpopulation gender analysis, an ANCOVA model with treatment group, gender, study, and gender by treatment group interaction as fixed factors and baseline as a covariate was performed.
--: not applicable
P value is from treatment by subpopulation interaction in the ANCOVA model described above.
† An ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate was performed separately for North America and for Europe; therefore no treatment-by-geographical region interaction is derived.

Appendix 1, Table 9 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Characteristics of OAB, Pooled Primary Phase 3 Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Type of OAB	Urge Incontinence	n		336	352	228	442	491	297
		Baseline	Mean (SE)	2.61 (0.132)	2.71 (0.142)	3.02 (0.180)	11.53 (0.146)	11.46 (0.138)	11.49 (0.175)
		Adjusted Diff. from Baseline	Mean (SE)	-1.20 (0.108)	-1.39 (0.106)	-1.51 (0.133)	-1.25 (0.122)	-1.82 (0.116)	-2.06 (0.150)
			95% 2-sided CI	(-1.41, -0.99)	(-1.60, -1.18)	(-1.77, -1.25)	(-1.49, -1.01)	(-2.05, -1.59)	(-2.35, -1.77)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.19 (-0.49, 0.10)	-0.31 (-0.64, 0.03)	--	-0.57 (-0.90, -0.25)	-0.81 (-1.19, -0.43)
	Mixed	n		364	350	232	415	412	271
		Baseline	Mean (SE)	3.13 (0.158)	3.09 (0.146)	3.00 (0.159)	11.41 (0.146)	11.53 (0.153)	11.47 (0.184)
		Adjusted Diff. from Baseline	Mean (SE)	-1.06 (0.106)	-1.58 (0.107)	-1.41 (0.132)	-1.05 (0.129)	-1.84 (0.128)	-1.61 (0.159)
			95% 2-sided CI	(-1.26, -0.85)	(-1.79, -1.37)	(-1.67, -1.15)	(-1.30, -0.80)	(-2.09, -1.59)	(-1.92, -1.30)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.52 (-0.81, -0.23)	-0.36 (-0.69, -0.03)	--	-0.79 (-1.14, -0.44)	-0.56 (-0.96, -0.17)
	Frequency	n		178	160	117	471	421	322
		Baseline	Mean (SE)	2.15 (0.165)	1.91 (0.167)	1.91 (0.152)	11.77 (0.150)	12.14 (0.168)	11.74 (0.172)
		Adjusted Diff. from Baseline	Mean (SE)	-0.99 (0.150)	-1.53 (0.158)	-1.68 (0.185)	-1.29 (0.119)	-1.59 (0.127)	-1.55 (0.146)
			95% 2-sided CI	(-1.28, -0.69)	(-1.84, -1.22)	(-2.04, -1.31)	(-1.53, -1.06)	(-1.83, -1.34)	(-1.83, -1.26)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.55 (-0.97, -0.12)	-0.69 (-1.16, -0.23)	--	-0.29 (-0.63, 0.04)	-0.25 (-0.62, 0.11)
		Interaction P value:			**0.33**			**0.10**	
Duration of OAB Symptoms	< 12 months	n		67	66	63	122	128	115
		Baseline	Mean (SE)	2.82 (0.339)	2.29 (0.321)	2.57 (0.276)	11.97 (0.310)	11.21 (0.235)	11.04 (0.242)
		Adjusted Diff. from Baseline	Mean (SE)	-1.21 (0.241)	-1.58 (0.243)	-1.82 (0.249)	-1.79 (0.231)	-1.93 (0.226)	-1.99 (0.239)
			95% 2-sided CI	(-1.69, -0.74)	(-2.06, -1.11)	(-2.31, -1.34)	(-2.24, -1.34)	(-2.37, -1.49)	(-2.46, -1.52)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.37 (-1.04, 0.30)	-0.61 (-1.29, 0.07)	--	-0.14 (-0.77, 0.49)	-0.20 (-0.85, 0.45)
	≥ 12 to < 60 months	n		345	370	212	561	568	361
		Baseline	Mean (SE)	2.60 (0.150)	2.84 (0.140)	2.64 (0.172)	11.45 (0.134)	11.79 (0.142)	11.48 (0.151)
		Adjusted Diff. from Baseline	Mean (SE)	-1.22 (0.106)	-1.55 (0.103)	-1.50 (0.137)	-1.19 (0.108)	-1.78 (0.107)	-1.85 (0.137)
			95% 2-sided CI	(-1.43, -1.02)	(-1.75, -1.35)	(-1.77, -1.23)	(-1.40, -0.98)	(-1.99, -1.57)	(-2.12, -1.58)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.33 (-0.62, -0.04)	-0.27 (-0.62, 0.07)	--	-0.59 (-0.89, -0.29)	-0.66 (-1.00, -0.32)
	≥ 60 month	n		466	426	302	645	628	414
		Baseline	Mean (SE)	2.81 (0.119)	2.67 (0.124)	2.94 (0.141)	11.61 (0.117)	11.72 (0.125)	11.81 (0.161)
		Adjusted Diff. from Baseline	Mean (SE)	-0.99 (0.092)	-1.42 (0.096)	-1.45 (0.116)	-1.09 (0.101)	-1.69 (0.103)	-1.58 (0.128)
			95% 2-sided CI	(-1.17, -0.81)	(-1.61, -1.24)	(-1.67, -1.22)	(-1.29, -0.90)	(-1.89, -1.49)	(-1.83, -1.33)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.44 (-0.70, -0.18)	-0.46 (-0.75, -0.17)	--	-0.59 (-0.87, -0.31)	-0.49 (-0.81, -0.17)
		Interaction P value:			**0.86**			**0.62**	
Prior OAB Surgery	Previous OAB surgery	n		97	108	60	114	126	74
		Baseline	Mean (SE)	3.16 (0.271)	2.79 (0.243)	3.31 (0.328)	11.54 (0.255)	11.54 (0.231)	11.79 (0.294)
		Adjusted Diff. from Baseline	Mean (SE)	-0.77 (0.202)	-1.34 (0.191)	-1.39 (0.256)	-1.02 (0.241)	-1.85 (0.229)	-1.58 (0.299)
			95% 2-sided CI	(-1.16, -0.37)	(-1.71, -0.96)	(-1.90, -0.89)	(-1.49, -0.54)	(-2.30, -1.40)	(-2.17, -0.99)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.57 (-1.11, -0.03)	-0.63 (-1.27, 0.01)	--	-0.83 (-1.48, -0.18)	-0.56 (-1.31, 0.19)

Table continued on next page.

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Prior OAB Surgery	No Previous OAB surgery	n		781	754	517	1214	1198	816
		Baseline	Mean (SE)	2.68 (0.095)	2.70 (0.096)	2.73 (0.107)	11.58 (0.090)	11.72 (0.095)	11.56 (0.108)
		Adjusted Diff. from Baseline	Mean (SE)	-1.14 (0.071)	-1.52 (0.072)	-1.52 (0.090)	-1.22 (0.074)	-1.74 (0.074)	-1.76 (0.093)
			95% 2-sided CI	(-1.28, -1.00)	(-1.66, -1.37)	(-1.69, -1.34)	(-1.36, -1.07)	(-1.89, -1.59)	(-1.94, -1.57)
		Adjusted Diff. vs Placebo	Mean	--	-0.38	-0.38	--	-0.52	-0.54
			95% 2-sided CI		(-0.57, -0.18)	(-0.61, -0.15)		(-0.73, -0.32)	(-0.77, -0.30)
	Interaction P value:				**0.72**			**0.62**	
Previous Treatment with OAB Medication	Previous OAB med	n		518	506	336	704	688	460
		Baseline	Mean (SE)	2.93 (0.118)	2.98 (0.120)	2.99 (0.141)	11.53 (0.110)	11.78 (0.119)	11.60 (0.144)
		Adjusted Diff. from Baseline	Mean (SE)	-0.92 (0.087)	-1.49 (0.088)	-1.42 (0.110)	-0.93 (0.097)	-1.67 (0.098)	-1.61 (0.122)
			95% 2-sided CI	(-1.09, -0.75)	(-1.66, -1.32)	(-1.64, -1.21)	(-1.12, -0.74)	(-1.86, -1.48)	(-1.85, -1.37)
		Adjusted Diff. vs Placebo	Mean	--	-0.57	-0.50	--	-0.74	-0.69
			95% 2-sided CI		(-0.81, -0.33)	(-0.77, -0.22)		(-1.01, -0.47)	(-0.99, -0.38)
	No Previous OAB med	n		360	356	241	624	636	430
		Baseline	Mean (SE)	2.44 (0.137)	2.33 (0.131)	2.50 (0.144)	11.62 (0.132)	11.61 (0.131)	11.55 (0.144)
		Adjusted Diff. from Baseline	Mean (SE)	-1.35 (0.104)	-1.50 (0.105)	-1.62 (0.129)	-1.51 (0.103)	-1.84 (0.102)	-1.87 (0.126)
			95% 2-sided CI	(-1.55, -1.14)	(-1.71, -1.29)	(-1.87, -1.36)	(-1.71, -1.31)	(-2.04, -1.64)	(-2.12, -1.63)
		Adjusted Diff. vs Placebo	Mean	--	-0.15	-0.27	--	-0.33	-0.36
			95% 2-sided CI		(-0.44, 0.14)	(-0.60, 0.06)		(-0.62, -0.05)	(-0.68, -0.04)
	Interaction P value:				**0.095**			**0.10**	
Reason for Discontinuing Prior OAB Medication	Insufficient Effect Yes	n		336	335	224	466	464	296
		Baseline	Mean (SE)	3.03 (0.151)	2.94 (0.141)	3.20 (0.183)	11.60 (0.142)	11.67 (0.142)	11.87 (0.196)
		Adjusted Diff. from Baseline	Mean (SE)	-0.86 (0.113)	-1.56 (0.114)	-1.50 (0.142)	-0.86 (0.115)	-1.54 (0.116)	-1.65 (0.148)
			95% 2-sided CI	(-1.09, -0.64)	(-1.78, -1.34)	(-1.78, -1.22)	(-1.09, -0.64)	(-1.77, -1.31)	(-1.94, -1.36)
		Adjusted Diff. vs Placebo	Mean	--	-0.70	-0.63	--	-0.67	-0.79
			95% 2-sided CI		(-1.01, -0.38)	(-0.99, -0.27)		(-0.99, -0.36)	(-1.16, -0.42)
	Insufficient Effect No	n		182	171	112	238	224	164
		Baseline	Mean (SE)	2.74 (0.188)	3.07 (0.225)	2.57 (0.206)	11.41 (0.171)	12.01 (0.216)	11.12 (0.191)
		Adjusted Diff. from Baseline	Mean (SE)	-1.33 (0.154)	-1.69 (0.159)	-1.59 (0.199)	-1.13 (0.162)	-2.06 (0.166)	-1.74 (0.197)
			95% 2-sided CI	(-1.64, -1.03)	(-2.00, -1.38)	(-1.98, -1.20)	(-1.44, -0.81)	(-2.38, -1.73)	(-2.13, -1.36)
		Adjusted Diff. vs Placebo	Mean	--	-0.35	-0.26	--	-0.93	-0.61
			95% 2-sided CI		(-0.79, 0.08)	(-0.75, 0.24)		(-1.38, -0.47)	(-1.12, -0.11)
	Interaction P value:				**0.34**			**0.38**	
	Poor Tolerability Yes	n		136	138	80	185	173	113
		Baseline	Mean (SE)	2.80 (0.226)	3.00 (0.234)	2.75 (0.234)	11.55 (0.187)	11.70 (0.223)	11.77 (0.337)
		Adjusted Diff. from Baseline	Mean (SE)	-1.09 (0.179)	-1.59 (0.178)	-1.65 (0.235)	-0.93 (0.183)	-1.81 (0.190)	-2.00 (0.236)
			95% 2-sided CI	(-1.44, -0.74)	(-1.94, -1.24)	(-2.11, -1.19)	(-1.29, -0.57)	(-2.19, -1.44)	(-2.46, -1.53)
		Adjusted Diff. vs Placebo	Mean	--	-0.50	-0.56	--	-0.88	-1.07
			95% 2-sided CI		(-1.00, -0.01)	(-1.14, 0.02)		(-1.40, -0.37)	(-1.66, -0.48)
	Poor Tolerability No	n		382	368	256	519	515	347
		Baseline	Mean (SE)	2.97 (0.139)	2.98 (0.140)	3.07 (0.170)	11.53 (0.134)	11.81 (0.140)	11.55 (0.157)
		Adjusted Diff. from Baseline	Mean (SE)	-1.01 (0.107)	-1.61 (0.109)	-1.49 (0.134)	-0.96 (0.110)	-1.67 (0.110)	-1.58 (0.138)
			95% 2-sided CI	(-1.22, -0.80)	(-1.82, -1.39)	(-1.76, -1.23)	(-1.18, -0.75)	(-1.89, -1.46)	(-1.85, -1.31)
		Adjusted Diff. vs Placebo	Mean	--	-0.60	-0.49	--	-0.71	-0.62
			95% 2-sided CI		(-0.90, -0.30)	(-0.82, -0.15)		(-1.01, -0.41)	(-0.97, -0.27)
	Interaction P value:				**0.87**			**0.43**	

Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All
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patients in the FAS who had least one incontinence episode in the baseline diary (Full Analysis Set-Incontinence [FAS-I]).
OAB: overactive bladder; --: not applicable.
Descriptive statistics for adjusted changes from baseline are generated from the analysis of covariance (ANCOVA) model with treatment group, gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
P value is from treatment by subpopulation interaction in the ANCOVA model described above.

Appendix 1, Table 10 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Intrinsic/Extrinsic Factors, Pooled Primary Phase 3 Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
History of BPH†	Yes	n		60	56	36	147	142	95
		Baseline	Mean (SE)	1.84 (0.237)	2.27 (0.338)	2.24 (0.320)	11.94 (0.280)	11.89 (0.291)	11.73 (0.339)
		Adjusted Diff. from Baseline	Mean (SE)	-0.84 (0.251)	-0.70 (0.260)	-0.81 (0.329)	-0.82 (0.218)	-0.99 (0.223)	-1.69 (0.277)
			95% 2-sided CI	(-1.33, -0.34)	(-1.21, -0.18)	(-1.45, -0.16)	(-1.25, -0.39)	(-1.42, -0.55)	(-2.24, -1.15)
		Adjusted Diff. vs Placebo	Mean	--	0.14	0.03	--	-0.16	-0.87
			95% 2-sided CI		(-0.57, 0.85)	(-0.79, 0.85)		(-0.77, 0.45)	(-1.57, -0.17)
	No	n		94	112	58	215	240	146
		Baseline	Mean (SE)	2.30 (0.333)	2.24 (0.228)	1.87 (0.234)	11.50 (0.233)	12.12 (0.216)	11.35 (0.256)
		Adjusted Diff. from Baseline	Mean (SE)	-1.36 (0.200)	-1.45 (0.183)	-1.33 (0.261)	-1.10 (0.181)	-1.58 (0.171)	-1.60 (0.226)
			95% 2-sided CI	(-1.76, -0.97)	(-1.81, -1.09)	(-1.84, -0.82)	(-1.46, -0.75)	(-1.91, -1.24)	(-2.04, -1.15)
		Adjusted Diff. vs Placebo	Mean	--	-0.09	0.04	--	-0.48	-0.50
			95% 2-sided CI		(-0.62, 0.44)	(-0.62, 0.69)		(-0.97, 0.01)	(-1.07, 0.08)
	Interaction P value:				**0.85**			**0.30**	
History of Diabetes	Yes	n		76	79	59	105	115	75
		Baseline	Mean (SE)	2.68 (0.228)	2.86 (0.314)	2.59 (0.325)	11.65 (0.298)	11.37 (0.256)	11.25 (0.342)
		Adjusted Diff. from Baseline	Mean (SE)	-0.99 (0.227)	-1.54 (0.222)	-1.34 (0.258)	-0.93 (0.250)	-1.71 (0.239)	-1.76 (0.296)
			95% 2-sided CI	(-1.43, -0.54)	(-1.98, -1.11)	(-1.85, -0.83)	(-1.42, -0.44)	(-2.18, -1.24)	(-2.34, -1.18)
		Adjusted Diff. vs Placebo	Mean	--	-0.55	-0.35	--	-0.78	-0.83
			95% 2-sided CI		(-1.18, 0.07)	(-1.03, 0.32)		(-1.45, -0.10)	(-1.59, -0.06)
	No	n		802	783	518	1223	1209	815
		Baseline	Mean (SE)	2.74 (0.096)	2.70 (0.093)	2.81 (0.107)	11.57 (0.089)	11.73 (0.094)	11.61 (0.107)
		Adjusted Diff. from Baseline	Mean (SE)	-1.11 (0.070)	-1.49 (0.071)	-1.52 (0.090)	-1.22 (0.073)	-1.75 (0.074)	-1.74 (0.093)
			95% 2-sided CI	(-1.25, -0.97)	(-1.63, -1.35)	(-1.70, -1.35)	(-1.37, -1.08)	(-1.90, -1.61)	(-1.92, -1.56)
		Adjusted Diff. vs Placebo	Mean	--	-0.38	-0.41	--	-0.53	-0.52
			95% 2-sided CI		(-0.57, -0.19)	(-0.64, -0.19)		(-0.73, -0.33)	(-0.75, -0.28)
	Interaction P value:				**0.78**			**0.69**	
Renal Status (CrCl CG), mL/min	≥ 90 Normal	n		471	431	319	728	697	498
		Baseline	Mean (SE)	2.81 (0.123)	2.77 (0.131)	2.72 (0.140)	11.58 (0.113)	11.85 (0.127)	11.60 (0.131)
		Adjusted Diff. from Baseline	Mean (SE)	-1.08 (0.091)	-1.38 (0.095)	-1.47 (0.113)	-1.14 (0.095)	-1.67 (0.097)	-1.66 (0.117)
			95% 2-sided CI	(-1.26, -0.90)	(-1.57, -1.20)	(-1.69, -1.25)	(-1.33, -0.95)	(-1.86, -1.48)	(-1.89, -1.43)
		Adjusted Diff. vs Placebo	Mean	--	-0.30	-0.39	--	-0.53	-0.52
			95% 2-sided CI		(-0.56, -0.04)	(-0.67, -0.10)		(-0.80, -0.27)	(-0.82, -0.22)
	60 to < 90 Mild Impairment	n		310	348	201	469	520	318
		Baseline	Mean (SE)	2.62 (0.152)	2.58 (0.130)	2.76 (0.155)	11.69 (0.152)	11.54 (0.134)	11.58 (0.177)
		Adjusted Diff. from Baseline	Mean (SE)	-1.10 (0.112)	-1.56 (0.106)	-1.45 (0.141)	-1.27 (0.118)	-1.76 (0.112)	-1.82 (0.145)
			95% 2-sided CI	(-1.32, -0.88)	(-1.77, -1.35)	(-1.73, -1.18)	(-1.51, -1.04)	(-1.98, -1.54)	(-2.10, -1.53)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.36	--	-0.48	-0.54
			95% 2-sided CI		(-0.76, -0.16)	(-0.71, 0.00)		(-0.80, -0.17)	(-0.91, -0.17)

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Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Renal Status (CrCl CG), mL/min	30 to < 60 Moderate Impairment	n		95	82	56	128	105	71
		Baseline	Mean (SE)	2.62 (0.234)	2.99 (0.321)	3.28 (0.398)	11.07 (0.238)	11.58 (0.296)	11.46 (0.400)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	-1.11 (0.202) (-1.51, -0.71)	-1.74 (0.218) (-2.17, -1.31)	-1.85 (0.265) (-2.37, -1.33)	-1.26 (0.226) (-1.70, -0.81)	-2.20 (0.250) (-2.69, -1.71)	-1.99 (0.305) (-2.59, -1.39)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.63 (-1.22, -0.05)	-0.74 (-1.40, -0.09)	--	-0.94 (-1.60, -0.29)	-0.73 (-1.48, 0.01)
	< 30 Severe Impairment	n		2	0	1	2	1	2
		Baseline	Mean (SE)	7.33 (6.667)	--	2.33	16.17 (0.500)	8.00	10.33 (1.333)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	--	--	--	-2.23 (1.807) (-5.77, 1.32)	-3.82 (2.555) (-8.83, 1.19)	-0.56 (1.806) (-4.10, 2.98)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	--	--	--	-1.60 (-7.73, 4.54)	1.67 (-3.34, 6.68)
	Interaction P value:				**0.69**			**0.75**	
Renal Status (GFR MDRD) mL/min/1.73 m^2	≥ 90 Normal	n		288	280	191	467	462	316
		Baseline	Mean (SE)	2.67 (0.153)	2.82 (0.164)	2.74 (0.182)	11.58 (0.146)	11.87 (0.152)	11.70 (0.165)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	-1.20 (0.116) (-1.43, -0.98)	-1.22 (0.118) (-1.45, -0.99)	-1.33 (0.145) (-1.62, -1.05)	-1.08 (0.118) (-1.31, -0.85)	-1.72 (0.119) (-1.96, -1.49)	-1.76 (0.146) (-2.05, -1.48)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.02 (-0.34, 0.30)	-0.13 (-0.49, 0.24)	--	-0.64 (-0.97, -0.32)	-0.68 (-1.05, -0.32)
	60 to < 90 Mild Impairment	n		525	501	341	768	751	509
		Baseline	Mean (SE)	2.68 (0.116)	2.63 (0.113)	2.86 (0.133)	11.62 (0.113)	11.66 (0.118)	11.56 (0.140)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	-1.06 (0.087) (-1.23, -0.89)	-1.60 (0.089) (-1.78, -1.43)	-1.57 (0.109) (-1.79, -1.36)	-1.27 (0.093) (-1.46, -1.09)	-1.74 (0.094) (-1.92, -1.55)	−1.69 (0.116) (-1.92, -1.47)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.54 (-0.78, -0.30)	-0.51 (-0.79, -0.24)	--	-0.46 (-0.72, -0.21)	-0.42 (-0.72, -0.13)
	30 to < 60 Moderate Impairment	n		65	80	44	93	110	63
		Baseline	Mean (SE)	3.36 (0.376)	2.87 (0.312)	2.41 (0.329)	11.17 (0.275)	11.31 (0.273)	11.15 (0.325)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	-0.94 (0.244) (-1.42, -0.46)	-1.73 (0.220) (-2.17, -1.30)	-1.70 (0.298) (-2.29, -1.12)	-1.21 (0.265) (-1.73, -0.69)	-1.95 (0.244) (-2.43, -1.47)	-2.01 (0.323) (-2.65, -1.38)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.80 (-1.44, -0.15)	-0.76 (-1.52, -0.01)	--	-0.74 (-1.44, -0.03)	-0.80 (-1.62, 0.02)
	< 30 Severe Impairment	n		0	0	1	0	0	2
		Baseline	Mean (SE)	--	--	2.33	--	--	10.33 (1.333)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	--	--	--	--	--	--
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	--	--	--	--	--
	Interaction P value:				**0.070**			**0.70**	
Ongoing Beta-blocker Use at baseline	Yes	n		154	127	102	206	185	156
		Baseline	Mean (SE)	2.76 (0.209)	2.77 (0.221)	2.81 (0.193)	11.17 (0.197)	11.37 (0.208)	11.77 (0.232)
		Adjusted Diff. from Baseline	Mean (SE) 95% 2-sided CI	-1.11 (0.159) (-1.42, -0.79)	-1.66 (0.175) (-2.00, -1.32)	-1.46 (0.197) (-1.84, -1.07)	-1.08 (0.178) (-1.43, -0.73)	-1.59 (0.188) (-1.96, -1.22)	-1.64 (0.206) (-2.05, -1.24)
		Adjusted Diff. vs Placebo	Mean 95% 2-sided CI	--	-0.55 (-1.02, -0.09)	-0.35 (-0.85, 0.14)	--	-0.51 (-1.02, -0.00)	-0.56 (-1.10, -0.03)

Table continued on next page.

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Ongoing Beta-blocker Use at baseline	No	n		724	735	475	1122	1139	734
		Baseline	Mean (SE)	2.72 (0.100)	2.70 (0.098)	2.78 (0.117)	11.65 (0.094)	11.75 (0.097)	11.54 (0.113)
		Adjusted Diff. from Baseline	Mean (SE)	-1.10 (0.074)	-1.46 (0.073)	-1.51 (0.093)	-1.22 (0.077)	-1.78 (0.076)	-1.76 (0.098)
			95% 2-sided CI	(-1.24, -0.95)	(-1.61, -1.32)	(-1.70, -1.33)	(-1.37, -1.07)	(-1.93, -1.63)	(-1.95, -1.57)
		Adjusted Diff. vs Placebo	Mean	--	-0.37	-0.42	--	-0.55	-0.54
			95% 2-sided CI		(-0.57, -0.17)	(-0.65, -0.18)		(-0.77, -0.34)	(-0.78, -0.29)
	Interaction P value:				**0.64**			**0.97**	
Concomitant Diuretic Use	Yes	n		151	141	103	211	192	143
		Baseline	Mean (SE)	2.93 (0.216)	2.62 (0.184)	2.81 (0.195)	11.17 (0.187)	11.09 (0.186)	11.82 (0.304)
		Adjusted Diff. from Baseline	Mean (SE)	-0.81 (0.161)	-1.69 (0.166)	-1.55 (0.196)	-0.91 (0.176)	-1.56 (0.185)	-1.33 (0.215)
			95% 2-sided CI	(-1.13, -0.50)	(-2.02, -1.36)	(-1.93, -1.17)	(-1.25, -0.56)	(-1.92, -1.20)	(-1.76, -0.91)
		Adjusted Diff. vs Placebo	Mean	--	-0.88	-0.74	--	-0.65	-0.43
			95% 2-sided CI		(-1.33, -0.43)	(-1.24, -0.24)		(-1.15, -0.15)	(-0.97, 0.12)
	No	n		727	721	474	1117	1132	747
		Baseline	Mean (SE)	2.69 (0.099)	2.73 (0.101)	2.78 (0.117)	11.65 (0.095)	11.80 (0.098)	11.53 (0.107)
		Adjusted Diff. from Baseline	Mean (SE)	-1.16 (0.073)	-1.45 (0.074)	-1.49 (0.093)	-1.26 (0.077)	-1.78 (0.076)	-1.82 (0.097)
			95% 2-sided CI	(-1.30, -1.01)	(-1.60, -1.31)	(-1.68, -1.31)	(-1.41, -1.10)	(-1.93, -1.63)	(-2.01, -1.63)
		Adjusted Diff. vs Placebo	Mean	--	-0.30	-0.34	--	-0.53	-0.56
			95% 2-sided CI		(-0.50, -0.09)	(-0.57, -0.10)		(-0.74, -0.32)	(-0.81, -0.32)
	Interaction P value:				**0.062**			**0.70**	
Concomitant Alpha-1-antagonist Use†	Yes	n		32	37	23	76	79	59
		Baseline	Mean (SE)	1.99 (0.334)	2.16 (0.412)	2.13 (0.494)	12.49 (0.399)	12.05 (0.352)	12.37 (0.519)
		Adjusted Diff. from Baseline	Mean (SE)	-1.01 (0.346)	-1.43 (0.324)	-1.17 (0.412)	-0.87 (0.304)	-0.98 (0.298)	-1.92 (0.348)
			95% 2-sided CI	(-1.69, -0.34)	(-2.07, -0.79)	(-1.98, -0.36)	(-1.46, -0.27)	(-1.57, -0.40)	(-2.61, -1.24)
		Adjusted Diff. vs Placebo	Mean	--	-0.42	-0.16	--	-0.12	-1.06
			95% 2-sided CI		(-1.35, 0.51)	(-1.21, 0.90)		(-0.95, 0.72)	(-1.96, -0.15)
	No	n		122	131	71	286	303	182
		Baseline	Mean (SE)	2.16 (0.268)	2.27 (0.213)	1.97 (0.195)	11.47 (0.199)	12.03 (0.199)	11.22 (0.209)
		Adjusted Diff. from Baseline	Mean (SE)	-1.20 (0.179)	-1.14 (0.172)	-1.11 (0.239)	-1.02 (0.158)	-1.46 (0.153)	-1.53 (0.204)
			95% 2-sided CI	(-1.55, -0.85)	(-1.48, -0.80)	(-1.58, -0.64)	(-1.33, -0.71)	(-1.76, -1.16)	(-1.93, -1.13)
		Adjusted Diff. vs Placebo	Mean	--	0.06	0.09	--	-0.44	-0.51
			95% 2-sided CI		(-0.42, 0.54)	(-0.51, 0.69)		(-0.87, -0.01)	(-1.03, 0.00)
	Interaction P value:				**0.67**			**0.25**	

Pooled studies include studies 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All patients in the FAS who had least one incontinence episode in the baseline diary (Full Analysis Set-Incontinence [FAS-I]).
Descriptive statistics for adjusted mean changes from baseline are generated from the analysis of covariance (ANCOVA) model with treatment group, gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
P value is from treatment by subpopulation interaction in the ANCOVA model described above.
--: not applicable; BPH: benign prostatic hyperplasia; CrCl CG: creatinine clearance by Cockcroft-Gault calculation; GFR MDRD: glomerular filtration rate by modification of diet in renal disease.
† Analysis performed for male patients only.

Appendix 1, Table 11 Efficacy of Antimuscarinics and Mirabegron Compared to Placebo

	Mirabegron 50 mg†	Fesoterodine 4 mg/day	Fesoterodine 8 mg/day	Oxybutynin IR 15 mg/day	Oxybutynin TDS 3.9 - 4.0 mg/day	Propiverine ER 20 mg/day	Solifenacin 5 mg/day	Solifenacin 10 mg/day	Tolterodine ER 4 mg/day	Tolterodine IR 2 mg/day	Tolterodine IR 4 mg/day
Mean change in incontinence episodes/day											
Mean	-0.40	-0.81	-1.08	-0.74	-0.58	-0.53	-0.77	-0.81	-0.4	-0.21	-0.5
95% CI	(-0.58,-0.21)	(-1.27, -0.35)	(-1.52, -0.64)	(-1.23, -0.26)	(-1.05, -0.11)	(-0.92, -0.14)	(-1.02, -0.52)	(-1.06, -0.56)	(-0.42, -0.38)	(-0.56, 0.14)	(-0.67, -0.32)
P value	P<0.001	P< 0.01	P< 0.01	P< 0.01	P = 0.02	P = 0.01	P< 0.01	P< 0.01	P< 0.01	P = 0.23	P< 0.01
n	862	410	434	312	612	578	1157	1170	3095	605	2614
Mean change in micturitions/day											
Mean	-0.55	-0.81	-0.93	-0.92	-0.54	-0.93	-0.99	-1.3	-0.77	-0.67	-0.71
95% CI	(-0.75, -0.36)	(-1.27, -0.35)	(-1.37, -0.49)	(-1.43, -0.40)	(-0.99, -0.10)	(-1.28, -0.58)	(-1.23, -0.75)	(-1.56, -1.04)	(-0.96, -0.58)	(-1.07, -0.27)	(-0.93, -0.50)
P value	P<0.001	P< 0.01	P< 0.01	P< 0.01	P = 0.02	P< 0.01	P< 0.01	P< 0.01	P< 0.01	P< 0.01	P< 0.01
n	1324	544	555	431	608	779	1803	1789	3223	637	3121

†Data from pooled primary phase 3 studies (studies 178-CL-046, 178-CL-047 and 178-CL-074). All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All patients in the FAS who had least one incontinence episode in the baseline diary (Full Analysis Set-Incontinence [FAS-I]). Differences for the adjusted means are calculated by subtracting the adjusted mean of placebo from that of the treatment group. P-values are from pairwise comparison vs. placebo within the analysis of covariance (ANCOVA) model. Statistical testing is significant at 0.05 level with multiplicity adjustment.
ER: extended release; IR: immediate release; TDS: transdermal system.
Source: Chapple et al, 2008.

Appendix 1, Table 12 Results for Change from Baseline to Week 12 in Number of Incontinence Episodes or Urge Incontinence Episodes per 24 Hours

OAB Agent	Study Number	n	Treatment	Mean Baseline Incontinence or Urge Incontinence Episodes (SE) †	Mean Change from Baseline to Week 12 (SE) †	Mean Difference from Placebo (95% CI)	P value
Number of Incontinence Episodes per 24 Hours							
Mirabegron	178-CL-046	291 293	Placebo Mirabegron 50 mg	2.67 (0.140) 2.83 (0.165)	-1.17 (0.113) -1.57 (0.113)	-0.41 (-0.72, -0.09)	0.003
	178-CL-047	325 312	Placebo Mirabegron 50 mg	3.03 (0.171) 2.77 (0.150)	-1.13 (0.112) -1.47 (0.114)	-0.34 (-0.66, -0.03)	0.026
	178-CL-074	262 257	Placebo Mirabegron 50 mg	2.43 (0.145) 2.51 (0.146)	-0.96 (0.122) -1.38 (0.123)	-0.42 (-0.76, -0.08)	0.001
Number of Urge Incontinence Episodes per 24 Hours							
Fesoterodine	SP-583	211 199 223	Placebo Fesoterodine 4 mg Fesoterodine 8 mg	3.7 (3.1) 3.8 (3.4) 3.7 (2.9)	-1.20 (3.3) -2.06 (2.7) -2.27 (2.4)	NA	0.001 < 0.001
	SP-584	205 228 218	Placebo Fesoterodine 4 mg Fesoterodine 8 mg	3.7 (3.3) 3.9 (3.5) 3.9 (3.3)	-1.0 (2.7) -1.77 (3.1) -2.42 (2.8)	NA	0.002 < 0.001
Trospium	IP631-003	256 253	Placebo Trospium 20 mg	4.33 (0.21) 3.89 (0.17)	-1.98 (0.18) -2.20 (0.16)	-0.22 (NA)	0.012
	IP631-005	325 323	Placebo Trospium 20 mg	3.91 (0.16) 3.83 (0.16)	-1.73 (0.14) -2.31 (0.14)	-0.58 (NA)	< 0.001
Trospium XR‡	IP631-018	292 300	Placebo Trospium XR 60 mg	4.14 (NA) 4.11 (NA)	-1.92 (NA) -2.48 (NA)	-0.57 (NA)	0.0002
	IP631-022	276 267	Placebo Trospium XR 60 mg	4.04 (NA) 4.02 (NA)	-1.62 (NA) -2.35 (NA)	-0.74 (NA)	< 0.0001

OAB: overactive bladder; NA: data not available; XR: extended release.
For all trials with the exception of Study IP631-005 for trospium, number of incontinence episodes or urge incontinence episodes per 24 hours were considered coprimary endpoints; in Study IP631-005, number of urge incontinence episodes per 24 hours was a secondary endpoint.
† Trials conducted for fesoterodine presented SD rather than SE for mean baseline and mean change from baseline.
‡ The statistical review of trospium XR cited the coprimary endpoints as change in urge urinary incontinence episodes frequency per day (presented here); the medical review of trospium XR presented results for urge urinary incontinence episodes per week.
Source: FDA documents: Center for Drug Evaluation and Research, Application Number 22-030 (Toviaz, Fesoterodine Fumarate); Center for Drug Evaluation and Research, Application Number 21-595 (Sanctura, Trospium Chloride) Medical Review(s) (Parts 1, 2, and 3); Center for Drug Evaluation and Research, Application Number 22-103 (Sanctura XR, Trospium Chloride) Medical Review(s).

Appendix 1, Table 13 Results for Change from Baseline to Week 6 or Week 12 in Number of Incontinence Episodes or Urge Incontinence Episodes per Week as a Primary Endpoint

OAB Agent	Study Number	N	Treatment	Mean Baseline Incontinence or Urge Incontinence Episodes	Mean Change from Baseline to Week 6 or Week 12†	Difference from Placebo (95% CI)	P value
Number of Incontinence Episodes per Week							
Darifenacin ‡, §	1001	113	Placebo	15.5	-9.0		
		109	Darifenacin 15 mg	16.2	-11.4	-2.4 (-5.2, -0.3)	0.049
	1002	108	Placebo	16.1	-5.9		
		108	Darifenacin 7.5 mg	14.0	-8.1	-2.8 (-4.8, -0.8)	0.007
		106	Darifenacin 15 mg	17.3	-10.4	-4.3 (-6.7, -2.2)	< 0.001
	1041	163	Placebo	16.6	-7.6		
		228	Darifenacin 7.5 mg	16.3	-9.0	-1.5 (-3.0, -0.4)	0.010
		115	Darifenacin 15 mg	17.0	-10.4	-2.1 (-3.5, -0.3)	0.017
Tolterodine ER	98-TOCR-007	508	Placebo	NA¶	-6.9		
		507	Tolterodine ER 4 mg		-11.8	-4.8 (1.0) ††	0.0001
		514	Tolterodine IR 2 mg		-10.6	-3.7 (NA)	0.0005
Number of Urge Incontinence Episodes per Week							
Oxybutynin XL	C-95-031	16	Placebo	20.7	-10.2 (2.0) ‡‡		
		34	Oxybutynin XL	20.7	-18.6 (1.5) ‡‡	-8.4 (-13.4, -3.5)	0.001
		32	Oxybutynin IR	20.7	-15.6	-5.4 (-10.6, -0.2)	0.041

ER extended release; IR: immediate release; NA: data not available; XL: extended release.
† For all trials with the exception of Study C-95-031 for oxybutynin XL, mean change from baseline to week 12 was presented; in Study C-95-031, mean change from baseline to week 6 was presented.
‡ Results presented for darifenacin were median value at baseline and median change from baseline.
§ Study 1001 and 1002 also included a treatment group for darifenacin 30 mg and Study 1041 included a treatment group for darifenacin 3.75 mg; however, the Sponsor was seeking approval for the 7.5 mg and 15 mg dose, therefore, the results for the other doses were not presented.
¶ The review indicated that mean baseline incontinence episodes ranged from 22.1 to 23.3 across all treatment groups.
†† SE was presented for the results of Study 98-TOCR-007.
‡‡ SEM was presented for the placebo and oxybutynin XL results in Study C-95-031.
Source: FDA documents: Center for Drug Evaluation and Research, Application Number 21-513 (Enablex, Darifenacin Hydrobromide) Medical Review(s); Center for Drug Evaluation and Research, Application Number 20-771 (Detrol, Tolterodine L-tartrate) Statistical Review(s) (Parts 1 and 2); Center for Drug Evaluation and Research, Application Number 20-897 (Ditropan XL, Oxybutynin Chloride) Medical Review(s).

Appendix 1, Table 14 Results for Change from Baseline to Week 12 in Number of Micturitions per 24 Hours as a Primary Endpoint

OAB Agent	Study Number	N	Treatment	Mean Baseline Micturitions (SE)	Mean Change from Baseline to Week 12 (SE) †	Mean Difference from Placebo (95% CI)	P value
Mirabegron	178-CL-046	480	Placebo	11.71 (0.143)	-1.34 (0.110)		
		473	Mirabegron 50 mg	11.65 (0.137)	-1.93 (0.111)	-0.60 (-0.90, -0.29)	< 0.001
	178-CL-047	433	Placebo	11.51 (0.157)	-1.05 (0.132)		
		425	Mirabegron 50 mg	11.80 (0.168)	-1.66 (0.133)	-0.61 (-0.98, -0.24)	0.001
	178-CL-074	415	Placebo	11.48 (0.142)	-1.18 (0.124)		
		426	Mirabegron 50 mg	11.66 (0.156)	-1.60 (0.122)	-0.42 (-0.76, -0.08)	0.015
Fesoterodine	SP-583	279	Placebo	12.0 (3.7)	-1.02 (3.0)		
		265	Fesoterodine 4 mg	11.6 (3.2)	-1.74 (2.7)	NA	< 0.001
		276	Fesoterodine 8 mg	11.9 (3.8)	-1.94 (3.1)		< 0.001
	SP-584	266	Placebo	12.2 (3.7)	-1.02 (3.4)		
		267	Fesoterodine 4 mg	12.9 (3.9)	-1.86 (3.6)	NA	0.032
		267	Fesoterodine 8 mg	12.0 (3.3)	-1.94 (3.0)		< 0.001
Solifenacin	905-CL-013	309	Placebo	11.5 (0.18)	-1.5 (0.15)		
		306	Solifenacin 10 mg	11.7 (0.18)	-3.0 (0.15)	-1.37 (-1.74, -1.01)	< 0.001
	905-CL-014	295	Placebo	11.8 (0.18)	-1.3 (0.16)		
		298	Solifenacin 10 mg	11.5 (0.18)	-2.4 (0.15)	-1.20 (-1.59, -0.81)	< 0.001
	905-CL-015	253	Placebo	12.2 (0.26)	-1.2 (0.21)		
		266	Solifenacin 5 mg	12.1 (0.24)	-2.2 (0.18)	-1.02 (-1.50, -0.53)	< 0.001
		264	Solifenacin 10 mg	12.3 (0.24)	-2.6 (0.20)	-1.39 (-1.87, -0.91)	< 0.001
		250	Tolterodine 4 mg	12.1 (0.22)	-1.9 (0.19)	-0.73 (-1.22, -0.24)	= 0.004
	905-CL-018	281	Placebo	12.3 (0.23)	-1.7 (0.19)		
		286	Solifenacin 5 mg	12.1 (0.23)	-2.4 (0.17)	-0.87 (-1.33, -0.42)	< 0.001
		290	Solifenacin 10 mg	12.1 (0.21)	-2.9 (0.18)	-1.25 (-1.70, -0.79)	< 0.001
Trospium	IP631-003	256	Placebo	12.93 (0.16)	-1.29 (0.17)		
		253	Trospium 20 mg	12.74 (0.16)	-2.37 (0.17)	-1.08 (NA)	< 0.001
	IP631-005	325	Placebo	13.17 (0.17)	-1.76 (0.15)		
		323	Trospium 20 mg	12.94 (0.17)	-2.67 (0.17)	-0.91 (NA)	< 0.001
Trospium XR	IP631-018	300	Placebo	12.74 (0.2)	-1.99 (0.2)		
		292	Trospium XR 60 mg	12.77 (0.2)	-2.80 (0.2)	-0.80 (NA)	< 0.0001
	IP631-022	276	Placebo	12.94 (0.2)	-1.80 (0.2)		
		267	Trospium XR 60 mg	12.84 (0.2)	-2.54 (0.2)	-0.74 (NA)	0.0002
Tolterodine	CTN 94-OATA-008	56	Placebo	11.7 (4.9)	-1.6 (3.6)		
		118	Tolterodine 2 mg	11.5 (4.4)	-2.7 (3.8)	-1.2 (-1.9, -0.4)	0.0022
		117	Oxybutynin 5 mg	10.7 (3.3)	-2.3 (2.7)	-0.7 (-1.5, 0.1)	0.068
	CTN 94-OATA-009	64	Placebo	11.3 (3.4)	-1.4 (2.3)		
		123	Tolterodine 1 mg	11.5 (3.7)	-2.3 (3.0)	-0.9 (-1.6, -0.3)	0.0029
		129	Tolterodine 2 mg	11.2 (3.1)	-2.3 (2.1)	-0.9 (-1.5, -0.3)	0.0045
	CTN 94-OATA-010	56	Placebo	11.6 (3.1)	-1.4 (2.8)		
		108	Tolterodine 2 mg	11.6 (2.9)	-1.7 (2.3)	-0.4 (-1.0, 0.3)	0.27
		112	Oxybutynin 5 mg	11.5 (3.5)	-1.7 (3.0)	-0.4 (-1.0, 0.3)	0.29

NA: not applicable; OAB: overactive bladder; XR: extended release.
† Trials conducted for fesoterodine and tolterodine presented SD rather than SE for mean baseline and mean change from baseline. Change from baseline values for mirabegron is adjusted mean change from baseline based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate.
Source: FDA documents: Center for Drug Evaluation and Research, Application Number 22-030 (Toviaz, Fesoterodine Fumarate) Medical Review(s) (Parts 1 and 2); Center for Drug Evaluation and Research, Application Number 21-518 (VESIcare, Solifenacin Succinate) Medical Review(s); Center for Drug Evaluation and Research, Application Number 21-595 (Sanctura, Trospium Chloride) Medical Review(s) (Parts 1, 2, and 3); Center for Drug Evaluation and Research, Application Number 22-103 (Sanctura XR, Trospium Chloride) Medical Review(s); Center for Drug Evaluation and Research, Application Number 21-228 (Detrol LA, Tolterodine) Statistical Review(s).

Appendix 1, Table 15 Listing of Patients with an SAE of Atrial Fibrillation or a TEAE Adjudicated as Atrial Fibrillation, Global OAB 12-week Phase 2/3 Population and EU/NA Long-term Controlled Population

Study Number Patient No. Age/Race/Gender	Treatment	MedDRA (v12.1) PT/ Verbatim Term	Onset/ Stop Day (Last Dose Day)	Outcome	Investigator-assessed Relationship to Study Drug	Discontinued Study Drug?	Adjudication
Global OAB 12-week Phase 2/3 Population							
178-CL-046 3225-2443 66/White/Male	Mirabegron 50 mg	Atrial fibrillation / Atrial fibrillation	81/86 (81)	Recovered	Not related	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-047 U00021797843 66/White/Male	Mirabegron 50 mg	Atrial fibrillation / Rapid atrial fibrillation	29/30 (28)	Recovered	Possibly	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
		Tachycardia / Tachycardia	27/28 (28)	Recovered with sequelae	Possibly	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-074 1534-72081 83/White/Female	Mirabegron 50 mg	Atrial fibrillation / Worsening rapid atrial fibrillation	34/36 (29)	Recovered	Possibly	Yes †	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-047 U00021786752 84/White/Female	Mirabegron 100 mg	Atrial tachycardia / Exacerbation of paroxysmol atrial tachycardia	32/ongoing (32)	Not recovered	Not related	Yes ‡	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
		Atrial fibrillation / Atrial Fibrillation	41/ongoing (32)	Not recovered	Not related		Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-046 3014-2243 § 90/White/Female	Mirabegron 100 mg	Atrial fibrillation / Episode of atrial fibrillation	80/90 (79)	Recovered	Possibly	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-047 U00021856334 82/White/Male	Mirabegron 100 mg	Atrial fibrillation / Atrial fibrillation	58/60 (85)	Recovered	Not related	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-047 U00020536564 46/Black or African American/Male	Mirabegron 100 mg	Tachycardia / Tachycardia	72/80 (71)	Recovered	Not related	N/A ¶	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)

Table continued on next page.

Study Number Patient No. Age/Race/Gender	Treatment	MedDRA (v12.1) PT/ Verbatim Term	Onset/ Stop Day (Last Dose Day)	Outcome	Investigator-assessed Relationship to Study Drug	Discontinued Study Drug?	Adjudication
178-CL-074 3225-70844 75/White/Male	Placebo	Atrial fibrillation / Atrial fibrillation	42/46 (42)	Recovering	Not related	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-046 3061-2316 80/White/Female	Tolterodine ER 4 mg	Arrhythmia / Arrhythmia	19/25 (18)	Recovered	Probably	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
EU/NA Long-term Controlled Population							
178-CL-049 3105-2977 76/White/Male	Mirabegron 50 mg	Atrial fibrillation / Atrial fibrillation	251/268 (224)	Recovered	Possibly	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-049 1681-6947 82/White/Female	Mirabegron 50 mg	Atrial fibrillation / Atrial fibrillation with ventricular response	166/172 (237)	Recovered	Possibly	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
		Respiratory failure / Respiratory failure	166/172 (237)	Recovered	Not related	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-049 3120-2849 77/White/Female	Mirabegron 50 mg	Sick sinus syndrome / Bradycardia tachycardia syndrome with incidens of MAS incomplete with incidens of syncope incomplete	22/29 (365)	Recovered	Not related	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia) Non-APTC/MACE (high grade atrioventricular block 3rd degree)
178-CL-049 3433-1273 85/Female/White	Mirabegron 50 mg	Atrial flutter / Atrial flutter	359/363 (359)	Recovered with sequelae	Possibly	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-049 3027-2525 69/Female/White	Mirabegron 100 mg	Arrhythmia / Rhythmic heart disturbance aggravated	74/ongoing (76)	Not recovered	Not related	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-049 1617-6199 71/White/Female	Tolterodine ER 4 mg	Atrial fibrillation / Atrial fibrillation	92/96 (92)	Recovered	Possibly	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)

Table continued on next page.

Study Number Patient No. Age/Race/Gender	Treatment	MedDRA (v12.1) PT/ Verbatim Term	Onset/ Stop Day (Last Dose Day)	Outcome	Investigator-assessed Relationship to Study Drug	Discontinued Study Drug?	Adjudication
178-CL-049 2027-6377 74/White/Male	Tolterodine ER 4 mg	Atrial fibrillation / Paroxysmal-atrial fibrillation	186/189 (197)	Recovered	Possibly	Yes	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)
178-CL-049 1597-6695 76/White/Female	Tolterodine ER 4 mg	Atrial fibrillation / Rapid atrial fibrillation	140/143 (196)	Recovered	Not related	No	Non-APTC/MACE (atrial fibrillation with no evidence of ischemia)

SAE: serious adverse event(s); APTC: Antiplatelet Trialists' Collaboration; MACE: major adverse cardiac events; ER: extended release; OAB: overactive bladder; MAS: Morgagni-Adams-Stokes; N/A: not applicable; PT: preferred term; TEAE: treatment-emergent adverse event(s); CHF: congestive heart failure.
† Patient No.178-CL-074, 1534-72081 discontinued study drug due to TEAE of liver function test abnormal and hypokalemia.
‡ Patient No. 178-CL-047, U00021786752 discontinued study drug due to TEAE of traumatic cerebral hemorrhage on day 32.
§ Patient No. 178-CL-046, 3014-2243 reported an SAE of CHF.
¶ Patient No. 178-CL-047, U00020536564 had already discontinued study drug due to a TEAE of impaired renal function on day 71.

Appendix 1, Table 16 Summary of Mean Difference Between Mirabegron and Placebo, Baseline-Adjusted in Time-Matched QTcI Interval (msec) on Days 10 and 11, Overall and by Gender, Study 178-CL-077

Hours postdose	Statistic†	Study Treatment								
		Overall			Female			Male		
		Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg
Predose	Diff from Plb	2.14	4.28	6.11	2.37	6.25	6.72	1.73	2.53	6.09
	90% CI	(0.98, 3.31)	(2.82, 5.73)	(4.46, 7.77)	(0.72, 4.02)	(4.28, 8.23)	(3.99, 9.46)	(-0.00, 3.46)	(0.48, 4.58)	(4.16, 8.02)
0.5	Diff from Plb	1.92	3.27	6.98	1.85	4.93	8.61	1.79	1.82	5.60
	90% CI	(0.65, 3.18)	(1.95, 4.60)	(5.45, 8.51)	(-0.32, 4.02)	(3.24, 6.63)	(5.96, 11.27)	(0.34, 3.24)	(-0.01, 3.65)	(3.95, 7.25)
1	Diff from Plb	2.33	3.34	6.13	1.96	4.79	6.94	2.36	2.12	5.39
	90% CI	(1.06, 3.60)	(1.93, 4.74)	(4.43, 7.83)	(-0.07, 3.98)	(2.55, 7.04)	(4.04, 9.83)	(0.74, 3.99)	(0.44, 3.80)	(3.38, 7.40)
1.5	Diff from Plb	2.07	3.47	6.97	2.56	4.57	8.59	1.14	2.60	5.66
	90% CI	(0.70, 3.45)	(1.93, 5.01)	(5.29, 8.66)	(0.35, 4.77)	(2.30, 6.83)	(5.52, 11.66)	(-0.55, 2.82)	(0.54, 4.66)	(4.08, 7.24)
2	Diff from Plb	2.25	3.15	7.15	2.34	4.73	8.33	1.86	1.84	6.00
	90% CI	(0.89, 3.61)	(1.58, 4.71)	(5.65, 8.64)	(0.31, 4.36)	(2.49, 6.96)	(5.72, 10.94)	(-0.07, 3.78)	(-0.16, 3.85)	(4.32, 7.68)
2.5	Diff from Plb	2.68	4.18	7.93	2.65	5.56	8.73	2.45	2.86	7.08
	90% CI	(1.35, 4.01)	(2.61, 5.75)	(6.33, 9.52)	(0.59, 4.71)	(3.44, 7.69)	(6.04, 11.41)	(0.64, 4.25)	(0.85, 4.88)	(5.15, 9.00)
3	Diff from Plb	2.92	5.16	7.91	3.52	7.27	8.96	1.90	3.19	7.12
	90% CI	(1.54, 4.29)	(3.60, 6.71)	(6.19, 9.62)	(1.47, 5.57)	(5.08, 9.46)	(6.09, 11.82)	(-0.01, 3.81)	(1.43, 4.95)	(5.07, 9.17)
3.5	Diff from Plb	3.25	5.68	7.95	4.49	7.66	9.33	1.63	3.83	6.88
	90% CI	(1.77, 4.72)	(4.28, 7.09)	(6.32, 9.58)	(2.17, 6.81)	(5.75, 9.57)	(6.65, 12.00)	(-0.25, 3.50)	(2.13, 5.52)	(4.82, 8.93)
4	Diff from Plb	3.66	6.19	7.57	4.00	7.70	7.98	2.96	4.63	7.33
	90% CI	(2.16, 5.16)	(4.72, 7.65)	(5.73, 9.41)	(1.70, 6.29)	(5.68, 9.72)	(4.72, 11.23)	(0.92, 5.00)	(2.81, 6.45)	(5.23, 9.42)
4.5	Diff from Plb	3.37	5.81	7.68	3.97	7.27	9.31	2.57	4.39	6.28
	90% CI	(2.07, 4.68)	(4.33, 7.29)	(5.85, 9.51)	(1.90, 6.04)	(4.94, 9.60)	(6.15, 12.47)	(0.88, 4.27)	(2.65, 6.14)	(4.18, 8.37)
5	Diff from Plb	3.49	4.95	8.21	3.67	6.71	10.42	2.89	3.39	6.02
	90% CI	(2.09, 4.89)	(3.37, 6.52)	(6.43, 9.99)	(1.62, 5.72)	(4.35, 9.07)	(7.40, 13.44)	(0.87, 4.90)	(1.39, 5.40)	(4.06, 7.99)
6	Diff from Plb	2.50	4.58	6.73	2.55	5.11	7.17	2.16	3.98	6.61
	90% CI	(1.13, 3.86)	(3.12, 6.04)	(4.90, 8.57)	(0.29, 4.81)	(2.70, 7.52)	(4.07, 10.28)	(0.58, 3.73)	(2.11, 5.85)	(4.36, 8.86)
7	Diff from Plb	1.91	4.20	5.20	2.49	4.54	4.66	1.48	3.94	5.78
	90% CI	(0.63, 3.19)	(2.96, 5.44)	(3.45, 6.94)	(0.43, 4.56)	(2.68, 6.40)	(1.62, 7.70)	(-0.05, 3.01)	(2.20, 5.67)	(3.86, 7.70)
8	Diff from Plb	1.74	3.98	5.78	2.25	4.27	6.38	1.21	3.89	5.11
	90% CI	(0.49, 2.99)	(2.66, 5.31)	(4.17, 7.39)	(0.31, 4.20)	(2.39, 6.15)	(3.77, 8.99)	(-0.49, 2.91)	(2.18, 5.60)	(3.08, 7.15)
10	Diff from Plb	1.46	3.57	6.73	1.51	5.28	8.08	1.59	1.95	5.33
	90% CI	(0.05, 2.88)	(2.16, 4.98)	(5.18, 8.28)	(-0.82, 3.83)	(3.29, 7.27)	(5.57, 10.59)	(-0.19, 3.37)	(0.14, 3.76)	(3.40, 7.26)
12	Diff from Plb	-0.01	1.99	5.63	-1.11	2.01	7.68	1.19	2.06	3.75
	90% CI	(-1.23, 1.21)	(0.74, 3.24)	(4.25, 7.01)	(-3.04, 0.81)	(0.06, 3.97)	(5.74, 9.63)	(-0.34, 2.72)	(0.34, 3.78)	(1.80, 5.71)
24	Diff from Plb	1.88	3.79	5.18	2.75	6.64	6.61	0.97	1.23	4.31
	90% CI	(0.58, 3.18)	(2.38, 5.21)	(3.48, 6.88)	(0.77, 4.74)	(4.76, 8.52)	(3.76, 9.45)	(-0.81, 2.75)	(-0.71, 3.17)	(2.36, 6.26)
25	Diff from Plb	2.45	2.85	5.51	2.82	5.13	6.98	2.22	0.97	4.25
	90% CI	(1.20, 3.70)	(1.23, 4.47)	(3.91, 7.11)	(0.80, 4.85)	(2.62, 7.64)	(4.21, 9.74)	(0.61, 3.84)	(-1.02, 2.96)	(2.48, 6.01)

Footnotes on next page

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Model used was a constrained longitudinal mixed effects model where the constraint was that the baseline mean responses in treatment period 1 for the 2 sequences were assumed equal.
Diff: difference; Plb: placebo; QTcI: QT interval corrected for heart rate using individual-specific correction formula.
† Treatment effect and CI for the time-matched difference from placebo, baseline adjusted.

Appendix 1, Table 17 TEAE by Gender (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

GENDER MedDRA (v12.1) PT†, n (%) of Patients	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total Mirabegron	
FEMALE	**n = 1002**	**n = 293**	**n = 982**	**n = 675**	**n = 1950**	**n = 361**
MALE	**n = 378**	**n = 139**	**n = 393**	**n = 254**	**n = 786**	**n = 134**
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
Female	487 (48.6%)	147 (50.2%)	466 (47.5%)	303 (44.9%)	916 (47.0%)	166 (46.0%)
Male	171 (45.2%)	63 (45.3%)	181 (46.1%)	99 (39.0%)	343 (43.6%)	65 (48.5%)
Hypertension	**105 (7.6%)**	**49 (11.3%)**	**103 (7.5%)**	**48 (5.2%)**	**200 (7.3%)**	**40 (8.1%)**
Female	70 (7.0%)	30 (10.2%)	60 (6.1%)	34 (5.0%)	124 (6.4%)	22 (6.1%)
Male	35 (9.3%)	19 (13.7%)	43 (10.9%)	14 (5.5%)	76 (9.7%)	18 (13.4%)
Nasopharyngitis	**35 (2.5%)**	**15 (3.5%)**	**54 (3.9%)**	**25 (2.7%)**	**94 (3.4%)**	**14 (2.8%)**
Female	27 (2.7%)	11 (3.8%)	31 (3.2%)	22 (3.3%)	64 (3.3%)	11 (3.0%)
Male	8 (2.1%)	4 (2.9%)	23 (5.9%)	3 (1.2%)	30 (3.8%)	3 (2.2%)
Urinary tract infection	**25 (1.8%)**	**18 (4.2%)**	**40 (2.9%)**	**25 (2.7%)**	**83 (3.0%)**	**10 (2.0%)**
Female	22 (2.2%)	17 (5.8%)	37 (3.8%)	18 (2.7%)	72 (3.7%)	10 (2.8%)
Male	3 (0.8%)	1 (0.7%)	3 (0.8%)	7 (2.8%)	11 (1.4%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 18 TEAE by Gender (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-term Controlled Population

GENDER MedDRA (v12.1) PT†, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
FEMALE	**n = 602**	**n = 608**	**n = 1210**	**n = 600**
MALE	**n = 210**	**n = 212**	**n = 422**	**n = 212**
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
Female	359 (59.6%)	382 (62.8%)	741 (61.2%)	376 (62.7%)
Male	126 (60.0%)	121 (57.1%)	247 (58.5%)	132 (62.3%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
Female	49 (8.1%)	57 (9.4%)	106 (8.8%)	53 (8.8%)
Male	26 (12.4%)	23 (10.8%)	49 (11.6%)	25 (11.8%)
Urinary tract infection	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
Female	44 (7.3%)	41 (6.7%)	85 (7.0%)	47 (7.8%)
Male	4 (1.9%)	4 (1.9%)	8 (1.9%)	5 (2.4%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
Female	25 (4.2%)	26 (4.3%)	51 (4.2%)	18 (3.0%)
Male	7 (3.3%)	9 (4.2%)	16 (3.8%)	7 (3.3%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
Female	28 (4.7%)	22 (3.6%)	50 (4.1%)	13 (2.2%)
Male	5 (2.4%)	4 (1.9%)	9 (2.1%)	7 (3.3%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
Female	14 (2.3%)	21 (3.5%)	35 (2.9%)	11 (1.8%)
Male	9 (4.3%)	8 (3.8%)	17 (4.0%)	2 (0.9%)

Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 19 TEAE by Age Group 1 (< 65 years, ≥ 65 years) (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

Age MedDRA (v12.1) PT†, n (%) of Patients	Placebo	Mirabegron				Tolt ER 4 mg
		25 mg	50 mg	100 mg	Total Mirabegron	
< 65 YEARS	**n = 859**	**n = 278**	**n = 861**	**n = 566**	**n = 1705**	**n = 303**
≥ 65 YEARS	**n = 521**	**n = 154**	**n = 514**	**n = 363**	**n = 1031**	**n = 192**
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
< 65 years	404 (47.0%)	126 (45.3%)	389 (45.2%)	244 (43.1%)	759 (44.5%)	136 (44.9%)
≥ 65 years	254 (48.8%)	84 (54.5%)	258 (50.2%)	158 (43.5%)	500 (48.5%)	95 (49.5%)
Hypertension	**105 (7.6%)**	**49 (11.3%)**	**103 (7.5%)**	**48 (5.2%)**	**200 (7.3%)**	**40 (8.1%)**
< 65 years	61 (7.1%)	28 (10.1%)	52 (6.0%)	20 (3.5%)	100 (5.9%)	17 (5.6%)
≥ 65 years	44 (8.4%)	21 (13.6%)	51 (9.9%)	28 (7.7%)	100 (9.7%)	23 (12.0%)
Nasopharyngitis	**35 (2.5%)**	**15 (3.5%)**	**54 (3.9%)**	**25 (2.7%)**	**94 (3.4%)**	**14 (2.8%)**
< 65 years	22 (2.6%)	8 (2.9%)	33 (3.8%)	19 (3.4%)	60 (3.5%)	7 (2.3%)
≥ 65 years	13 (2.5%)	7 (4.5%)	21 (4.1%)	6 (1.7%)	34 (3.3%)	7 (3.6%)
Urinary tract infection	**25 (1.8%)**	**18 (4.2%)**	**40 (2.9%)**	**25 (2.7%)**	**83 (3.0%)**	**10 (2.0%)**
< 65 years	10 (1.2%)	8 (2.9%)	24 (2.8%)	12 (2.1%)	44 (2.6%)	7 (2.3%)
≥ 65 years	15 (2.9%)	10 (6.5%)	16 (3.1%)	13 (3.6%)	39 (3.8%)	3 (1.6%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); tolt: tolterodine.
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 20 TEAE by Age Group 1 (< 65 years, ≥ 65 years) (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-term Controlled Population

AGE MedDRA (v12.1) PT †, n (%) of Patients	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mirabegron	Tolterodine ER 4 mg
< 65 YEARS	**n = 523**	**n = 504**	**n = 1027**	**n = 509**
≥ 65 YEARS	**n = 289**	**n = 316**	**n = 605**	**n = 303**
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
< 65 years	297 (56.8%)	303 (60.1%)	600 (58.4%)	313 (61.5%)
≥ 65 years	188 (65.1%)	200 (63.3%)	388 (64.1%)	195 (64.4%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
< 65 years	45 (8.6%)	33 (6.5%)	78 (7.6%)	39 (7.7%)
≥ 65 years	30 (10.4%)	47 (14.9%)	77 (12.7%)	39 (12.9%)
Urinary tract infection	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
< 65 years	25 (4.8%)	24 (4.8%)	49 (4.8%)	27 (5.3%)
≥ 65 years	23 (8.0%)	21 (6.6%)	44 (7.3%)	25 (8.3%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
< 65 years	23 (4.4%)	21 (4.2%)	44 (4.3%)	19 (3.7%)
≥ 65 years	9 (3.1%)	14 (4.4%)	23 (3.8%)	6 (2.0%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
< 65 years	29 (5.5%)	18 (3.6%)	47 (4.6%)	11 (2.2%)
≥ 65 years	4 (1.4%)	8 (2.5%)	12 (2.0%)	9 (3.0%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
< 65 years	13 (2.5%)	23 (4.6%)	36 (3.5%)	8 (1.6%)
≥ 65 years	10 (3.5%)	6 (1.9%)	16 (2.6%)	5 (1.7%)

Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 21 TEAE by Baseline Use of Alpha-1 Antagonists (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

Baseline Use of Alpha-1 Antagonists MedDRA (v12.1) PT †, n (%) of Patients	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mira	Tolterodine ER 4 mg
YES	**n = 82**	**n = 32**	**n = 92**	**n = 68**	**n = 192**	**n = 34**
NO	**n = 1298**	**n = 400**	**n = 1283**	**n = 861**	**n = 2544**	**n = 461**
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
Yes	36 (43.9%)	15 (46.9%)	43 (46.7%)	29 (42.6%)	87 (45.3%)	17 (50.0%)
No	622 (47.9%)	195 (48.8%)	604 (47.1%)	373 (43.3%)	1172 (46.1%)	214 (46.4%)
Hypertension	**105 (7.6%)**	**49 (11.3%)**	**103 (7.5%)**	**48 (5.2%)**	**200 (7.3%)**	**40 (8.1%)**
Yes	4 (4.9%)	6 (18.8%)	11 (12.0%)	5 (7.4%)	22 (11.5%)	5 (14.7%)
No	101 (7.8%)	43 (10.8%)	92 (7.2%)	43 (5.0%)	178 (7.0%)	35 (7.6%)
Nasopharyngitis	**35 (2.5%)**	**15 (3.5%)**	**54 (3.9%)**	**25 (2.7%)**	**94 (3.4%)**	**14 (2.8%)**
Yes	2 (2.4%)	0	7 (7.6%)	1 (1.5%)	8 (4.2%)	1 (2.9%)
No	33 (2.5%)	15 (3.8%)	47 (3.7%)	24 (2.8%)	86 (3.4%)	13 (2.8%)
Urinary tract infection	**25 (1.8%)**	**18 (4.2%)**	**40 (2.9%)**	**25 (2.7%)**	**83 (3.0%)**	**10 (2.0%)**
Yes	1 (1.2%)	0	1 (1.1%)	2 (2.9%)	3 (1.6%)	0
No	24 (1.8%)	18 (4.5%)	39 (3.0%)	23 (2.7%)	80 (3.1%)	10 (2.2%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; mira: mirabegron; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 22 SAE by Baseline Use of Alpha-1 Antagonists (Reported by ≥ 0.1% in the Total Mirabegron Group), EU/NA OAB 12-week Phase 3 Population

Baseline Use of Alpha-1 Antagonists MedDRA (v12.1) PT †, n (%) of Patients	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron Total Mirabegron	Tolterodine ER 4 mg
YES	**n = 82**	**n = 32**	**n = 92**	**n = 68**	**n = 192**	**n = 34**
Overall	3 (3.7%)	0	3 (3.3%)	5 (7.4%)	8 (4.2%)	1 (2.9%)
Chest pain	0	0	0	2 (2.9%)	2 (1.0%)	0
Cardiac failure	0	0	0	1 (1.5%)	1 (0.5%)	0
Fall	0	0	0	1 (1.5%)	1 (0.5%)	0
Humerus fracture	0	0	1 (1.1%)	0	1 (0.5%)	0
Post procedural haematoma	0	0	0	1 (1.5%)	1 (0.5%)	0
Retinitis	0	0	1 (1.1%)	0	1 (0.5%)	0
Urinary retention	1 (1.2%)	0	1 (1.1%)	0	1 (0.5%)	0
Urinary tract infection	0	0	1 (1.1%)	0	1 (0.5%)	0
NO	**n = 1298**	**n = 400**	**n = 1283**	**n = 861**	**n = 2544**	**n = 461**
Overall	26 (2.0%)	7 (1.8%)	26 (2.0%)	21 (2.4%)	54 (2.1%)	10 (2.2%)
Atrial fibrillation	1 (0.1%)	0	3 (0.2%)	2 (0.2%)	5 (0.2%)	0
Bunion operation	0	0	0	2 (0.2%)	2 (0.1%)	0
Chest pain	2 (0.2%)	1 (0.3%)	0	1 (0.1%)	2 (0.1%)	0
Prostate cancer	0	0	2 (0.2%)	0	2 (0.1%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
ER: extended release; OAB: overactive bladder; PT: preferred term; SAE: serious adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 23 TEAE by Baseline Use of Alpha-1 Antagonists (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-term Controlled Population

Baseline Use of Alpha-1 Antagonists MedDRA (v12.1) PT †, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
YES	**n = 47**	**n = 49**	**n = 96**	**n = 48**
NO	**n = 765**	**n = 771**	**n = 1536**	**n = 764**
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
Yes	32 (68.1%)	24 (49.0%)	56 (58.3%)	29 (60.4%)
No	453 (59.2%)	479 (62.1%)	932 (60.7%)	479 (62.7%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
Yes	4 (8.5%)	9 (18.4%)	13 (13.5%)	8 (16.7%)
No	71 (9.3%)	71 (9.2%)	142 (9.2%)	70 (9.2%)
Urinary tract infection	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
Yes	2 (4.3%)	1 (2.0%)	3 (3.1%)	2 (4.2%)
No	46 (6.0%)	44 (5.7%)	90 (5.9%)	50 (6.5%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
Yes	1 (2.1%)	1 (2.0%)	2 (2.1%)	2 (4.2%)
No	31 (4.1%)	34 (4.4%)	65 (4.2%)	23 (3.0%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
Yes	0	1 (2.0%)	1 (1.0%)	0
No	33 (4.3%)	25 (3.2%)	58 (3.8%)	20 (2.6%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
Yes	3 (6.4%)	1 (2.0%)	4 (4.2%)	1 (2.1%)
No	20 (2.6%)	28 (3.6%)	48 (3.1%)	12 (1.6%)

Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 24 SAE by Baseline Use of Alpha-1 Antagonists (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA Long-term Controlled Population

Baseline Use of Alpha-1 Antagonists MedDRA (v12.1) PT †, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
YES	**n = 47**	**n = 49**	**n = 96**	**n = 48**
NO	**n = 765**	**n = 771**	**n = 1536**	**n = 764**
Overall	**42 (5.2%)**	**51 (6.2%)**	**93 (5.7%)**	**44 (5.4%)**
Yes	5 (10.6%)	5 (10.2%)	10 (10.4%)	3 (6.3%)
No	37 (4.8%)	46 (6.0%)	83 (5.4%)	41 (5.4%)
Cerebrovascular accident	**3 (0.4%)**	**0**	**3 (0.2%)**	**1 (0.1%)**
Yes	1 (2.1%)	0	1 (1.0%)	0
No	2 (0.3%)	0	2 (0.1%)	1 (0.1%)
Osteoarthritis	**2 (0.2%)**	**1 (0.1%)**	**3 (0.2%)**	**1 (0.1%)**
Yes	0	0	0	0
No	2 (0.3%)	1 (0.1%)	3 (0.2%)	1 (0.1%)
Abscess intestinal	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	0	0	0	0
No	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Atrial fibrillation	**2 (0.2%)**	**0**	**2 (0.1%)**	**3 (0.4%)**
Yes	1 (2.1%)	0	1 (1.0%)	1 (2.1%)
No	1 (0.1%)	0	1 (0.1%)	2 (0.3%)
Breast cancer	**0**	**2 (0.2%)**	**2 (0.1%)**	**2 (0.2%)**
Yes	0	0	0	0
No	0	2 (0.3%)	2 (0.1%)	2 (0.3%)
Gastritis	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	1 (2.1%)	0	1 (1.0%)	0
No	0	1 (0.1%)	1 (0.1%)	0
Hypertension	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	0	1 (2.0%)	1 (1.0%)	0
No	1 (0.1%)	0	1 (0.1%)	0
Hysterectomy	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	0	0	0	0
No	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Liver function test abnormal	**0**	**2 (0.2%)**	**2 (0.1%)**	**0**
Yes	0	0	0	0
No	0	2 (0.3%)	2 (0.1%)	0
Lung neoplasm malignant	**0**	**2 (0.2%)**	**2 (0.1%)**	**0**
Yes	0	0	0	0
No	0	2 (0.3%)	2 (0.1%)	0
Prostate cancer	**0**	**2 (0.2%)**	**2 (0.1%)**	**0**
Yes	0	1 (2.0%)	1 (1.0%)	0
No	0	1 (0.1%)	1 (0.1%)	0
Upper gastrointestinal haemorrhage	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	0	1 (2.0%)	1 (1.0%)	0
No	1 (0.1%)	0	1 (0.1%)	0
Uterine polyp	**1 (0.1%)**	**1 (0.1%)**	**2 (0.1%)**	**0**
Yes	0	0	0	0
No	1 (0.1%)	1 (0.1%)	2 (0.1%)	0

Study included: 178-CL-049.
ER: extended release; PT: preferred term; SAE: serious adverse event(s).
† Sorting order: PT, by decreasing frequency in total mirabegron group.

Appendix 1, Table 25 Tolerability of Antimuscarinics and Mirabegron Compared to Placebo Control

Tolerability Parameter	Mirabegron 50 mg/day†	Darifenacin 7.5 mg/day	Darifenacin 7.5 mg/day titrated	Darifenacin 15 mg/day	Fesoterodine 4 mg/day	Fesoterodine 8 mg/day	Oxybutynin IR 5 mg/day	Oxybutynin IR 7.5 - 10 mg/day	Oxybutynin IR 15 mg/day
Total withdrawals									
Relative Risk	0.97 [0.95]	0.74	1.25	0.98	1.3	1.08	1.6	1.33	1.72
95% CI	0.82 – 1.16	0.43 - 1.27	0.62 - 2.51	0.70 - 1.36	0.85 - 2	0.69 - 1.68	0.59 - 4.33	1.01 - 1.76	1.18 - 2.49
P value	p = 0.77	P = 0.27	P = 0.54	P = 0.88	P = 0.23	P = 0.73	P = 0.36	P = 0.04	P< 0.01
n	4273 [2755]	938	398	1416	557	573	60	1054	751
Withdrawals due to AE									
Relative Risk	1.20 [1.16]	0.67	2.16	1.83	1.4	1.33	1.5	1.91	1.89
95% CI	0.86 – 1.66	0.11 - 3.95	0.75 - 6.25	0.95 - 3.55	0.69 - 2.82	0.65 - 2.71	0.27 - 8.34	1.18 - 3.1	1.23 - 2.9
P value	p = 0.28	P = 0.66	P = 0.16	P = 0.07	P = 0.35	P = 0.44	P = 0.64	P = 0.01	P< 0.01
n	4273 [2755]	217	398	657	926	929	60	488	743

Tolerability Parameter	Propiverine IR 30 mg/day	Propiverine ER 20 mg/day	Propiverine ER 30 mg/day	Solifenacin 5 mg/day	Solifenacin 10 mg/day	Tolterodine ER 4 mg/day	Tolterodine IR 2 mg/day	Tolterodine IR 4 mg/day	Trospium chloride 40 mg/day
Total withdrawals									
Relative Risk	1.21	1.07	1.08	0.83	0.81	0.87	1.32	0.98	1
95% CI	0.61 - 2.4	0.69 - 1.68	0.54 - 2.17	0.64 - 1.07	0.63 - 1.05	0.68 - 1.1	0.66 - 2.65	0.76 - 1.26	0.73 - 1.37
P value	P = 0.59	P = 0.76	P = 0.83	P = 0.15	P = 0.1	P = 0.24	P = 0.44	P = 0.87	--
n	597	805	593	2710	2689	2113	398	2261	832
Withdrawals due to AE									
Relative Risk	7.67	2.39	5.68	1.16	1.53	0.71	0.9	0.88	1.27
95% CI	1.02 - 57.66	1.20 - 4.78	0.74 - 43.71	0.79 - 1.72	1.02 - 2.3	0.53 - .95	0.44 - 1.83	0.66 - 1.17	0.86 - 1.88
P value	P = 0.05	P = 0.01	P = 0.1	P = 0.44	P = 0.04	P = 0.02	P = 0.77	P = 0.39	P = 0.23
n	597	805	593	3575	2689	3777	851	3973	1490

†The values for mirabegron 50 mg/day are for the Global OAB 12-week Phase 2/3 population. The values between brackets [xx] are for the EU/NA OAB 12-week Phase 3 population. n represents the number of patients who contributed to the meta-analysis (mirabegron 50 mg and placebo). Relative risk versus placebo for mirabegron 50 mg/day was estimated using Cochran Mantel Haenszel stratified by study. This methodology is consistent with the methodology used to estimate the relative risk for the antimuscarinics.
--: not applicable; AE: adverse event (s); ER: extended release; IR: immediate release.
Source: Chapple et al, 2008.

Appendix 1, Table 26 Urinary Retention TEAE, Global OAB 12-week Phase 2/3 Population

MedDRA (v12.1) SOC HLT PT, n (%) of Patients LLT †	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Total Mirabegron (n = 4414)	Tolterodine ER 4 mg (n = 958)
Overall	7 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Investigations	1 (< 0.1%)	0	0	0	0	0	0
Urinary tract function analyses NEC	1 (< 0.1%)	0	0	0	0	0	0
Residual urine volume increased	1 (< 0.1%)	0	0	0	0	0	0
Residual urine volume increased	1 (< 0.1%)	0	0	0	0	0	0
Renal and urinary disorders	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Bladder and urethral symptoms	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Urinary retention	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Acute retention of urine	3 (0.1%)	0	1 (< 0.1%)	0	0	1 (< 0.1%)	3 (0.3%)
Urinary retention	3 (0.1%)	0	0	0	1 (0.6%)	1 (< 0.1%)	0

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
AE: adverse event(s); ER: extended release; HLT: higher level term; LLT: lower level term; NEC: not elsewhere classified; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent ad verse event(s).
† Sorting order: alphabetic by SOC, alphabetic by HLT, alphabetic by PT and alphabetic by LLT.

Appendix 1, Table 27 Shift Table for PVR Volume Results from Baseline to the Highest Value (mL), Global OAB 12-week Phase 2/3 Population

n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolt ER 4 mg (n = 958)
Baseline 0 to < 150 (mL)						
Postbaseline						
0 to < 150	1944 (99.3%)	751 (99.6%)	1909 (98.8%)	1181 (99.0%)	153 (99.4%)	891 (99.0%)
150 to < 300	12 (0.6%)	3 (0.4%)	22 (1.1%)	11 (0.9%)	1 (0.6%)	8 (0.9%)
≥ 300	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
Total	1957	754	1932	1193	154	900
Baseline 150 to < 300 (mL)						
Postbaseline						
0 to < 150	22 (75.9%)	3 (60.0%)	23 (74.2%)	11 (73.3%)	1 (100.0%)	6 (85.7%)
150 to < 300	4 (13.8%)	2 (40.0%)	7 (22.6%)	3 (20.0%)	0	1 (14.3%)
≥ 300	3 (10.3%)	0	1 (3.2%)	1 (6.7%)	0	0
Total	29	5	31	15	1	7
Baseline ≥ 300 (mL)						
Postbaseline						
0 to < 150	2 (100.0%)	1 (100.0%)	0	0	0	0
150 to < 300	0	0	1 (100.0%)	0	0	0
≥ 300	0	0	0	0	0	0
Total	2	1	1	0	0	0
Baseline total (mL)						
Postbaseline						
0 to < 150	1968 (99.0%)	755 (99.3%)	1932 (98.4%)	1192 (98.7%)	154 (99.4%)	897 (98.9%)
150 to < 300	16 (0.8%)	5 (0.7%)	30 (1.5%)	14 (1.2%)	1 (0.6%)	9 (1.0%)
≥ 300	4 (0.2%)	0	2 (0.1%)	2 (0.2%)	0	1 (0.1%)
Total	1988	760	1964	1208	155	907

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
The percentages are based on the total number of patients with a postbaseline PVR volume within each baseline category.
ER: extended release; OAB: overactive bladder; PVR: postvoid residual (volume); Tolt: tolterodine.

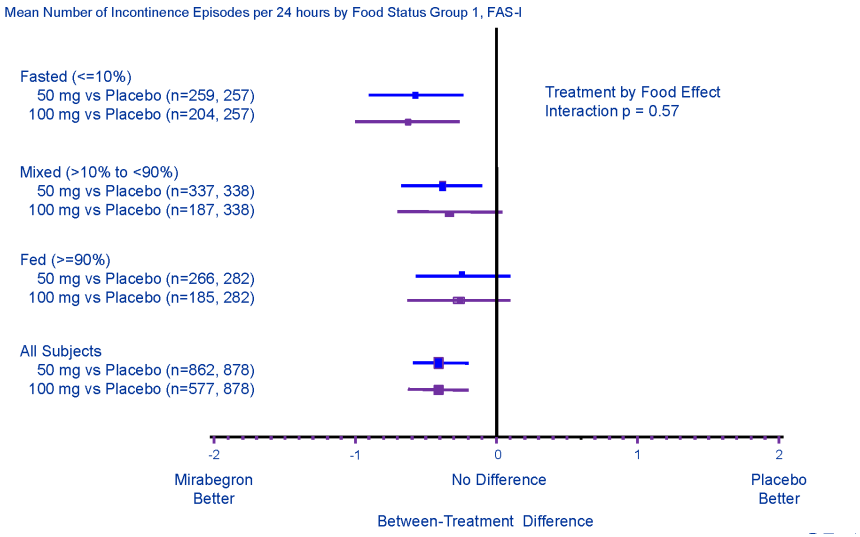
Appendix 1, Table 28 Urinary Retention TEAE, EU/NA Long-term Controlled Population

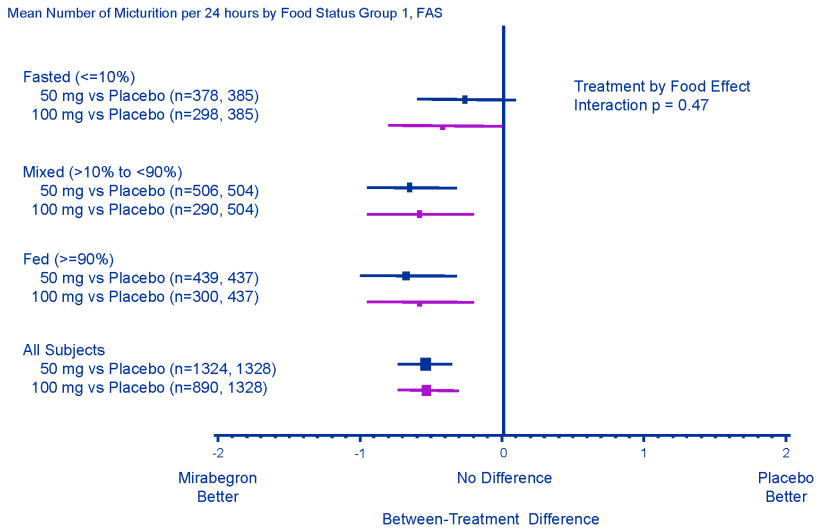
MedDRA (v12.1) SOC HLT PT, n (%) of Patients LLT †	Mirabegron			Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	
Overall	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Renal and urinary disorders	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Bladder and urethral symptoms	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Urinary retention	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Acute retention of urine	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Bladder inability to empty	0	0	0	1 (0.1%)
Urinary retention	1 (0.1%)	0	1 (0.1%)	1 (0.1%)

Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
AE: adverse event(s); ER: extended release; HLT: higher level term; LLT: lower level term; PT: preferred term; TEAE: treatment-emergent adverse event(s).
† Sorting order: alphabetic by SOC, alphabetic by HLT, alphabetic by PT and alphabetic by LLT.

Appendix 2 Supplementary Figures

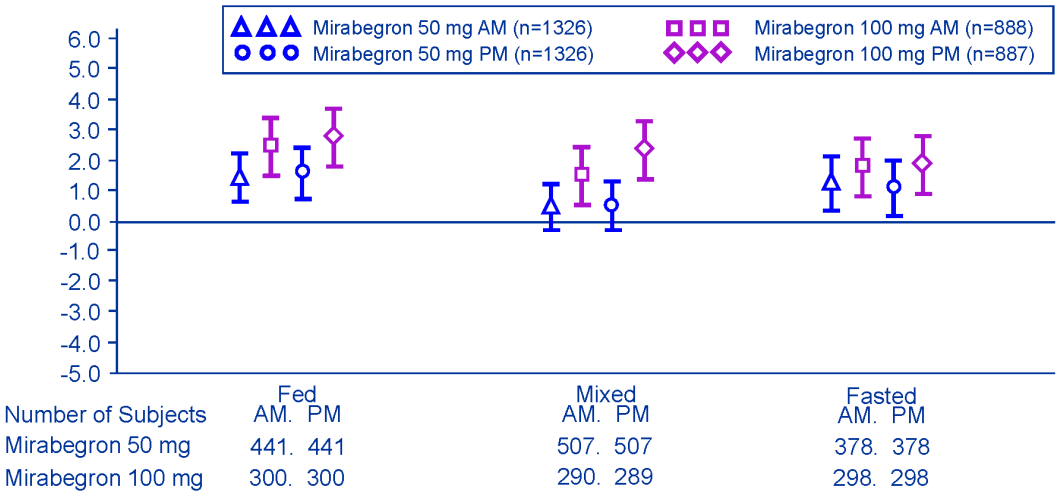
Appendix 2, Figure 1 Adjusted Mean Difference Versus Placebo for Change from Baseline to Final Visit in Mean Number of Incontinence Episodes and Mean Number of Micturitions per 24 Hours by Food Status Group 1, Pooled Primary Phase 3 Studies





Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).
Horizontal bars represent 95% CIs for the adjusted mean difference vs placebo.
Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 50 mg, and mirabegron 100 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. Pooled overall analysis results are from an ANCOVA model with treatment group (placebo, mirabegron 50 mg and mirabegron 100 mg), gender, and study as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; OAB: overactive bladder.

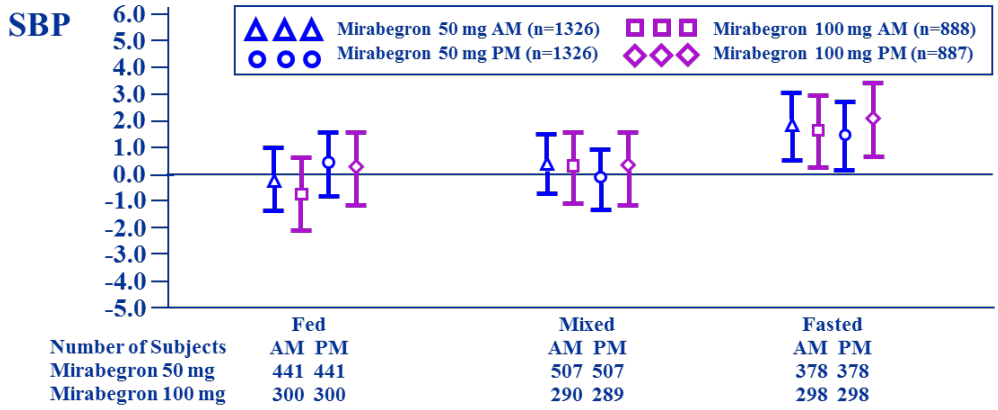
Appendix 2, Figure 2 Adjusted Mean Difference Versus Placebo for Change from Baseline to Final Visit in Pulse Rate Measured by Patient Diary, AM and PM Measurements, by Food Status Group 1, EU/NA OAB 12-week Phase 3 Population



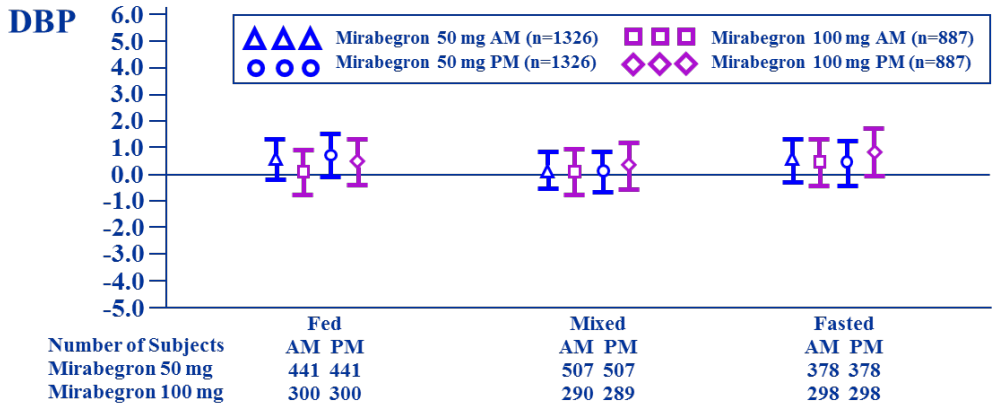
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from adjusted mean of the treatment group.
The adjusted means and 95% CIs were calculated using an ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, food status group 1 and treatment-by-food status group 1 as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; ER: extended release.

Appendix 2, Figure 3 Adjusted Mean Difference Versus Placebo for Change from Baseline to Final Visit in SBP and DBP Measured by Patient Diary, AM and PM Measurements, by Food Status Group 1, EU/NA OAB 12-week Phase 3 Population

A. SBP

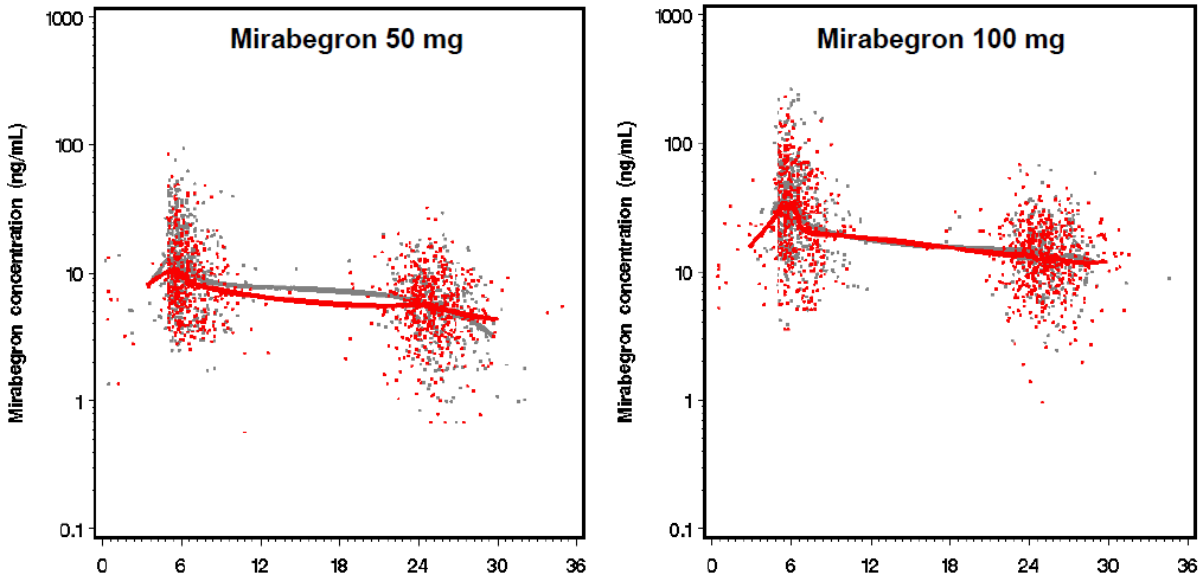


B. DBP



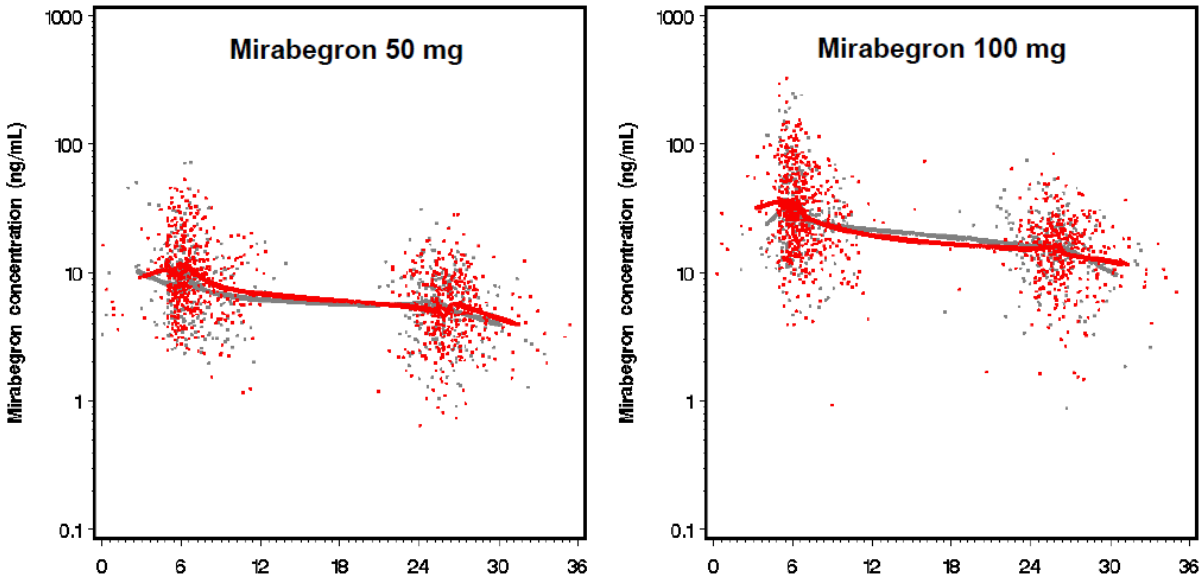
Studies included: 178-CL-046, 178-CL-047, and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from adjusted mean of the treatment group.
The adjusted means and 95% CIs were calculated using an ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, food status group 1 and treatment-by-food status group 1 as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; ER: extended release; SBP: systolic blood pressure.

Appendix 2, Figure 4 Mirabegron Concentration vs Time After Dose by Food Status, Study 178-CL-046



Red data points represent fed status and grey data points represent fasting status.

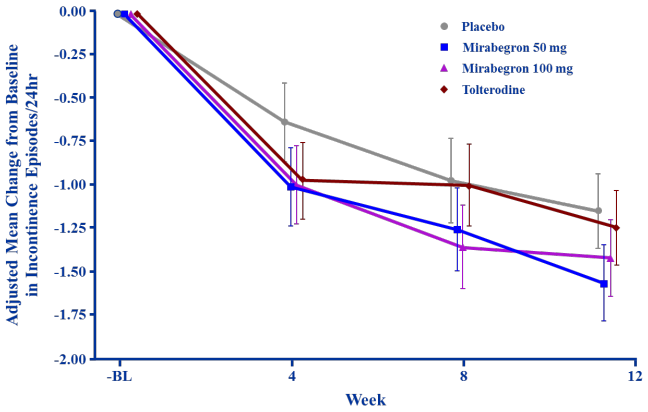
Appendix 2, Figure 5 Mirabegron Concentration vs Time After Dose by Food Status, Study 178-CL-047



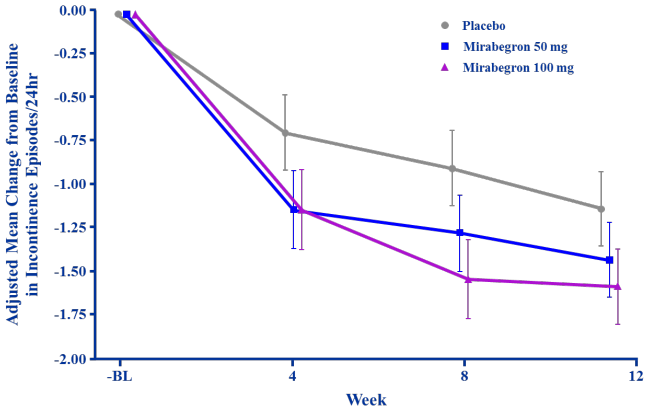
Red data points represent fed status and grey data points represent fasting status.

Appendix 2, Figure 6 Adjusted Mean Change from Baseline to Weeks 4, 8 and 12 in Mean Number of Incontinence Episodes per 24 Hours, Primary Phase 3 Studies, FAS-I

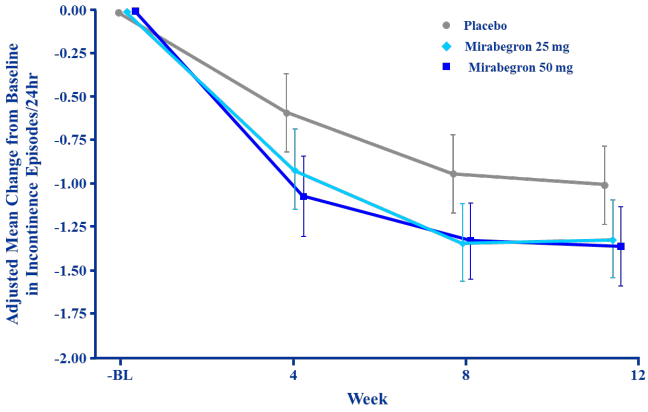
(A) Study 178-CL-046



(B) Study 178-CL-047



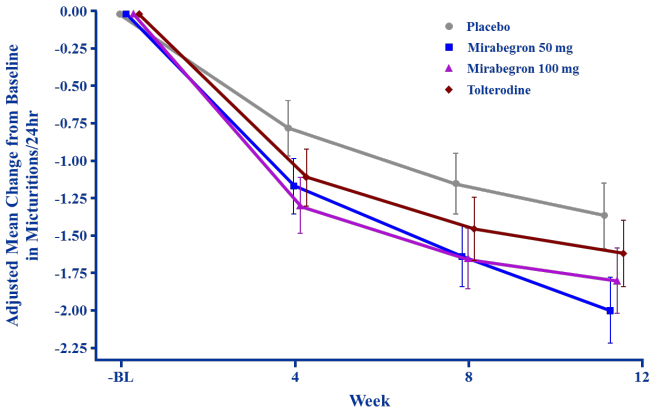
(C) Study 178-CL-074



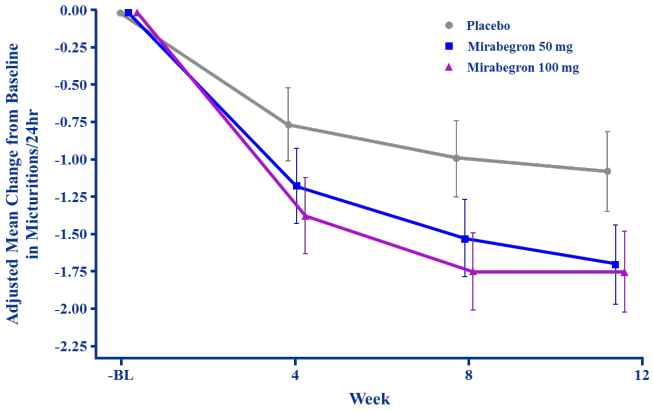
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).Error bars represent 2-sided 95% CIs. Adjusted mean change from baseline and CIs by visit are based on repeated measures model including treatment, gender, visit, geographical region, treatment-by-visit interaction and gender-by-visit interaction as fixed factors and baseline value and baseline by-visit interaction as covariates.

Appendix 2, Figure 7 Adjusted Mean Change from Baseline to Weeks 4, 8 and 12 in Mean Number of Micturitions per 24 hours, Primary Studies, FAS

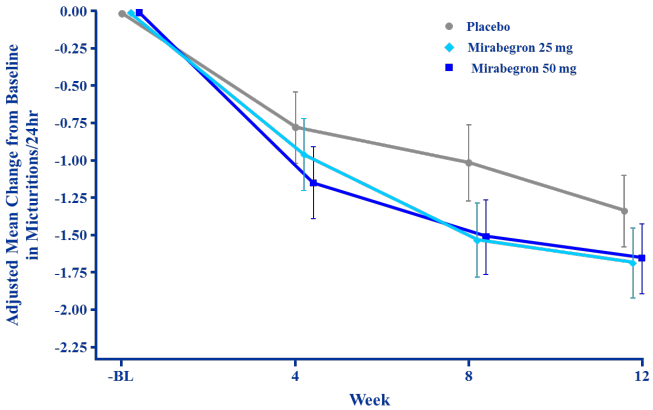
(A) Study 178-CL-046



(B) Study 178-CL-047



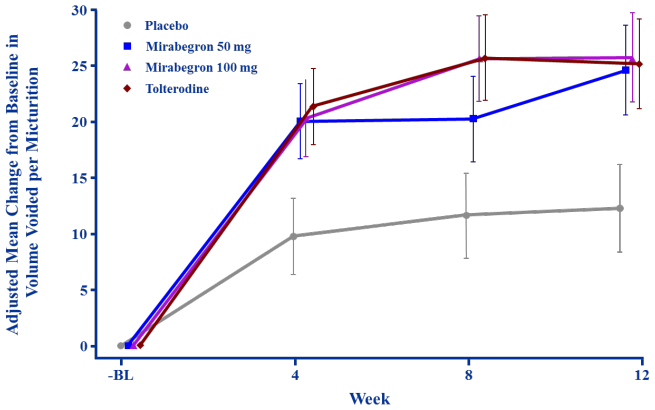
(C) Study 178-CL-074



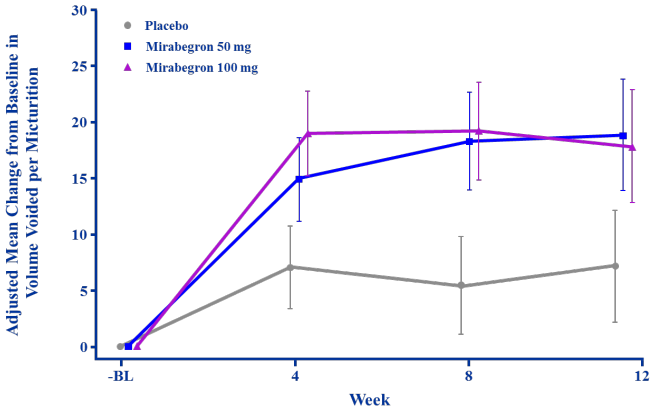
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). Error bars represent 2-sided 95% CIs. Adjusted mean change from baseline and CIs by visit are based on repeated measures model including treatment, gender, visit, geographical region, treatment-by-visit interaction and gender-by-visit interaction as fixed factors and baseline value and baseline-by-visit interaction as covariates.

Appendix 2, Figure 8 Adjusted Mean Change from Baseline to Weeks 4, 8 and 12 in Mean Volume Voided per Micturition (mL), Primary Phase 3 Studies, FAS

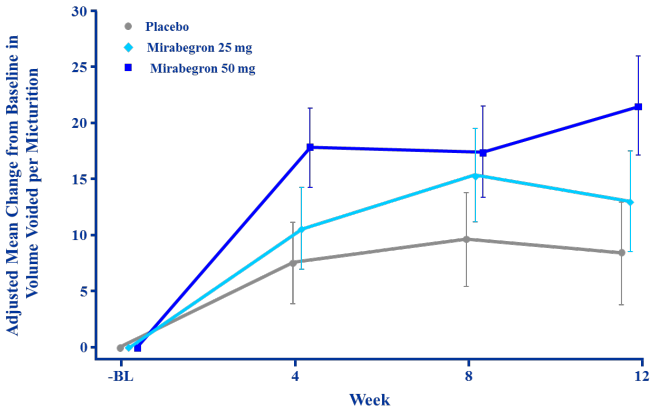
(A) Study 178-CL-046



(B) Study 178-CL-047

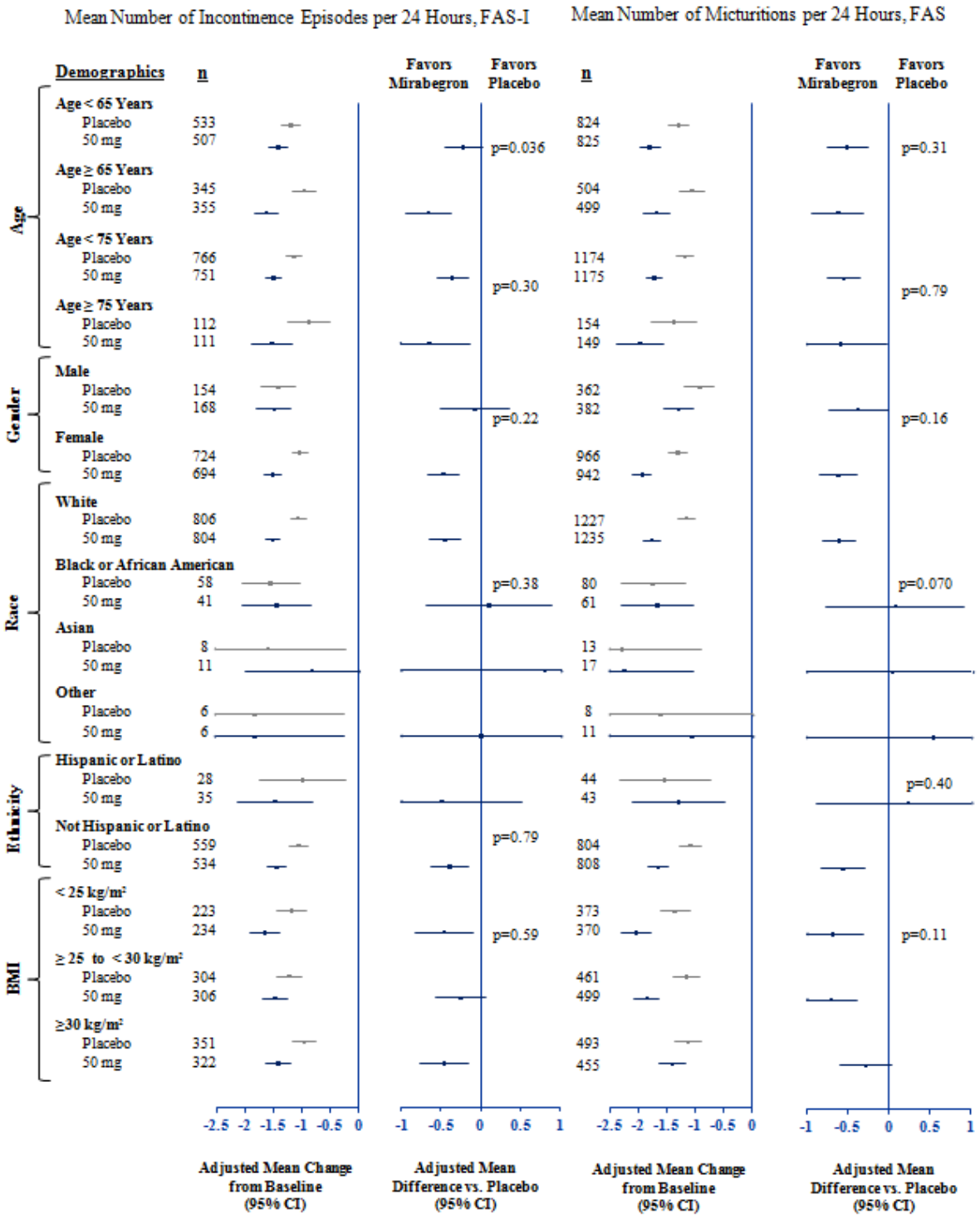


(C) Study 178-CL-074



All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). Error bars represent 2-sided 95% CIs. Adjusted means and CIs by visit are based on repeated measures model including treatment, gender, visit, geographical region, treatment-by-visit interaction and gender-by-visit interaction as fixed factors and baseline value and baseline-by-visit interaction as covariates.

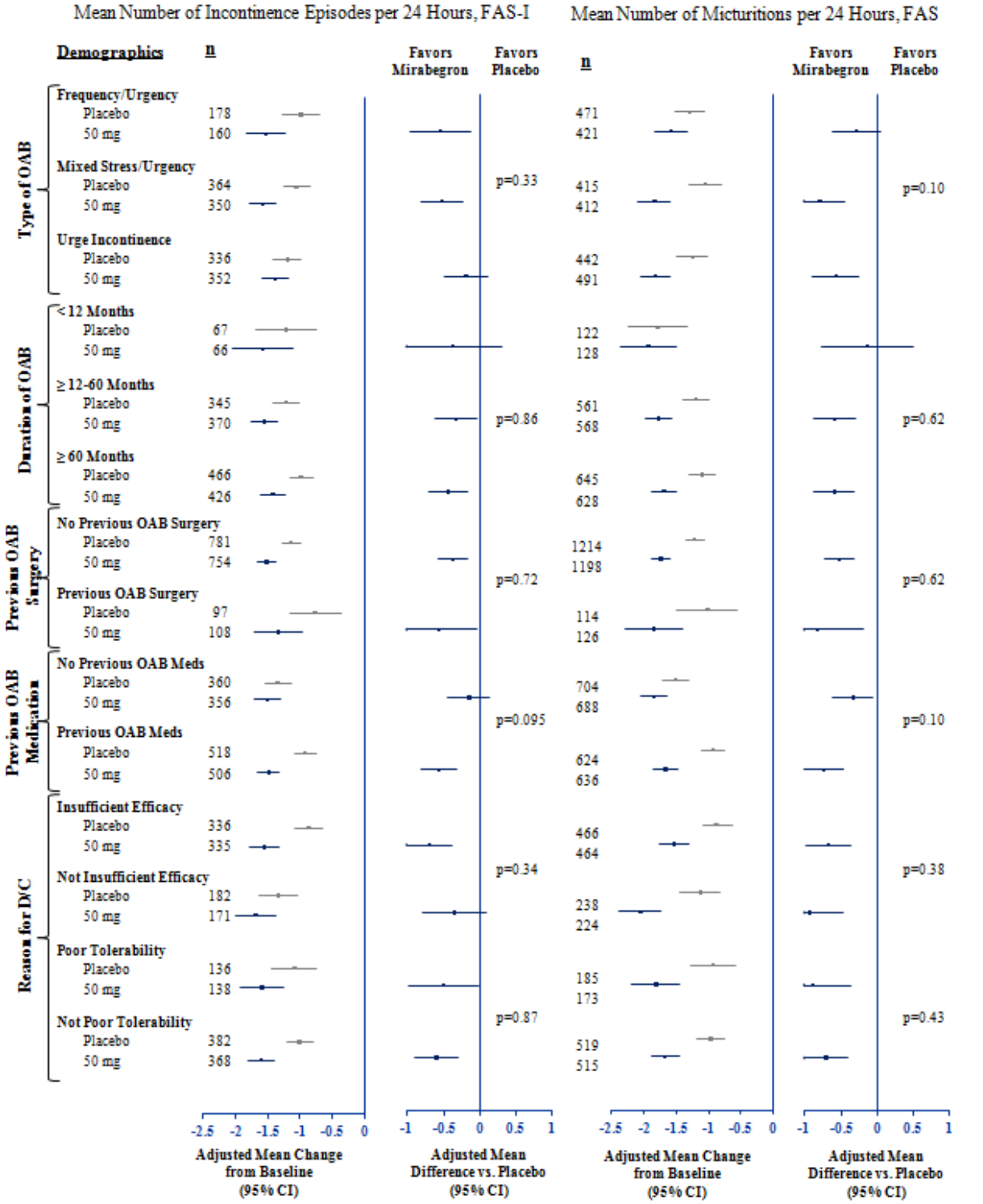
Appendix 2, Figure 9 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Demographic Characteristics, Pooled Primary Phase 3 Studies



Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Footnotes continued on next page.

All patients in the FAS who had least one incontinence episode recorded in the baseline 3-day micturition diary (Full Analysis Set-Incontinence [FAS-I]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subpopulation analysis results for age, race, ethnicity, and BMI are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 50 mg, and mirabegron 100 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. Pooled subpopulation results for gender are from an ANCOVA model with treatment group (placebo, mirabegron 50 mg, and mirabegron 100 mg), gender, study, and treatment by gender interaction as fixed factors and baseline as a covariate. P values are from treatment by subpopulation interactions in the ANCOVA models described above.
BMI: body mass index; OAB: overactive bladder.

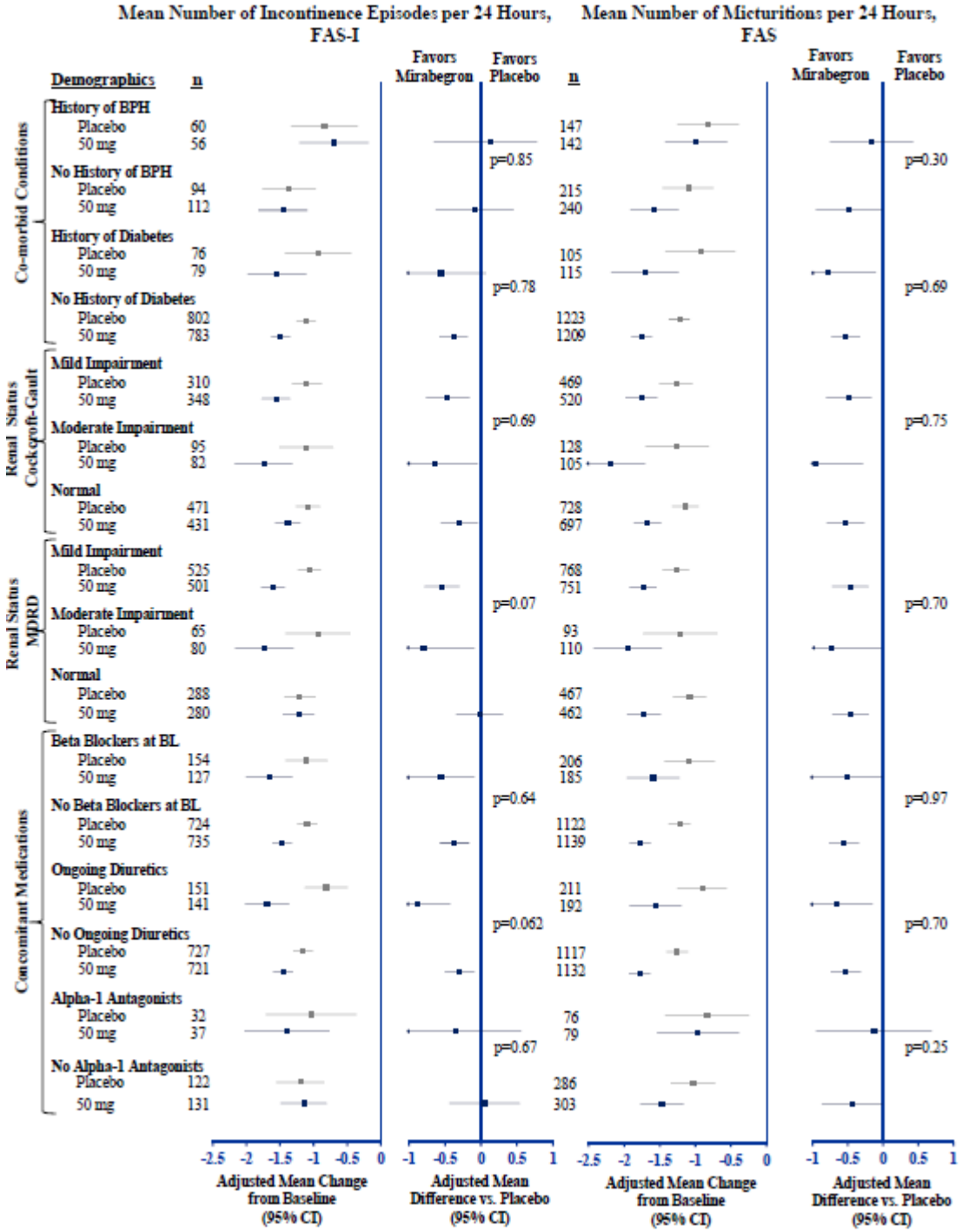
Appendix 2, Figure 10 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Baseline Characteristics of OAB, Pooled Primary Phase 3 Studies



Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
Footnotes continued on next page.

All patients in the FAS who had least one incontinence episode recorded in the baseline 3-day micturition diary (Full Analysis Set-Incontinence [FAS-I]).
The baseline characteristic of reason for discontinuation represents reasons for discontinuating prior OAB medication.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 50 mg and mirabegron 100 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. P values are from treatment by subpopulation interactions in the ANCOVA model described above.
D/C: discontinuation; OAB: overactive bladder.

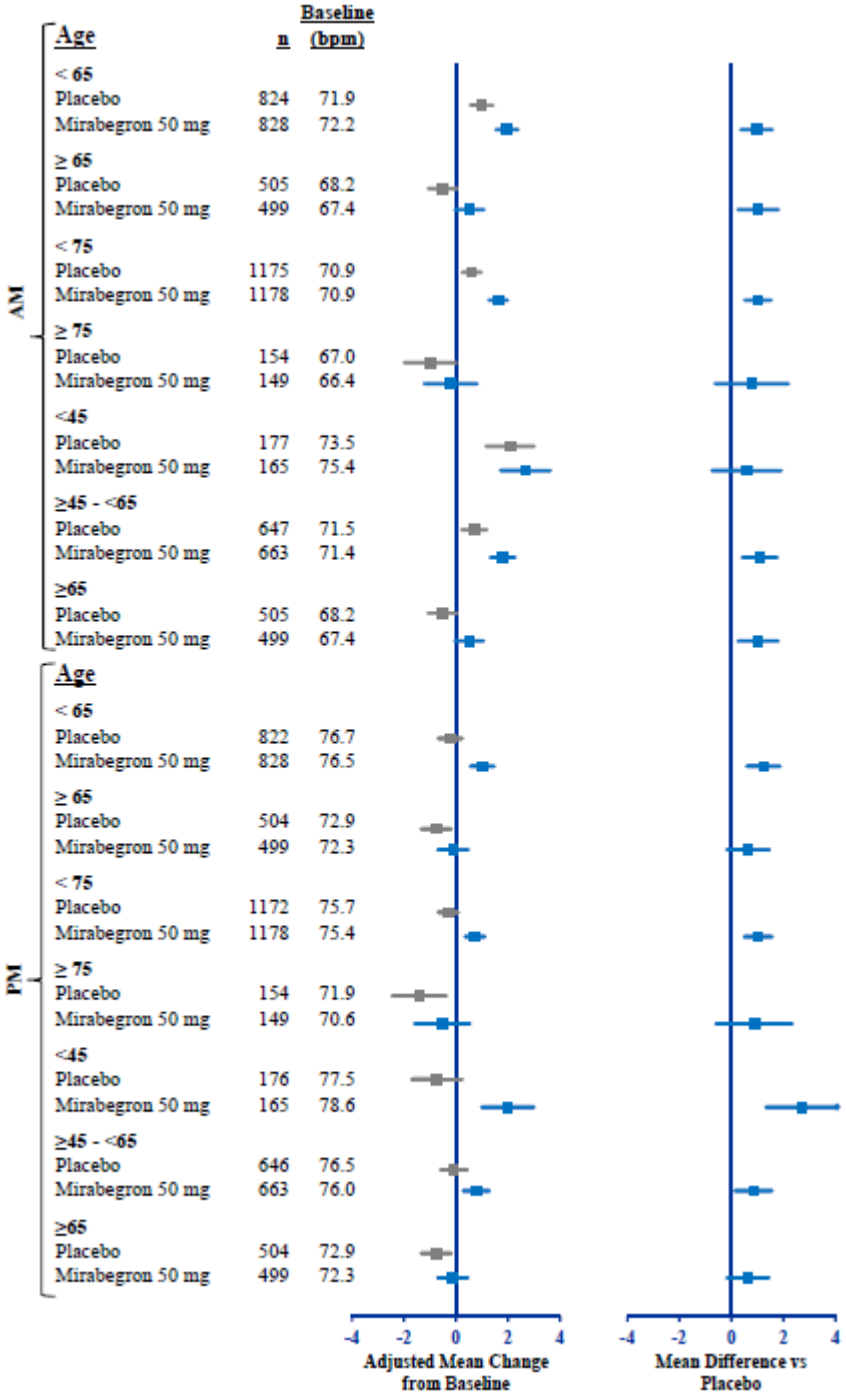
Appendix 2, Figure 11 Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Intrinsic/Extrinsic Factors, Pooled Primary Phase 3 Studies



Pooled studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All patients in the FAS who had least one incontinence episode recorded in the baseline 3-day micturition diary (Full Analysis Set-Incontinence [FAS-I]).
Footnotes continued on next page.

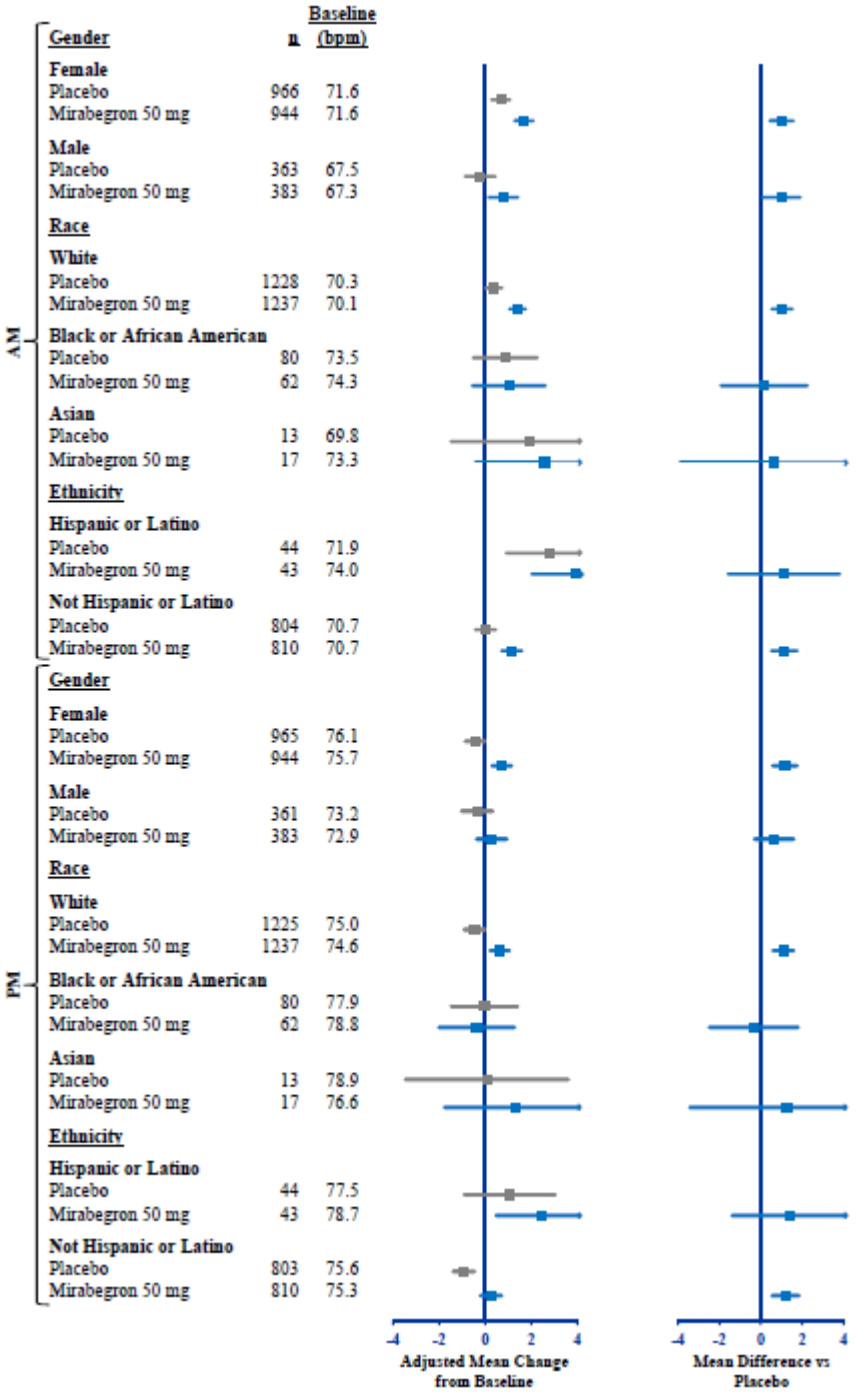
Concomitant medications represented concomitant medications at baseline.
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 50 mg and mirabegron 100 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. P values are from treatment by subpopulation interaction in the ANCOVA model described above.
Subpopulation analysis for BPH and use of alpha-1 antagonist at baseline was performed on male patients only.
BPH: benign prostatic hyperplasia; MDRD: modification of diet in renal disease; BL: baseline.

Appendix 2, Figure 12 Change from Baseline to Final Visit for Pulse Rate by Age, EU/NA OAB 12-week Phase 3 Population



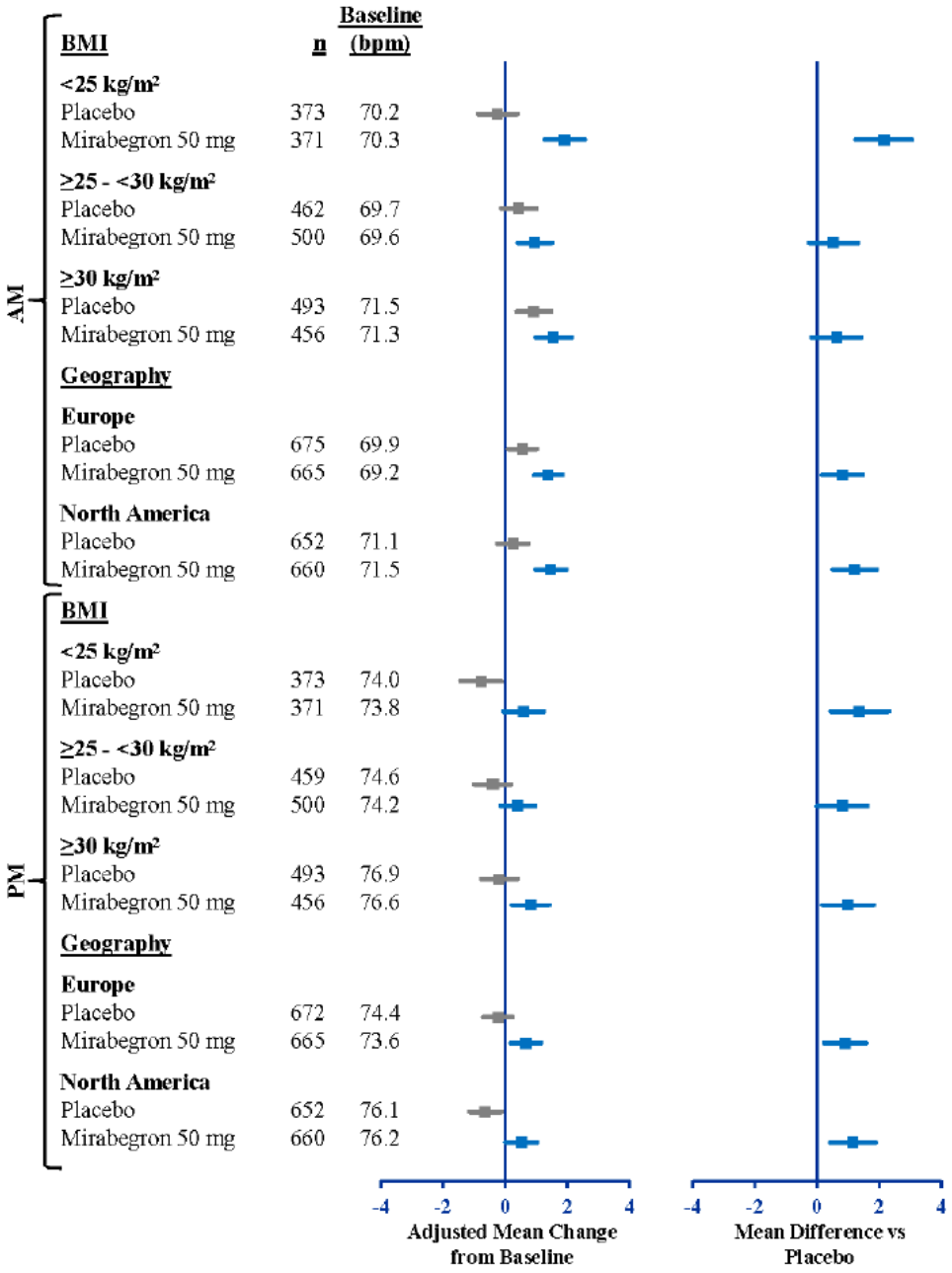
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Age is presented in years. Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute.

Appendix 2, Figure 13 Change from Baseline to Final Visit for Pulse Rate by Demographics, EU/NA OAB 12-week Phase 3 Population



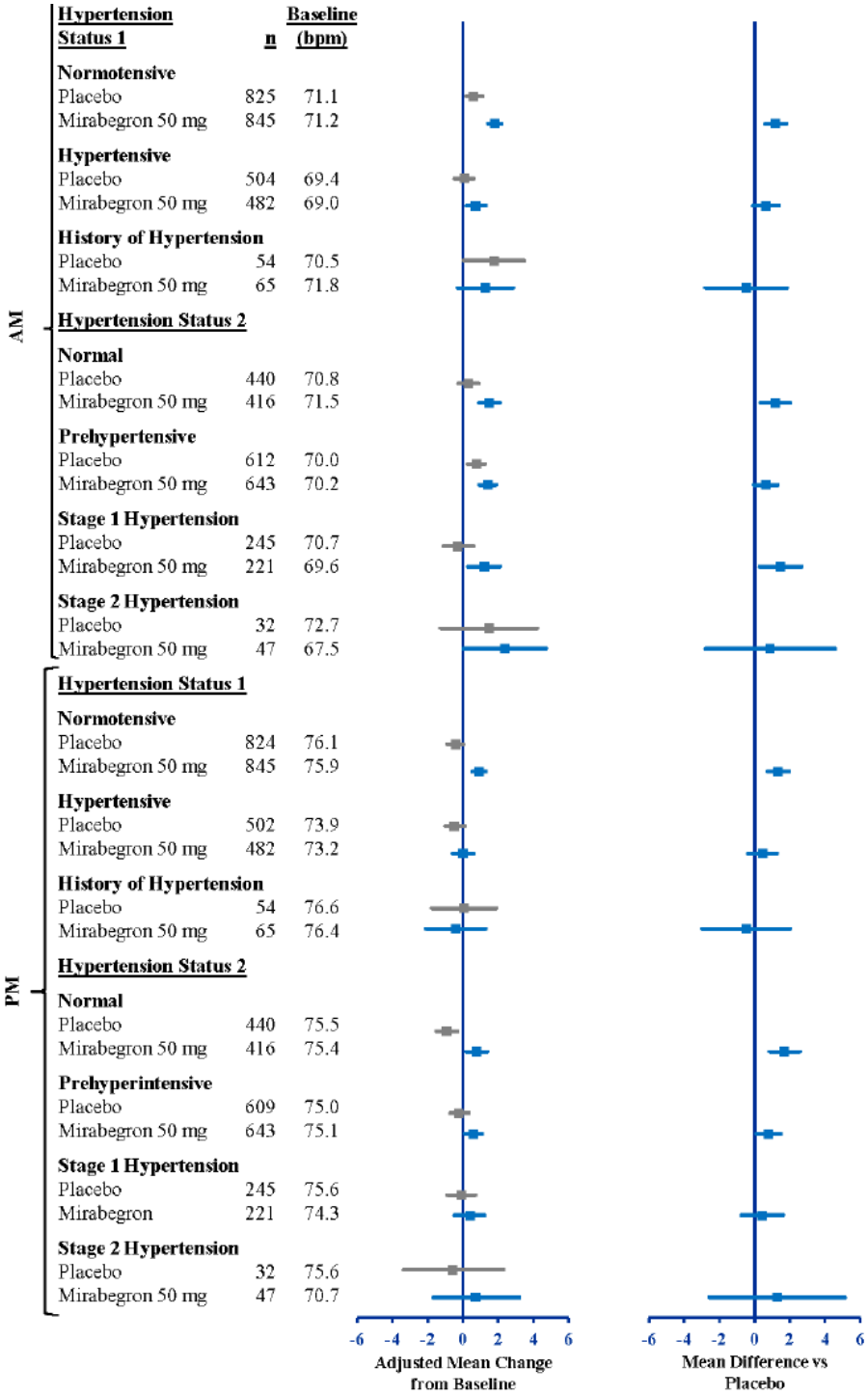
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074. All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]). Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subpopulation analysis results for race and ethnicity are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. Pooled subpopulation analysis results for gender are from an ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, and treatment by gender interaction as fixed factors and baseline as a covariate. ANCOVA: analysis of covariance; bpm: beats per minute; OAB: overactive bladder.

Appendix 2, Figure 14 Change from Baseline to Final Visit for Pulse Rate by BMI and Geographical Region, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results for BMI are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. For each geographical region, a seperate ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, and study as fixed factors and baseline as a covariate was performed.
ANCOVA: analysis of covariance; BMI; body mass index; bpm: beats per minute; OAB: overactive bladder.

Appendix 2, Figure 15 Change from Baseline to Final Visit for Pulse Rate by Baseline Hypertension Status, EU/NA OAB 12-week Phase 3 Population

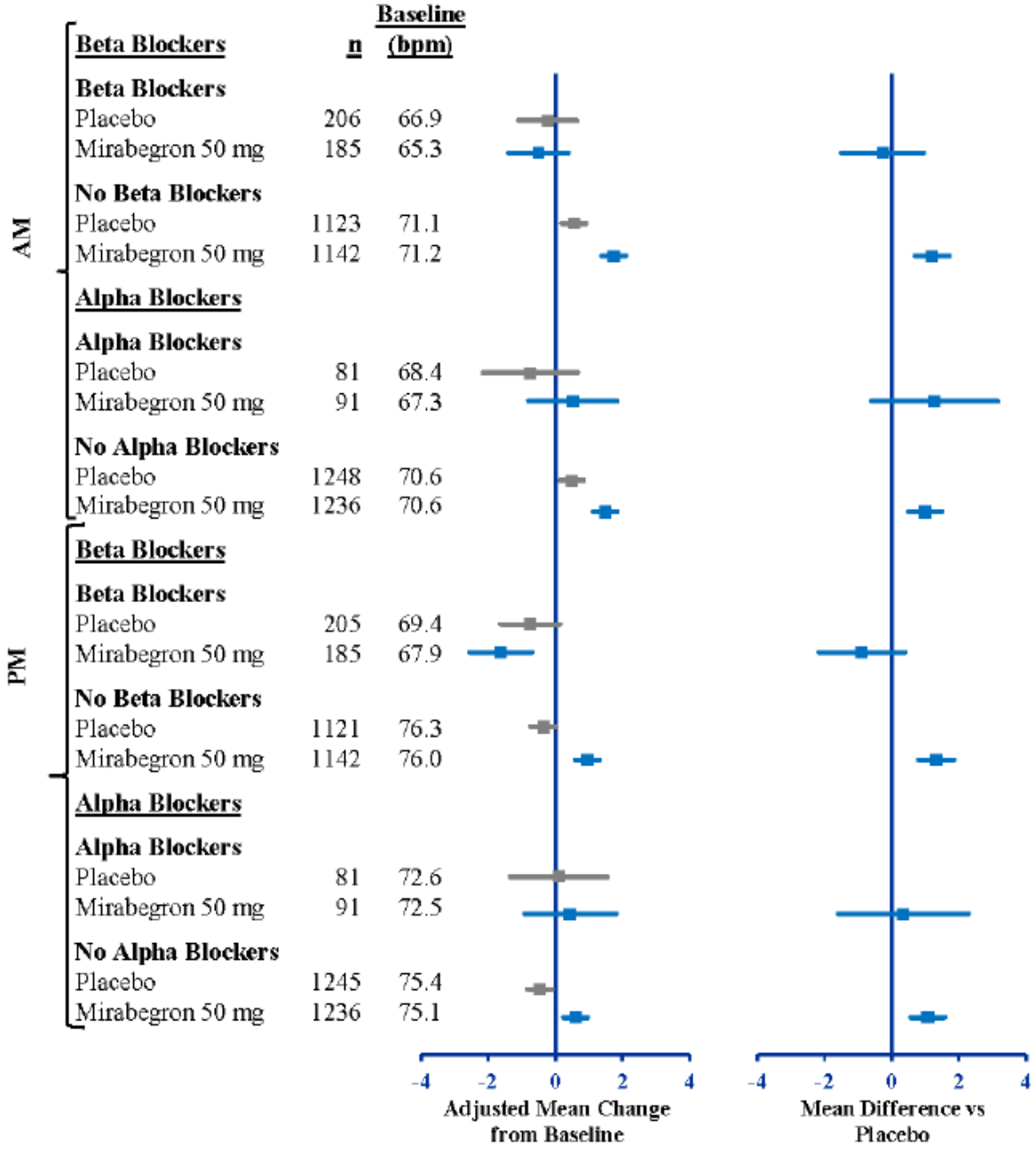


Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
For each hypertensive status 1 and hypertensive status 2 category, a seperate ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, and study as fixed factors and baseline as a covariate was performed.
Footnotes continued on next page.

Baseline hypertension status 1 and past history of hypertension are based on medical history and use of concomitant anti-hypertensive medication. The hypertensive population was defined as any patient who had a medical history of hypertension and received concurrent antihypertensive treatment at the time of the screening visit. The normotensive population was defined as any patient who did not meet the definition of hypertensive. The past history of hypertension population was defined as any patient who had a medical history of hypertension and did not receive concurrent antihypertensive treatment at the time of the screening visit. A patient included in the past history of hypertension population was also included in the normotensive population.

Baseline hypertension status 2 is based on baseline diary SBP/DBP measurements: Normal: SBP < 120 mmHg and DBP < 80 mmHg, Pre-Hypertension: SBP 120 to 139 mmHg or DBP 80 to 89 mmHg, Stage 1 Hypertension: SBP 140 to 159 mmHg or DBP 90 to 99 mmHg and Stage 2 Hypertension: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg.
ANCOVA: analysis of covariance; bpm: beats per minute; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

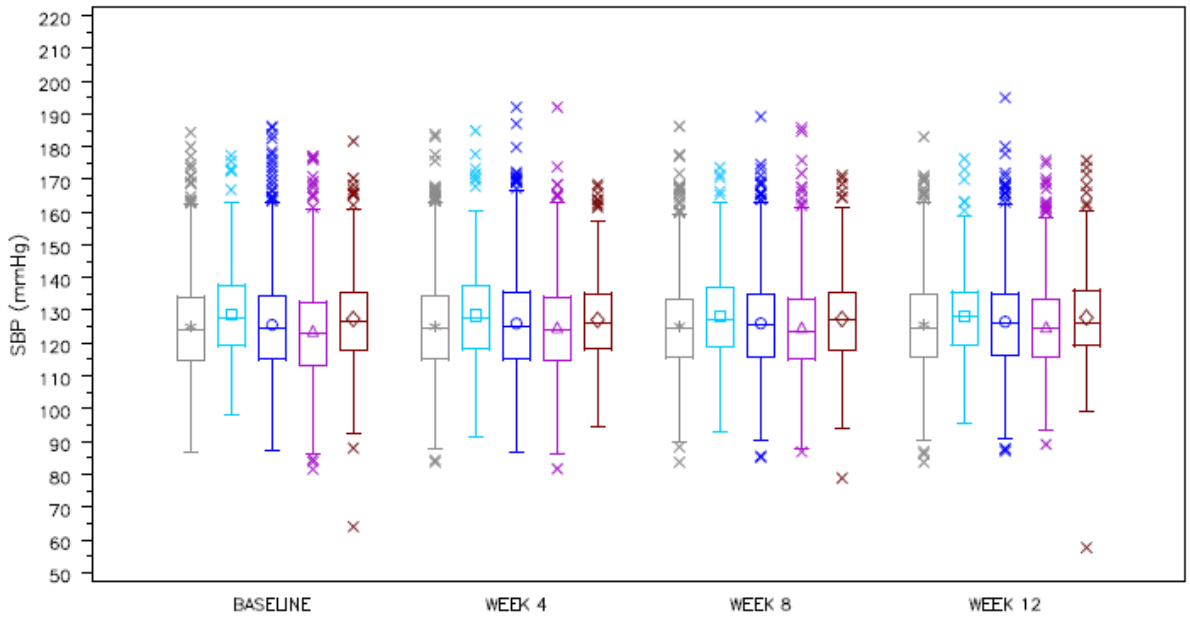
Appendix 2, Figure 16 Change from Baseline to Final Visit for Pulse Rate by Baseline Medication Use, EU/NA OAB 12-week Phase 3 Population



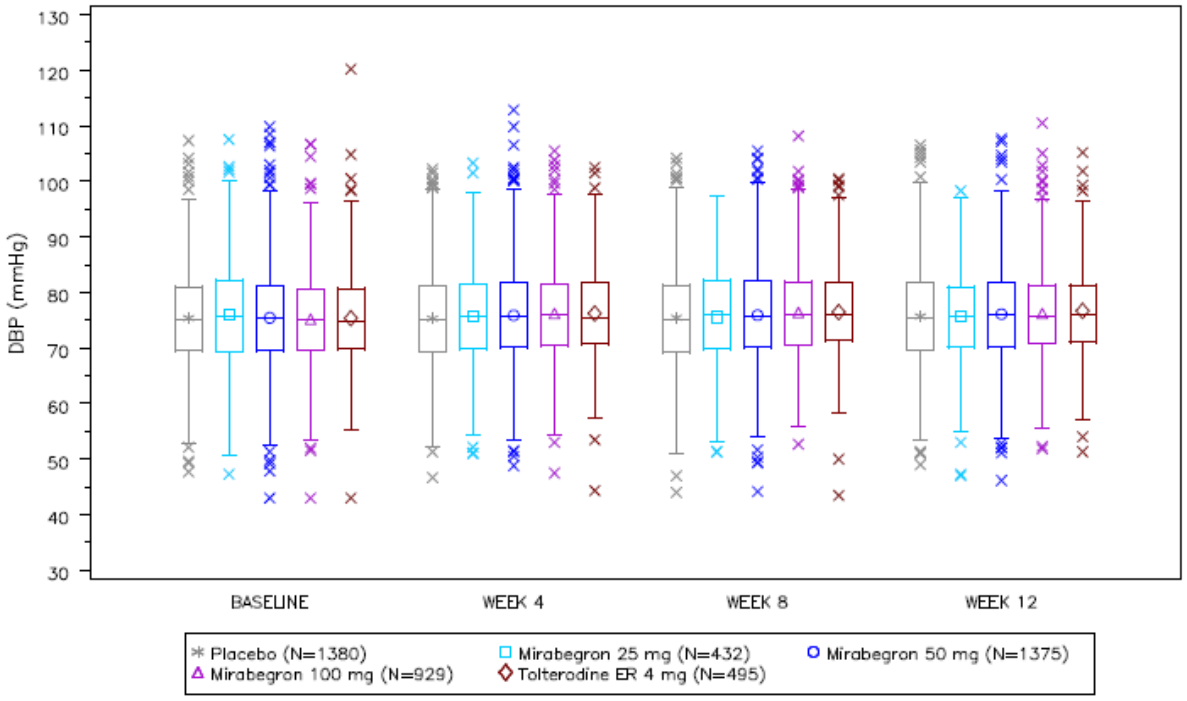
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute; OAB: overactive bladder.

Appendix 2, Figure 17 Box Plots of PM SBP/DBP Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) SBP (mm Hg)



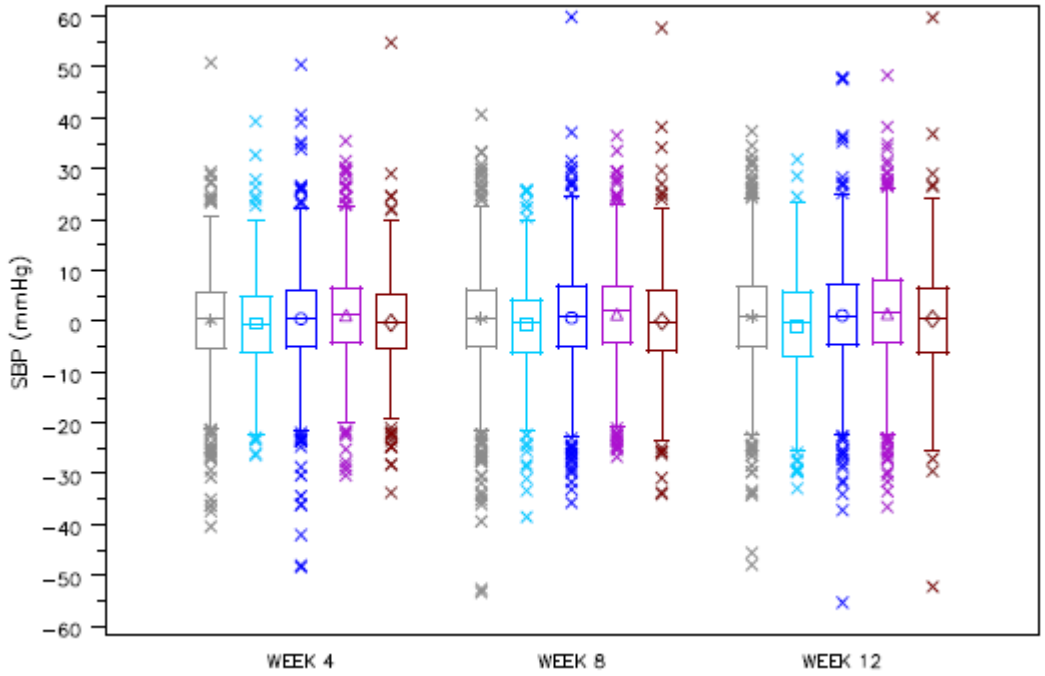
(B) DBP (mm Hg)



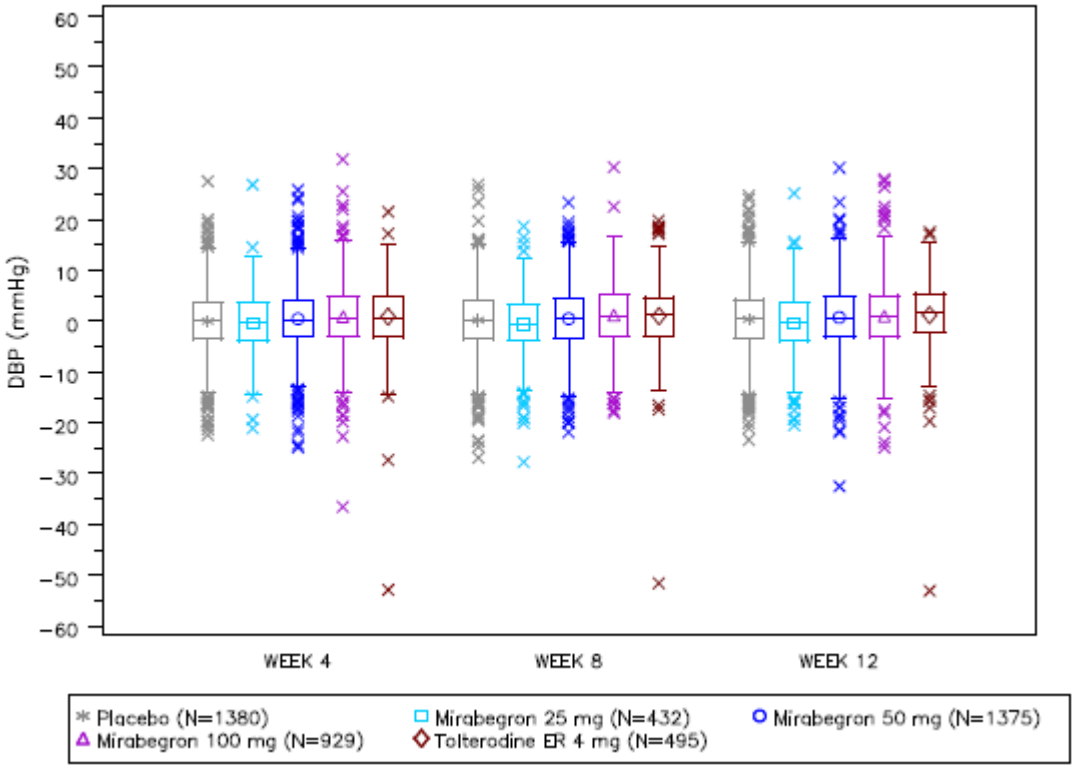
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 2, Figure 18 Box Plots of Change from Baseline in PM SBP/DBP Values at Each Visit, EU/NA OAB 12-week Phase 3 Population

(A) SBP (mm Hg)



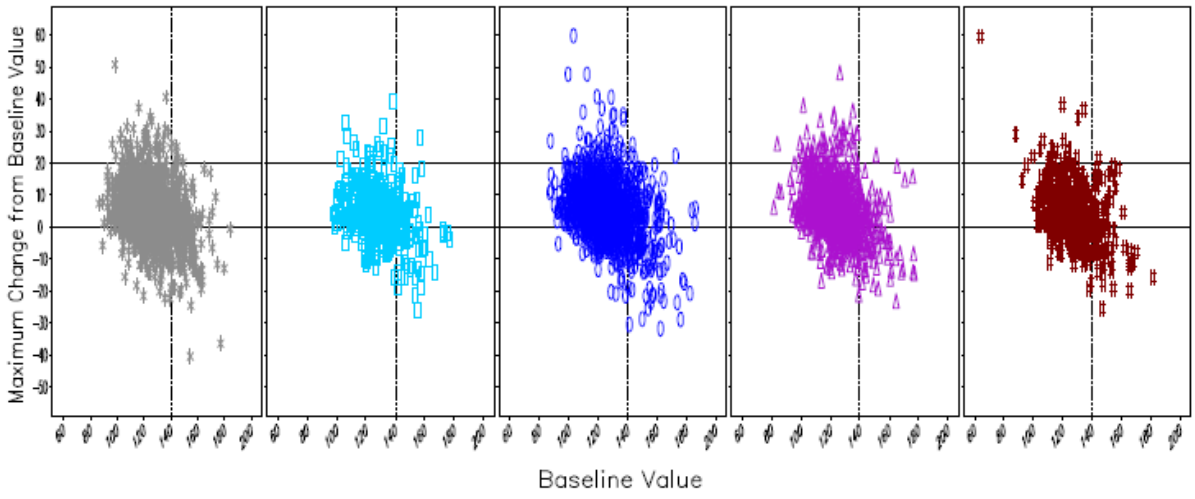
(B) DBP (mm Hg)



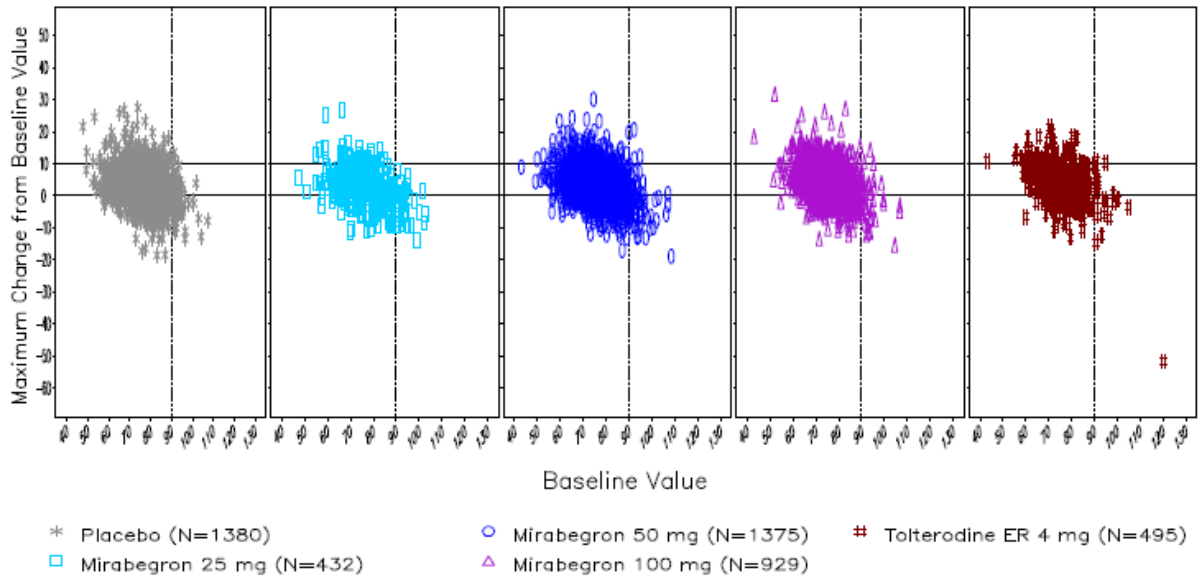
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]). DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 2, Figure 19 Scatterplots of Maximum Change from Baseline Values Versus Baseline Values in PM SBP/DBP, EU/NA OAB 12-week Phase 3 Population

(A) SBP (mm Hg)



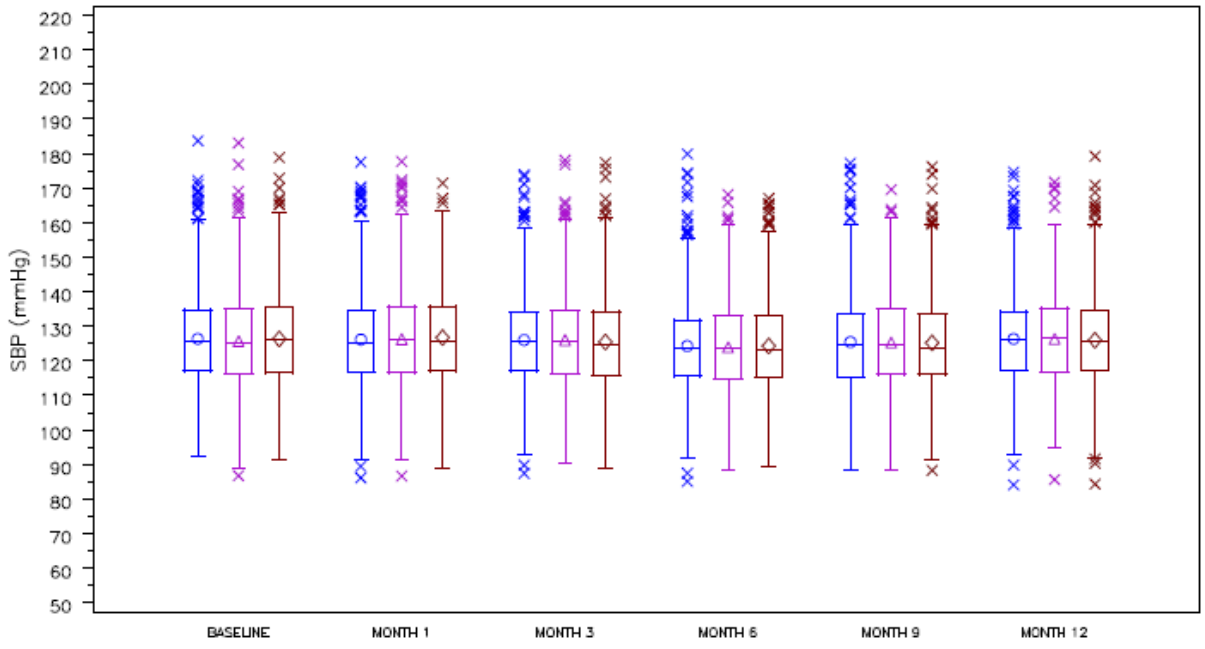
(B) DBP (mm Hg)



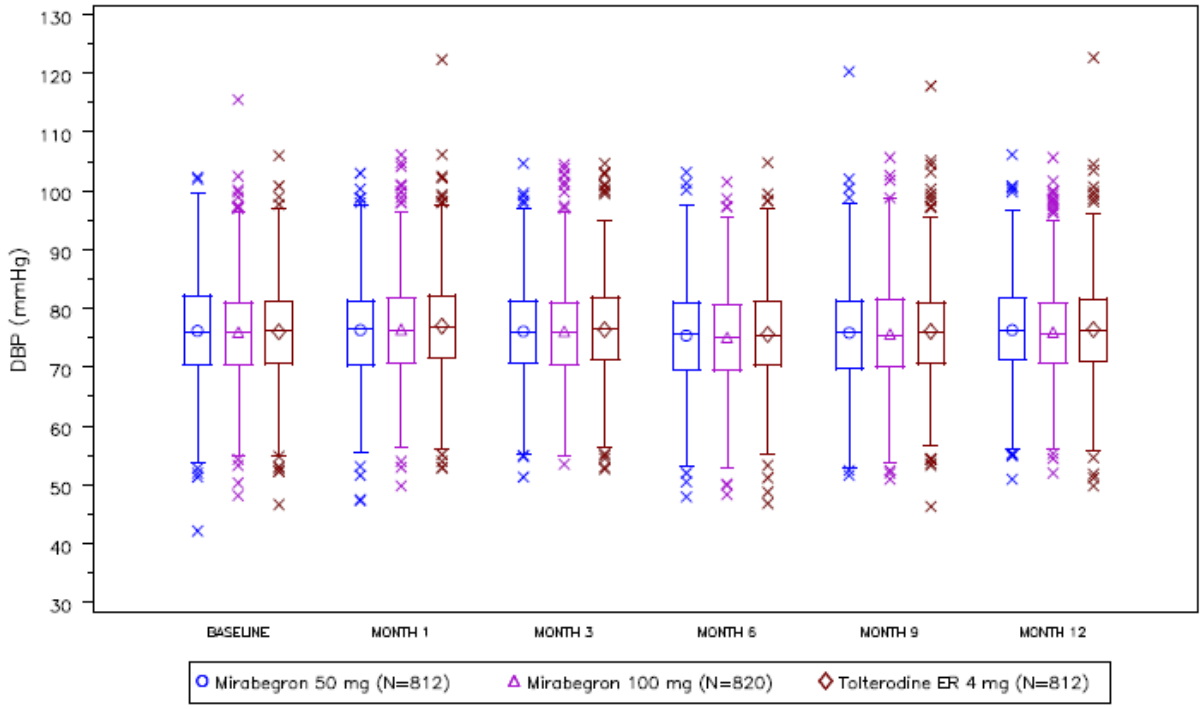
Study included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
DBP: diastolic blood pressure; OAB: overactive bladder SBP: systolic blood pressure.

Appendix 2, Figure 20 Box Plots of PM SBP/DBP Values at Each Visit, EU/NA Long-term Controlled Population

(A) SBP (mm Hg)



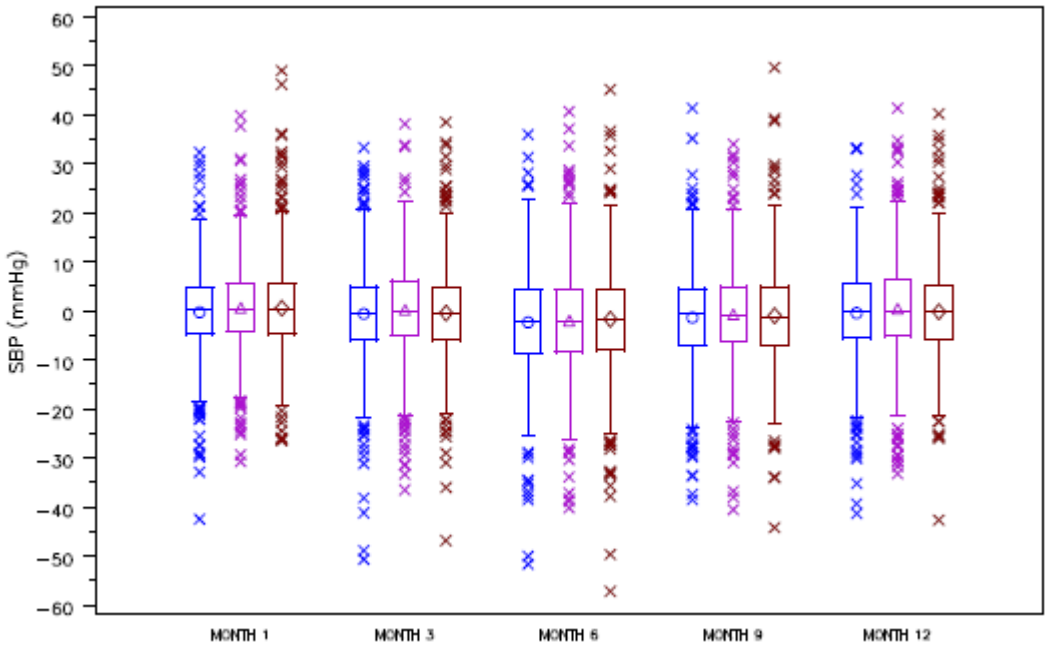
(B) DBP (mm Hg)



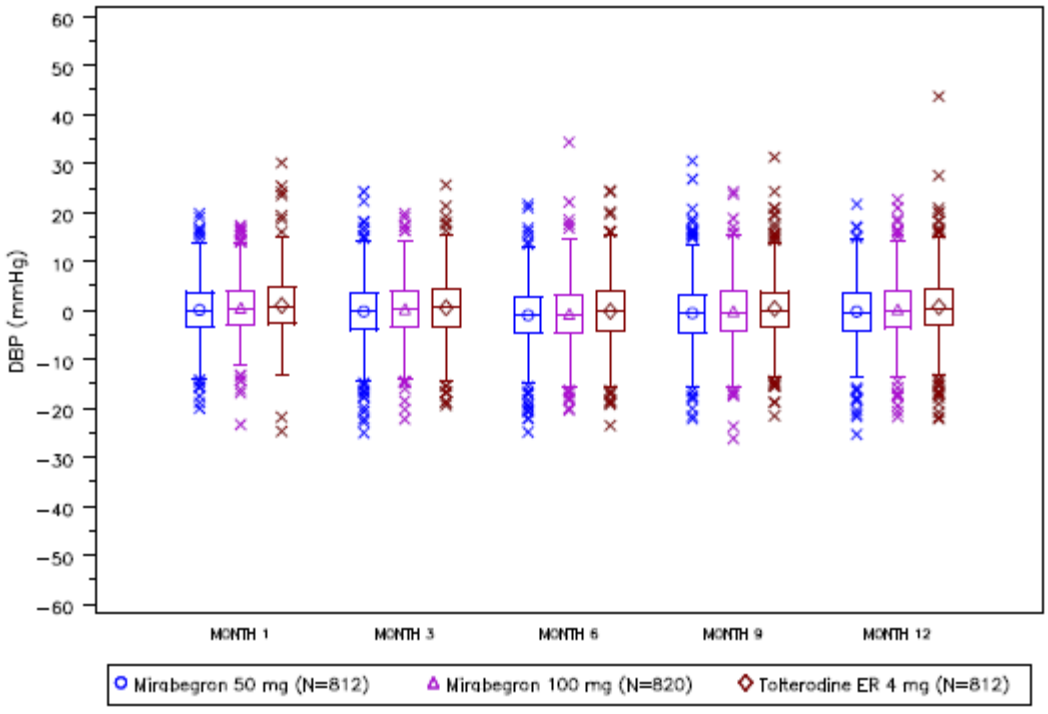
Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
DBP: diastolic blood pressure; SBP: systolic blood pressure.

Appendix 2, Figure 21 Box Plots of Change from Baseline in PM SBP/DBP Values at Each Visit, EU/NA Long-term Controlled Population

(A) SBP (mm Hg)



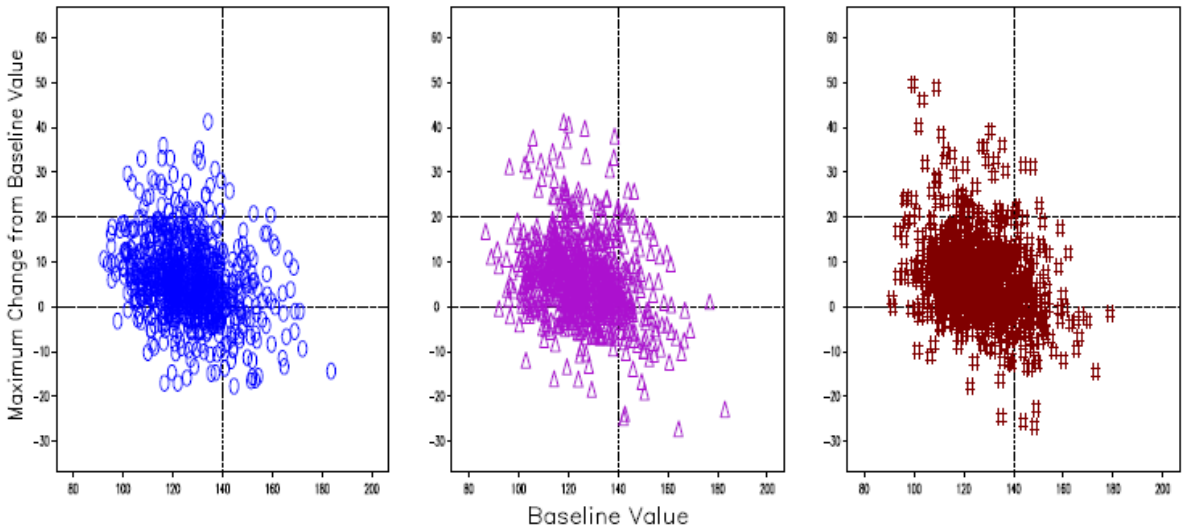
(B) DBP (mm Hg)



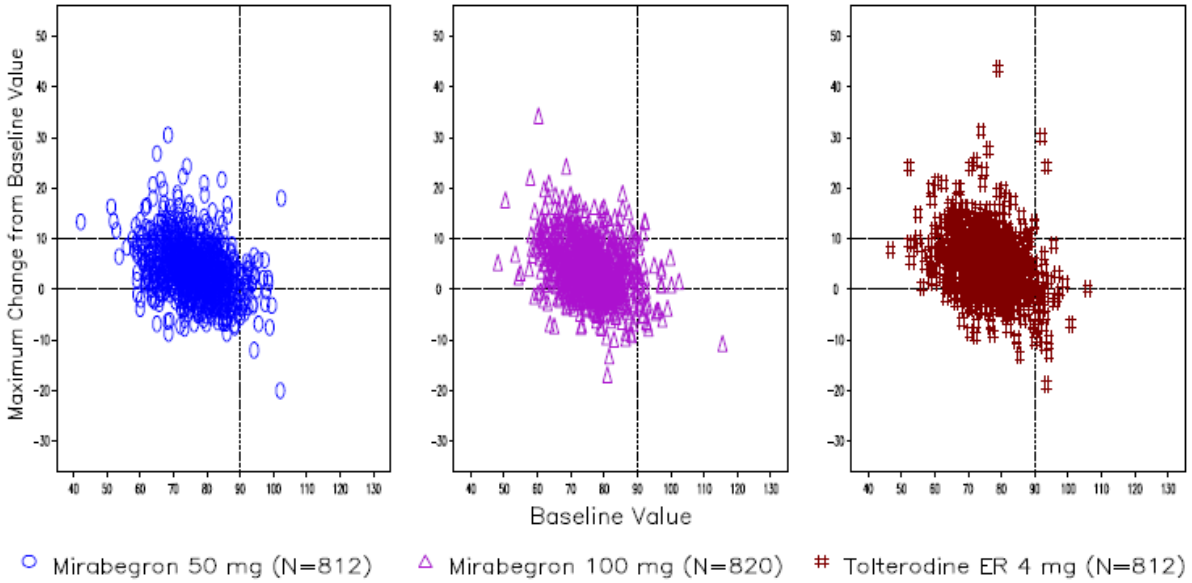
Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]). DBP: diastolic blood pressure; SBP: systolic blood pressure.

Appendix 2, Figure 22 Scatterplots of Maximum Change from Baseline Values Versus Baseline Values in PM SBP/DBP, EU/NA OAB Long-term Controlled Population

(A) SBP (mm Hg)

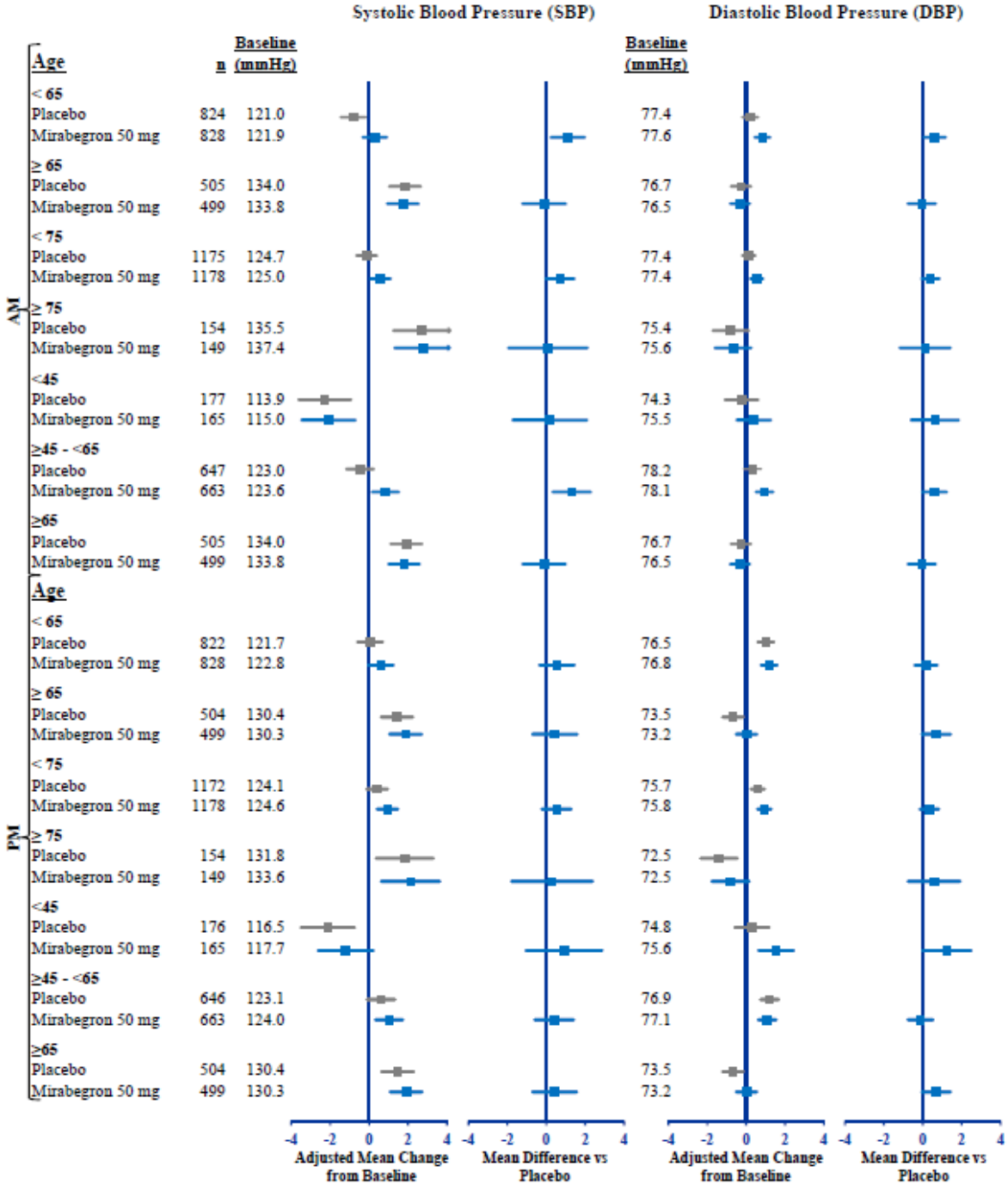


(B) DBP (mm Hg)



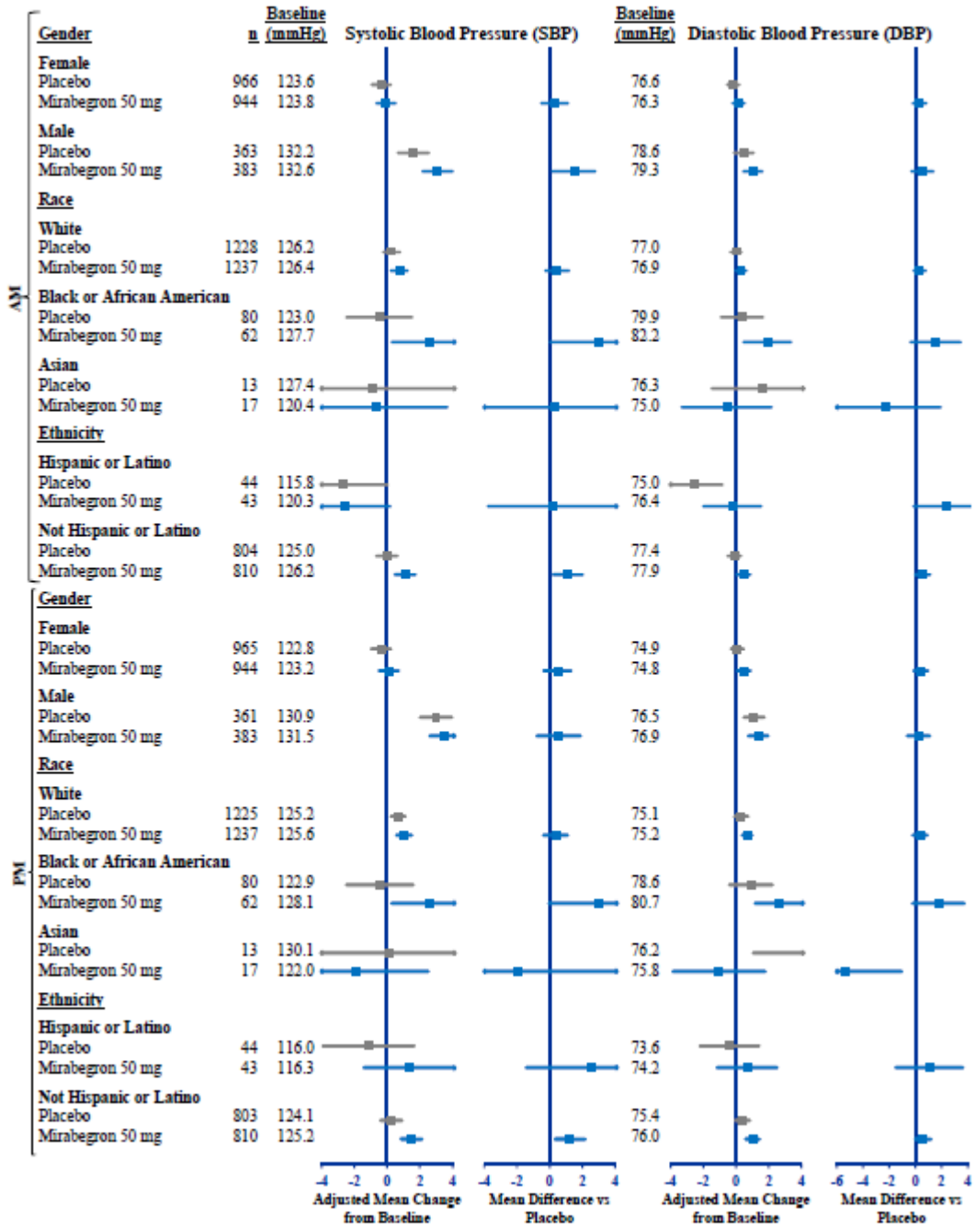
Study included: 178-CL-049.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
DBP: diastolic blood pressure; SBP: systolic blood pressure.

Appendix 2, Figure 23 Change from Baseline to Final Visit for SBP/DBP by Age, EU/NA OAB 12-week Phase 3 Population



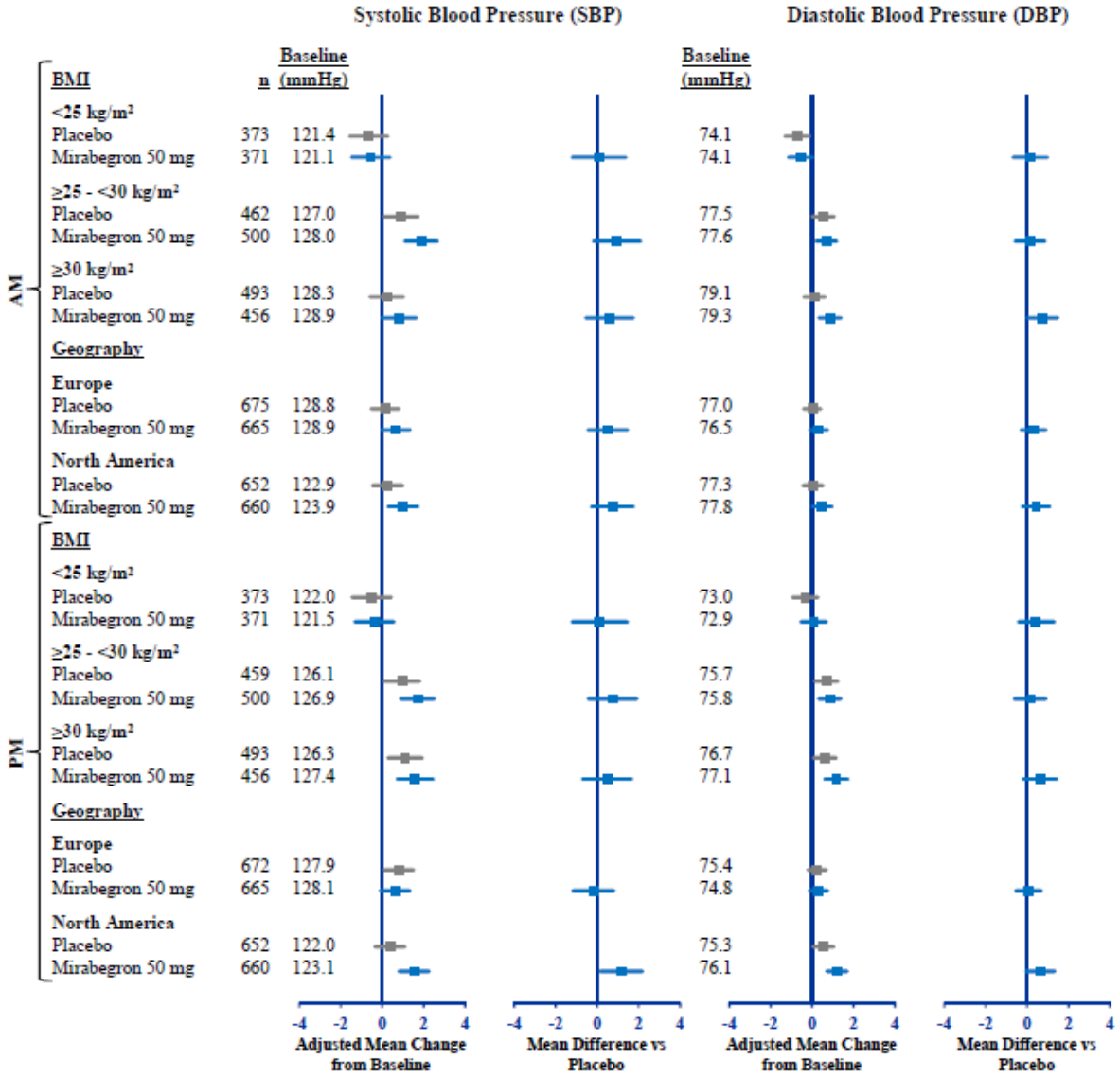
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Age is presented in years. Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 2, Figure 24 Change from Baseline to Final Visit for SBP/DBP by Demographics, EU/NA OAB 12-week Phase 3 Population



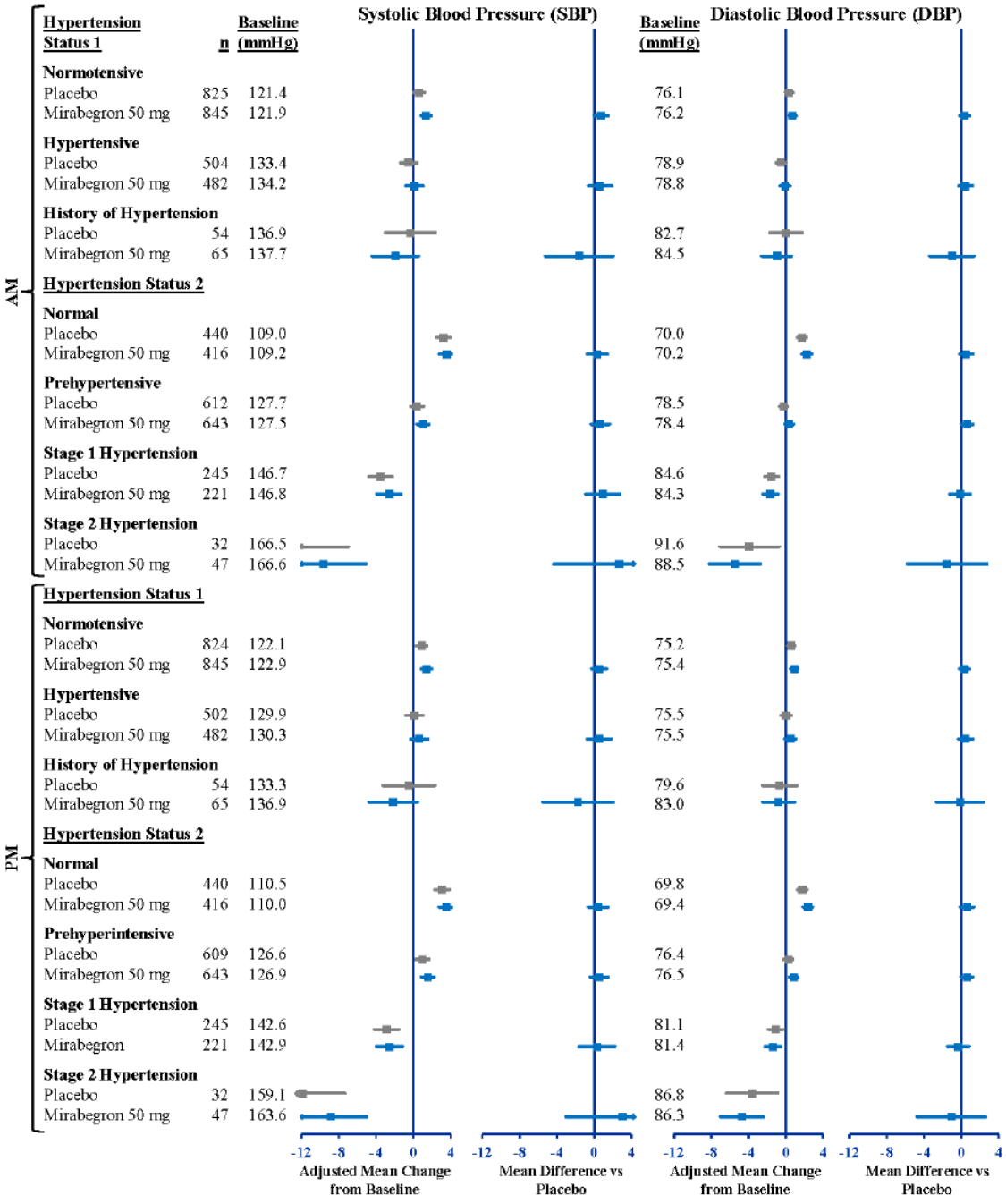
Studies included: 178-CL-046, 178-CL-047 and 178-CL-074. All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]). Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo. Pooled subpopulation analysis results for race and ethnicity are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. Pooled subpopulation analysis results for gender are from an ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, and treatment by gender interaction as fixed factors and baseline as a covariate. ANCOVA: analysis of covariance; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 2, Figure 25 Change from Baseline to Final Visit for SBP/DBP by BMI and Geographical Location, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results for BMI are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate. For each geographical region, a seperate ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, and study as fixed factors and baseline as a covariate was performed.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

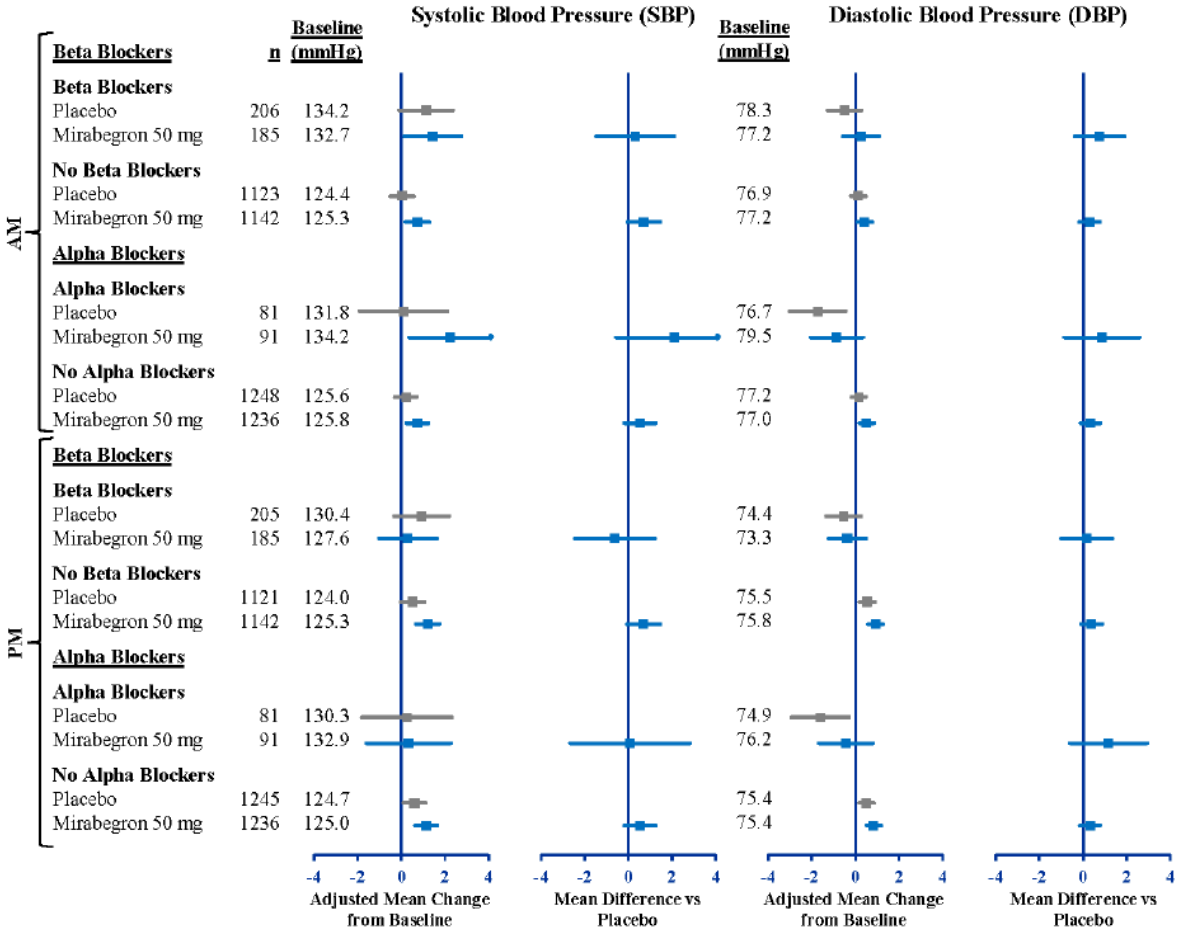
Appendix 2, Figure 26 Change from Baseline to Final Visit for SBP/DBP by Baseline Hypertension Status, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
For each hypertensive status 1 and hypertensive status 2 category, a seperate ANCOVA model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, and study as fixed factors and baseline as a covariate was performed.
Baseline hypertension status 1 and past history of hypertension are based on medical history and use of concomitant anti-hypertensive medication. The hypertensive population was defined as any patient who had a medical history of hypertension and received concurrent antihypertensive treatment at the time of the screening visit.
Footnotes continued on next page.

The normotensive population was defined as any patient who did not meet the definition of hypertensive.
The past history of hypertension population was defined as any patient who had a medical history of hypertension and did not receive concurrent antihypertensive treatment at the time of the screening visit. A patient included in the past history of hypertension population was also included in the normotensive population.
Baseline hypertension status 2 is based on baseline diary SBP/DBP measurements: Normal: SBP < 120 mmHg and DBP < 80 mmHg, Pre-Hypertension: SBP 120 to 139 mmHg or DBP 80 to 89 mmHg, Stage 1 Hypertension: SBP 140 to 159 mmHg or DBP 90 to 99 mmHg and Stage 2 Hypertension: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 2, Figure 27 Change from Baseline to Final Visit for SBP/DBP by Baseline Medication Use, EU/NA OAB 12-week Phase 3 Population



Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Horizontal bars represent 95% CIs for the adjusted mean change from baseline or the adjusted mean difference vs placebo.
Pooled subpopulation analysis results are from an analysis of covariance (ANCOVA) model with treatment group (placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg), gender, study, subpopulation, and treatment by subpopulation interaction as fixed factors and baseline as a covariate.
ANCOVA: analysis of covariance; DBP: diastolic blood pressure; OAB: overactive bladder; SBP: systolic blood pressure.

Appendix 3 Cardiovascular Results in Phase 1 Studies

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1 INTRODUCTION

Of the 29 phase 1 studies conducted in Europe, the US or Japan, 3 studies are best representative for evaluating changes in vital sign parameters in healthy volunteers: Study 178-CL-077, Study 178-CL-081 and Study 178-CL-072. The rationale for focusing on these 3 studies is:

- Study 178-CL-077 was a large, double-blind, randomized, placebo- and active-controlled, parallel crossover, TQT study in which each active treatment was investigated in a separate group crossed over with placebo. The study evaluated repeated administration of 3 doses of mirabegron (50, 100 and 200 mg) and a single dose of moxifoxacin 400 mg. 352 healthy volunteers were randomized in the study, with equal proportions of male and female volunteers in each dose group. Vital signs were measured at multiple points throughout the study, including baseline (last value prior to dosing on day 1 within each period) and at 3, 6 and 9 hours postdose on day 1, day 5 and day 9. Blood pressure was measured using automated cuffs with the volunteers in supine quiet rest for at least 5 minutes. Blood pressures were obtained with the same cuff size and from the same arm at each collection. A complete description of the collection of ECGs is presented in the clinical study report (CSR) [Study 178-CL-077]. This large clinical pharmacology study evaluated mirabegron 50, 100 and 200 mg (associated with an approximately 8.4- and 6.5-fold increased C_{max} and AUC_{tau} compared with the proposed therapeutic dose of 50 mg) and placebo for 10 days.
- Study 178-CL-081 was a double-blind, randomized, placebo-controlled parallel-group study evaluating 56-day administration of mirabegron 100 mg and placebo on intraocular pressure (IOP). 320 volunteers were randomized in the study and received at least one dose of study drug, including approximately equal proportions of male and female volunteers. Vital signs were measured throughout the study, including baseline (last value prior to dosing on day 1) and at day 10 and day 56, in the morning. Pulse rate and vital signs were measured with the volunteer quietly seated for at least 5 minutes. Blood pressure was measured using automated cuffs. A complete description of the vital sign assessments are presented in the CSR [Study 178-CL-081]. This large clinical pharmacology study evaluated multiple doses of mirabegron 100 mg (associated with an approximately 2.9- and 2.6-fold increased C_{max} and AUC_{tau} compared with the proposed therapeutic dose of 50 mg) and placebo for a duration of 8 weeks.
- Study 178-CL-072 was an open-label, randomized, 2-way crossover study examining 36 young (aged 18 to $\leq$ 45 years) and 39 older (aged $\geq$ 55 years) male and female volunteers, evaluating 3 doses of mirabegron (25, 50 and 100 mg). Vital signs were measured at multiple time points throughout the study, including predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose on day -1 (baseline) and day 6 for time-matched vital sign evaluation. Blood pressure was measured using automated cuffs with the volunteers in supine quiet rest for at least 5 minutes [Study 178-CL-072]. While this study was not blinded or placebo-controlled, the study provides time-matched change from baseline data for mirabegron under steady-state conditions over the dose range of 25 to 100 mg in male and female, young and older volunteers.

2 EVALUATION OF DATA FROM INDIVIDUAL STUDIES

2.1 Study 178-CL-077

Study 178-CL-077 was a large, double-blind, randomized, placebo- and active-controlled, parallel crossover, TQT study in which each active treatment was investigated in a separate group crossed over with placebo. The study evaluated repeated administration of 3 doses of mirabegron (50, 100 and 200 mg) and a single dose of moxifloxacin 400 mg. 352 healthy volunteers (median age 30.0 to 31.0 years across treatment groups) were randomized in the study, with equal proportions of male and female volunteers in each dose group. Vital sign measurements were not time-matched to baseline;

baseline value was the predose value on day 1. Mean changes relative to placebo for pulse rate, SBP and DBP measurements at day 9 in Study 178-CL-077 are presented in [Table 1].

There was a dose-related increase in pulse rate, SBP and DBP following administration of mirabegron with increases in adjusted mean difference vs placebo for change from baseline of 4.0 to 6.3, 4.7 to 9.3 and 9.9 to 15.5 bpm for pulse rate, 2.9 to 4.0, 4.1 to 7.7 and 9.3 to 11.6 mm Hg for SBP and 0.9 to 3.7, 3.0 to 4.8 and 5.1 to 7.1 mm Hg for DBP following mirabegron 50, 100 and 200 mg, respectively, in all volunteers [Table 1]. In general, the greatest increase from baseline was observed 3 to 6 hours following dose administration.

There was a greater increase in pulse rate, SBP and DBP in females compared with males following administration of mirabegron, with increases in adjusted mean difference vs placebo for change from baseline of 4.6 to 7.5, 6.8 to 11.9 and 11.2 to 18.0 bpm for pulse rate, 2.4 to 4.5, 4.1 to 6.4 and 8.2 to 13.2 mm Hg for SBP and 1.2 to 3.4, 2.4 to 5.0 and 4.8 to 7.4 mm Hg for DBP following mirabegron 50, 100 and 200 mg in female volunteers and 2.2 to 5.1, 2.6 to 7.0 and 8.5 to 13.1 bpm for pulse rate, 2.3 to 4.5, 3.8 to 8.9 and 9.4 to 11.7 mm Hg for SBP and 0.3 to 4.0, 1.8 to 4.5 and 5.5 to 7.0 mm Hg for DBP following mirabegron 50, 100 and 200 mg in male volunteers [Table 2]. In general, the greatest increase for males and females from baseline was observed 3 to 6 hours following dose administration.

Table 1 Change from Baseline to Day 9 in Pulse Rate, SBP and DBP, ANCOVA Model, Study 178-CL-077

	Pulse Rate (bpm)			SBP (mm Hg)			DBP (mm Hg)		
	Mirabegron			Mirabegron			Mirabegron		
Time Point	50 mg (n = 84)	100 mg (n = 82)	200 mg (n = 83)	50 mg (n = 84)	100 mg (n = 82)	200 mg (n = 83)	50 mg (n = 84)	100 mg (n = 82)	200 mg (n = 83)
Baseline†									
Mean (SE)	62.7 (0.85)	63.0 (1.00)	59.9 (0.79)	110.6 (1.09)	109.5 (1.13)	110.2 (1.19)	68.3 (0.77)	67.1 (0.77)	67.7 (0.90)
Predose									
Mean difference vs pbo (SE)	4.1 (0.85)	4.7 (0.90)	10.3 (1.04)	3.4 (1.11)	5.8 (1.37)	9.9 (1.40)	1.3 (1.03)	3.5 (1.00)	5.6 (0.73)
95% 2-sided CI‡	(2.43, 5.83)	(2.89, 6.46)	(8.25, 12.40)	(1.21, 5.65)	(3.08, 8.53)	(7.11, 12.71)	(-0.73, 3.38)	(1.48, 5.46)	(4.15, 7.06)
3 hours									
Mean difference vs pbo (SE)	4.3 (0.82)	9.3 (0.88)	11.7 (1.07)	4.0 (1.01)	7.7 (1.03)	11.6 (1.35)	1.6 (0.87)	4.1 (0.99)	6.7 (0.85)
95% 2-sided CI‡	(2.61, 5.90)	(7.51, 11.02)	(9.61, 13.87)	(1.96, 5.98)	(5.64, 9.75)	(8.88, 14.25)	(-0.09, 3.37)	(2.11, 6.07)	(5.03, 8.41)
6 hours									
Mean difference vs pbo (SE)	6.3 (0.97)	7.0 (1.09)	15.5 (0.96)	4.0 (1.20)	4.1 (1.18)	9.3 (1.40)	3.7 (0.87)	3.0 (0.96)	6.1 (0.91)
95% 2-sided CI‡	(4.38, 8.26)	(4.82, 9.14)	(13.60, 17.44)	(1.64, 6.43)	(1.70, 6.40)	(6.48, 12.05)	(1.92, 5.39)	(1.11, 4.92)	(4.34, 7.95)
9 hours									
Mean difference vs pbo (SE)	4.6 (0.88)	7.9 (1.10)	13.2 (1.27)	3.0 (1.03)	5.2 (1.10)	10.0 (1.25)	0.9 (0.92)	3.5 (0.97)	5.1 (0.85)
95% 2-sided CI‡	(2.86, 6.37)	(5.70, 10.08)	(10.66, 15.73)	(0.97, 5.07)	(3.04, 7.41)	(7.52, 12.51)	(-0.92, 2.74)	(1.56, 5.44)	(3.46, 6.84)
24 hours									
Mean difference vs pbo (SE)	4.0 (0.81)	6.4 (0.92)	9.9 (0.74)	2.9 (1.14)	6.9 (0.93)	10.0 (1.17)	1.3 (0.80)	4.8 (0.78)	7.1 (0.90)
95% 2-sided CI‡	(2.37, 5.61)	(4.57, 8.21)	(8.45, 11.41)	(0.68, 5.21)	(5.06, 8.77)	(7.65, 12.32)	(-0.33, 2.88)	(3.23, 6.34)	(5.31, 8.88)

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Model used was an ANCOVA with change from baseline as the response, treatment, sex and period as fixed effects, volunteer as a random effect, and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; pbo: placebo.
† Baseline was defined as the last observation prior to dose in each period.
‡ Treatment effect and CI for the time-matched difference from placebo, baseline adjusted.

Table 2 Change from Baseline to Day 9 in Pulse Rate, SBP and DBP by Gender, ANCOVA Model, Study 178-CL-077

	Pulse Rate (bpm)			SBP (mm Hg)			DBP (mm Hg)		
	Mirabegron			Mirabegron			Mirabegron		
Time Point	**50 mg**	**100 mg**	**200 mg**	**50 mg**	**100 mg**	**200 mg**	**50 mg**	**100 mg**	**200 mg**
Female	**(n = 41)**	**(n = 41)**	**(n = 40)**	**(n = 41)**	**(n = 41)**	**(n = 40)**	**(n = 41)**	**(n = 41)**	**(n = 40)**
Baseline†									
Mean (SE)	65.2 (1.21)	65.9 (1.23)	61.5 (1.20)	106.9 (1.55)	105.3 (1.51)	106.3 (1.31)	65.5 (0.94)	65.4 (1.22)	66.7 (1.16)
Predose									
Mean difference vs pbo (SE) 95% 2-sided CI‡	4.8 (1.16) (2.41, 7.10)	6.8 (1.43) (3.92, 9.70)	11.7 (1.23) (9.24, 14.25)	2.4 (1.71) (-1.04, 5.94)	4.1 (1.80) (0.42, 7.69)	10.8 (2.21) (6.31, 15.30)	0.1 (1.47) (-2.89, 3.06)	2.7 (1.33) (-0.03, 5.37)	5.0 (1.10) (2.73, 7.22)
3 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	4.6 (1.27) (2.02, 7.17)	11.9 (1.07) (9.72, 14.06)	14.9 (1.42) (12.05, 17.81)	4.5 (1.46) (1.56, 7.48)	6.4 (1.12) (4.16, 8.69)	13.2 (1.92) (9.36, 17.13)	2.6 (1.13) (0.34, 4.94)	4.1 (1.32) (1.38, 6.73)	7.4 (1.21) (4.94, 9.86)
6 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	7.5 (1.61) (4.19, 10.72)	8.8 (1.59) (5.53, 11.98)	18.0 (1.29) (15.35, 20.56)	3.6 (1.62) (0.28, 6.84)	4.3 (1.70) (0.85, 7.76)	9.1 (1.61) (5.79, 12.32)	3.4 (1.33) (0.68, 6.08)	4.4 (1.46) (1.41, 7.33)	7.0 (1.40) (4.14, 9.80)
9 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	5.5 (1.12) (3.21, 7.75)	9.3 (1.60) (6.05, 12.51)	16.1 (1.53) (12.98, 19.17)	2.8 (1.31) (0.15, 5.46)	6.3 (1.55) (3.13, 9.41)	10.5 (1.95) (6.53, 14.41)	1.5 (1.23) (-0.98, 4.01)	2.4 (1.32) (-0.23, 5.13)	4.8 (1.23) (2.25, 7.25)
24 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	5.7 (1.37) (2.90, 8.46)	8.2 (1.31) (5.57, 10.89)	11.2 (0.94) (9.31, 13.13)	3.5 (1.26) (0.88, 6.03)	5.3 (1.18) (2.91, 7.68)	8.2 (1.65) (4.85, 11.53)	1.2 (1.16) (-1.20, 3.51)	5.0 (1.29) (2.38, 7.62)	7.0 (1.38) (4.16, 9.75)
Male	**(n = 43)**	**(n = 41)**	**(n = 43)**	**(n = 43)**	**(n = 41)**	**(n = 43)**	**(n = 43)**	**(n = 41)**	**(n = 43)**
Baseline‡									
Mean (SE)	60.3 (1.09)	60.1 (1.47)	58.3 (0.99)	114.0 (1.33)	113.6 (1.44)	113.8 (1.80)	70.9 (1.06)	68.7 (0.90)	68.8 (1.36)
Predose									
Mean difference vs pbo (SE) 95% 2-sided CI‡	3.4 (1.24) (0.89, 5.94)	2.6 (0.99) (0.62, 4.61)	8.8 (1.61) (5.51, 12.00)	4.4 (1.44) (1.52, 7.34)	7.6 (2.03) (3.46, 11.67)	9.4 (1.83) (5.66, 13.06)	2.5 (1.50) (-0.50, 5.55)	4.4 (1.40) (1.60, 7.24)	6.3 (1.00) (4.31, 8.37)
3 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	3.8 (1.09) (1.60, 6.01)	7.0 (1.25) (4.47, 9.52)	8.5 (1.37) (5.69, 11.22)	3.4 (1.43) (0.50, 6.30)	8.9 (1.69) (5.44, 12.30)	9.9 (1.90) (6.09, 13.78)	0.3 (1.28) (-2.29, 2.89)	4.1 (1.52) (1.02, 7.18)	6.2 (1.20) (3.72, 8.58)
6 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	5.1 (1.18) (2.74, 7.50)	5.5 (1.38) (2.68, 8.29)	13.1 (1.36) (10.31, 15.83)	4.5 (1.82) (0.86, 8.23)	3.8 (1.68) (0.44, 7.21)	9.4 (2.34) (4.68, 14.16)	4.0 (1.22) (1.54, 6.46)	1.8 (1.26) (-0.76, 4.32)	5.5 (1.16) (3.15, 7.87)
9 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	3.8 (1.38) (0.99, 6.56)	6.6 (1.49) (3.54, 9.57)	10.1 (1.91) (6.27, 13.97)	3.2 (1.62) (-0.07, 6.50)	4.0 (1.57) (0.79, 7.14)	9.7 (1.63) (6.46, 13.04)	0.3 (1.42) (-2.58, 3.15)	4.4 (1.41) (1.56, 7.27)	5.5 (1.21) (3.08, 7.96)
24 hours									
Mean difference vs pbo (SE) 95% 2-sided CI‡	2.2 (0.89) (0.44, 4.06)	4.7 (1.25) (2.15, 7.22)	8.6 (1.08) (6.41, 10.76)	2.3 (1.87) (-1.51, 6.02)	8.7 (1.42) (5.79, 11.54)	11.7 (1.61) (8.37, 14.95)	1.3 (1.18) (-1.06, 3.71)	4.5 (0.95) (2.55, 6.39)	7.0 (1.14) (4.74, 9.36)

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).

Footnotes continued on next page.

Model used was an ANCOVA with change from baseline as the response, treatment, and period as fixed effects, volunteer as a random effect, and baseline as a covariate.
ANCOVA: analysis of covariance; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; pbo: placebo.
† Baseline was defined as the last observation prior to dose in each period.
‡ Treatment effect and CI for the time-matched difference from placebo, baseline adjusted.

Few volunteers in the mirabegron 50 mg treatment group had changes in pulse rate, SBP or DBP that exceeded PCS criteria, with greater proportions of patients meeting PCS criteria in the mirabegron 100 and 200 mg groups [Table 3].

Table 3 PCS Changes in Pulse Rate, SBP and DBP During Treatment, Study 178-CL-077

Clinically Significant Criterion†, n (%) of Volunteers	Placebo‡	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Moxifloxacin 400 mg
Overall	**n = 339**	**n = 84**	**n = 83**	**n = 86**	**n = 85**
Pulse rate (bpm)					
> 100 bpm and change from baseline > 15 bpm	4 (1.2%)	0	10 (12.0%)	14 (16.3%)	4 (4.7%)
> 100 bpm	4 (1.2%)	0	11 (13.3%)	14 (16.3%)	4 (4.7%)
SBP (mm Hg)					
> 140 and change from baseline > 20 mm Hg	10 (2.9%)	9 (10.7%)	9 (10.8%)	13 (15.1%)	5 (5.9%)
DBP (mm Hg)					
> 90 and Change from baseline > 15 mm Hg	3 (0.9%)	2 (2.4%)	4 (4.8%)	1 (1.2%)	1 (1.2%)
Females	**n = 168**	**n = 41**	**n = 42**	**n = 43**	**n = 42**
Pulse rate (bpm)					
> 100 bpm and change from baseline > 15 bpm	4 (2.4%)	0	8 (19.0%)	10 (23.3%)	4 (9.5%)
> 100 bpm	4 (2.4%)	0	8 (19.0%)	10 (23.3%)	4 (9.5%)
SBP (mm Hg)					
> 140 and change from baseline > 20 mm Hg	1 (0.6%)	3 (7.3%)	0	4 (9.3%)	2 (4.8%)
DBP (mm Hg)					
> 90 and Change from baseline > 15 mm Hg	1 (0.6%)	2 (4.9%)	1 (2.4%)	1 (2.3%)	1 (2.4%)
Males	**n = 171**	**n = 43**	**n = 41**	**n = 43**	**n = 43**
Pulse rate (bpm)					
> 100 bpm and change from baseline > 15 bpm	0	0	2 (4.9%)	4 (9.3%)	0
> 100 bpm	0	0	3 (7.3%)	4 (9.3%)	0
SBP (mm Hg)					
> 140 and change from baseline > 20 mm Hg	9 (5.3%)	6 (14.0%)	9 (22.0%)	9 (20.9%)	3 (7.0%)
DBP (mm Hg)					
> 90 and Change from baseline > 15 mm Hg	2 (1.2%)	0	3 (7.3%)	0	0

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
The denominator was the number of volunteers who had at least one nonmissing value during treatment.
PCS: potentially clinically significant; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.
† For each volunteer, the worst case among all postbaseline measurements was used, i.e., difference between maximum value and baseline value (the last measurement prior to first dose in each treatment period) was used.
‡ Placebo was pooled across all treatment groups.

In the overall population (both female and male volunteers), TEAE related to the SOC of cardiac disorders were higher in the mirabegron 200 mg group (15/86 [17.4%]) compared with the placebo (7/339 [2.1%]), mirabegron 50 mg (5/84 [6.0%]), mirabegron 100 mg (5/83 [6.0%]) and moxifloxacin (4/85 [4.7%]) groups, respectively. Palpitations (based on the PT) was higher in the mirabegron 200 mg (15/86 [17.4%]) compared with placebo (5/339 [1.5%]), mirabegron 50 mg (5/84 [6.0%]), mirabegron 100 mg (5/83 [6.0%]) and moxifloxacin (3/85 [3.5%]) groups, respectively. TEAE of

tachycardia were numerically higher in the mirabegron 100 mg (2/83 [2.4%]) group compared with the mirabegron 200 mg (1/86 [1.2%]) group. TEAE of tachycardia were not reported in the mirabegron 50 mg, moxifloxacin or placebo groups. All TEAE of palpitations and tachycardia were mild in severity.

There were 2 female volunteers (Volunteer No. 178-CL-077, 0885-5421; and Volunteer No. 178-CL-077, 2274-7648) and one male volunteer (Volunteer No. 178-CL-077, 2274-7563) that were permanently discontinued from study drug due to a TEAE of palpitations or tachycardia.

No volunteer in Study 178-CL-077 had cardiovascular SAE or deaths that were adjudicated by the Cardiovascular Adjudication Committee.

2.2 Study 178-CL-081

Study 178-CL-081 was a double-blind, randomized, placebo-controlled parallel-group study evaluating 56-day administration of mirabegron 100 mg and placebo on IOP. 320 volunteers were randomized and took at least one dose of study drug (median age 34.0 years), including approximately equal proportions of male and female volunteers. Mean changes relative to placebo for pulse rate, SBP and DBP measurements at day 10 and at day 56 in Study 178-CL-081 are presented in [Table 4].

There was a mean placebo-adjusted increase from baseline pulse rate of 4.4 and 3.8 bpm, a mean placebo-adjusted increase from baseline SBP of 1.1 and 1.4 mm Hg and a mean placebo-adjusted increase from baseline DBP of 1.1 and 0.7 mm Hg following administration of mirabegron 100 mg at day 10 and day 56, respectively [Table 4].

Table 4 Change from Baseline to Day 10 and Day 56 in Pulse Rate, SBP and DBP, ANCOVA Model, Study 178-CL-081

	Pulse Rate (bpm)	SBP (mm Hg)	DBP (mm Hg)
Parameter	Mirabegron 100 mg	Mirabegron 100 mg	Mirabegron 100 mg
Day 10			
n	158	158	158
Baseline mean (SE)	70.2 (0.88)	123.1 (0.94)	76.0 (0.65)
Mean difference vs placebo (SE)	4.4 (0.84)	1.1 (1.14)	1.1 (0.82)
95% 2-sided CI	(2.7, 6.0)	(-1.1, 3.4)	(-0.5, 2.7)
Day 56			
n	154	154	154
Baseline mean (SE)	69.9 (0.89)	123.0 (0.94)	75.8 (0.66)
Mean difference vs placebo (SE)	3.8 (0.90)	1.4 (1.12)	0.7 (0.77)
95% 2-sided CI	(2.0, 5.5)	(-0.9, 3.6)	(-0.8, 2.2)

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
Model used was an ANCOVA with treatment group as a fixed factor, and baseline as a covariate. Differences in the adjusted means are calculated by subtracting the adjusted mean of placebo from that of the mirabegron treatment group.
ANCOVA: analysis of covariance; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.

A comparative table of the change from baseline for mirabegron 100 mg to day 9 (3 hours postdose) from Study 178-CL-077 and change from baseline to day 10 (2 to 4 hours postdose) from Study 178-CL-081 are presented below in [Table 5]. The volunteers in both Studies 178-CL-077 and 178-CL-081 were of young, healthy volunteers of similar age (median age of approximately 30-34 years). In Study 178-CL-077, volunteers were in the clinic for the entire dosing duration with minimal physical activity whereas in Study 178-CL-081, volunteers were in the clinic for approximately 1 day (overnight) for assessments, but spent the majority of time on study drug in their own environment with no limitations on activity.

Table 5 Pulse Rate, SBP and DBP Mean Placebo-adjusted Change from Baseline, Study 178-CL-077 (Day 9, 3 Hours Postdose) and Study 178-CL-081 (Day 10, 2 to 4 Hours Postdose)

	Pulse Rate (bpm)		SBP (mm Hg)		DBP (mm Hg)	
Parameter	Study 178-CL-077 Mirabegron 100 mg	Study 178-CL-081 Mirabegron 100 mg	Study 178-CL-077 Mirabegron 100 mg	Study 178-CL-081 Mirabegron 100 mg	Study 178-CL-077 Mirabegron 100 mg	Study 178-CL-081 Mirabegron 100 mg
n	82	158	82	158	82	158
Baseline mean (SE)	63.0 (1.00)	70.2 (0.88)	109.5 (1.13)	123.1 (0.94)	67.1 (0.77)	76.0 (0.65)
Mean difference vs placebo (SE)	9.3 (0.88)	4.4 (0.84)	7.7 (1.03)	1.1 (1.14)	4.1 (0.99)	1.1 (0.82)
95% 2-sided CI	(7.51, 11.02)	(2.7, 6.0)	(5.64, 9.75)	(-1.1, 3.4)	(2.11, 6.07)	(-0.5, 2.7)

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).

Model in Study 178-CL-077 was an ANCOVA with change from baseline as the response, treatment, sex and period as fixed effects, volunteer as a random effect, and baseline as a covariate. Model in Study 178-CL-081 was an ANCOVA with treatment group as a fixed factor, and baseline as a covariate.

Differences in the adjusted means are calculated by subtracting the adjusted mean of placebo from that of the mirabegron treatment group.

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

† Baseline was defined as the last observation prior to dose in each period.

Few volunteers in the mirabegron treatment group had changes in pulse rate, SBP or DBP that exceeded PCS criteria, with similar proportions of volunteers meeting PCS criteria in the mirabegron 100 mg and placebo groups [Table 6].

Table 6 PCS Changes in Pulse Rate During Treatment, Study 178-CL-081

Clinically Significant Criterion†, n (%) of Volunteers	Placebo	Mirabegron 100 mg
Overall	n = 159	n = 161
Pulse Rate > 100 bpm and change from baseline > 15 bpm	0/159	0/160
SBP > 140 and change from baseline > 20 mm Hg	1/159 (0.6%)	4/160 (2.5%)
DBP > 90 and Change from baseline > 15 mm Hg	4/159 (2.5%)	0/160

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
† PCS criterion was based on the highest value among all postbaseline measurements.
PCS: potentially clinically significant; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.

In the overall population (both female and male volunteers), the occurrence of TEAE in the SOC of cardiac disorders was 2/159 (1.3%) for the placebo group and 2/161 (1.2%) in the mirabegron 100 mg group. Both TEAE in the mirabegron 100 mg and placebo treatment groups were for the PT of palpitations.

No volunteer in this study permanently discontinued study drug due to a TEAE of palpitations. No volunteers in Study 178-CL-081 had cardiovascular SAE or death that were adjudicated by the Cardiovascular Adjudication Committee.

Overall, the pulse rate, SBP and DBP data from Study 178-CL-081, in which volunteers were exposed to a supratherapeutic dose of mirabegron 100 mg (providing plasma levels up to 3-fold greater than the proposed therapeutic dose of mirabegron 50 mg) for 56 days, support the safety and tolerability of mirabegron 50 mg.

2.3 Study 178-CL-072

Study 178-CL-072 was an open-label, randomized, 2-way crossover study examining young (aged 18 to ≤ 45 years) and older (aged ≥ 55 years) male and female volunteers, evaluating 3 doses of mirabegron (25, 50 and 100 mg). Each subject received 2 of the 3 doses. Time-matched adjusted

mean changes from baseline for pulse rate, SBP and DBP for the entire population with age included as a fixed factor in the ANCOVA model are provided for age cut-off of < 55 years and ≥ 55 years and < 45, ≥ 45 to < 65, and ≥ 65 years. Time-matched adjusted mean changes from baseline for pulse rate, SBP and DBP measurements at day 6 at 6 hours postdose in Study 178-CL-072 are presented by gender and age category in [Table 7].

A dose-dependent increase in supine pulse rate was observed with mirabegron 25, 50 and 100 mg in the entire study population. A maximum time-matched difference from baseline was observed at 6 hours postdose; mean differences from baseline ranged from 2.9 bpm with mirabegron 25 mg to 10.7 bpm with mirabegron 100 mg. Changes in supine SBP were observed with mirabegron 25 and 50 mg (+3.9 mm Hg; 3 hours postdose) whereas a maximum mean increase from baseline in SBP of 7.1 mm Hg was observed with a 100 mg dose at 6 hours postdose. An increase from baseline in mean supine DBP was shown at 6 hours postdose with mirabegron 100 mg (+3.8 mm Hg).

Across the age categories [Table 7], mirabegron demonstrated an increase in supine pulse rate with a dose-dependency in young male and female volunteers (< 45 years). The mean difference from baseline at 6 hours after dosing ranged from 2.2 to 11.9 bpm and from 0.3 to 11.3 bpm in male and female volunteers, respectively [Table 7]. In the older (≥ 45 to < 65 years) and elderly (≥ 65 years) groups, mirabegron 50 mg demonstrated less increase in pulse rate compared with young volunteers. In each age category, female volunteers generally showed a higher pulse rate response to mirabegron compared with male volunteers.

The largest mean difference from baseline in supine SBP across all doses of mirabegron at 6 hours after dosing was observed in young volunteers (9.0 and 9.1 mm Hg in male and female volunteers, respectively). In the older (≥ 45 to < 65 years) and elderly groups (≥ 65 years) SBP tended to increase to a lesser extent compared with young volunteers (≥ 45 to < 65 years: largest mean difference across all doses of 3.8 and 5.8 mm Hg in male and female volunteers, respectively; ≥ 65 years: largest mean difference across all doses of 5.3 and 6.3 mm Hg in male and female volunteers, respectively) and dose-dependency was not present. Across age categories, no discernable differences by gender were observed.

Changes from baseline in DBP were small and inconsistent for mirabegron 25 mg and 50 mg across all age categories [Table 7]. DBP tended to increase with mirabegron 100 mg in each age and gender category.

Table 7 Time-matched Change from Baseline to Day 6 (6 Hours Postdose) in Pulse Rate, SBP and DBP Based on Age and Gender Categories, ANCOVA Model, Study 178-CL-072

	Pulse Rate (bpm)			SBP (mm Hg)			DBP (mm Hg)		
	Mirabegron			Mirabegron			Mirabegron		
Subgroup	**25 mg**	**50 mg**	**100 mg**	**25 mg**	**50 mg**	**100 mg**	**25 mg**	**50 mg**	**100 mg**
< 45 years, Male									
n	11	12	11	11	12	11	11	12	11
Adjusted mean change from BL (SE) †	2.2 (2.46)	7.5 (2.25)	11.9 (2.49)	3.1 (4.16)	1.5 (3.95)	9.0 (4.20)	-2.1 (2.01)	3.3 (1.92)	5.0 (2.02)
95% 2-sided CI	(-2.9, 7.3)	(2.9, 12.2)	(6.7, 17.0)	(-5.5, 11.7)	(-6.6, 9.7)	(0.3, 17.7)	(-6.2, 2.1)	(-0.6, 7.3)	(0.8, 9.2)
< 45 years, Female									
n	11	12	10	11	12	10	11	12	10
Adjusted mean change from BL (SE) †	0.3 (3.03)	10.1 (3.11)	11.3 (3.25)	-3.3 (1.86)	3.0 (1.90)	9.1 (2.01)	-3.5 (2.24)	2.3 (2.29)	2.8 (2.40)
95% 2-sided CI	(-5.9, 6.6)	(3.7, 16.6)	(4.5, 18.0)	(-7.2, 0.5)	(-0.9, 7.0)	(5.0, 13.3)	(-8.1, 1.1)	(-2.4, 7.1)	(-2.2, 7.8)
≥ 45 to < 65 years, Male									
n	10	7	8	10	7	8	10	7	8
Adjusted mean change from BL (SE) †	3.0 (3.06)	2.8 (3.95)	11.2 (3.65)	3.8 (3.06)	2.2 (3.92)	3.8 (3.71)	1.4 (1.86)	-0.4 (2.46)	4.3 (2.26)
95% 2-sided CI	(-3.6, 9.5)	(-5.6, 11.2)	(3.4, 19.0)	(-2.7, 10.3)	(-6.1, 10.6)	(-4.1, 11.7)	(-2.5, 5.4)	(-5.7, 4.8)	(-0.5, 9.2)
≥ 45 to < 65 years, Female									
n	5	6	6	5	6	6	5	6	6
Adjusted mean change from BL (SE) †	6.3 (1.36)	5.1 (1.20)	13.3 (1.27)	2.3 (3.25)	5.8 (2.56)	2.5 (3.06)	0.8 (2.28)	-1.1 (1.95)	5.3 (2.06)
95% 2-sided CI	(3.1, 9.5)	(2.3, 8.0)	(10.3, 16.3)	(-5.4, 9.9)	(-0.3, 11.8)	(-4.7, 9.7)	(-4.6, 6.2)	(-5.8, 3.5)	(0.4, 10.2)
≥ 65 years, Male									
n	4	4	7	4	4	7	4	4	7
Adjusted mean change from BL (SE) †	2.8 (4.08)	5.8 (4.31)	5.4 (2.91)	-9.8 (4.62)	-8.0 (5.18)	5.3 (3.67)	1.1 (3.38)	0.7 (2.95)	1.6 (2.08)
95% 2-sided CI	(-7.2, 12.8)	(-4.8, 16.3)	(-1.8, 12.5)	(-21.1, 1.6)	(-20.7, 4.6)	(-3.7, 14.3)	(-7.1, 9.4)	(-6.5, 8.0)	(-3.5, 6.7)
≥ 65 years, Female									
n	7	5	6	7	5	6	7	5	6
Adjusted mean change from BL (SE) †	4.9 (1.91)	3.4 (2.46)	10.6 (2.20)	1.0 (4.25)	-3.1 (5.49)	6.3 (4.90)	1.6 (3.31)	8.1 (4.29)	6.0 (3.79)
95% 2-sided CI	(0.5, 9.2)	(-2.1, 9.0)	(5.6, 15.6)	(-8.6, 10.6)	(-15.5, 9.3)	(-4.8, 17.3)	(-5.9, 9.1)	(-1.6, 17.8)	(-2.5, 14.6)

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
ANCOVA: analysis of covariance; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; BL: baseline.
† Adjusted changes from baseline were generated from an ANCOVA model with treatment group, sequence and period as fixed factors and baseline as a covariate.

3 SUMMARY OF VITAL SIGNS IN PHASE 1 STUDIES IN HEALTHY VOLUNTEERS

In Study 178-CL-077 (median age 30.0 to 31.0 years across treatment groups), the adjusted mean difference vs placebo for increases from baseline following administration of mirabegron 50 mg on day 9 across all treatment groups were 4.0 to 6.3 bpm for pulse, 2.9 to 4.0 mm Hg for SBP, and 0.9 to 3.7 mm Hg for DBP in the overall population. In general, the greatest increase from baseline was seen 3 to 6 hours following dose administration. The distribution of changes from baseline to day 9 in pulse rate (at the 6-hour time point) and SBP and DBP (at the 3-hour time point) was similar in male and female volunteers receiving mirabegron 50 mg except for an increased distribution for pulse rate change in females. Few volunteers in the mirabegron 50 mg group had changes in pulse rate, SBP, or DBP values that exceeded clinically significant criteria, with greater numbers generally seen in the mirabegron 100 and 200 mg groups.

In Study 178-CL-081 (median age 34.0 years), the mean placebo-adjusted increases from baseline following 56-day administration of mirabegron 100 mg were 3.8 bpm for pulse rate, 1.4 mm Hg for SBP and 0.7 mm Hg for DBP. These measurements were obtained 2 to 4 hours after administration of study drug in the fasted condition.

In Study 178-CL-072, there was a dose-dependent increase in pulse rate in young volunteers (< 45 years) treated with mirabegron 25, 50 and 100 mg; the mean difference from baseline at 6 hours after dosing ranged from 2.2 to 11.9 bpm and from 0.3 to 11.3 bpm in male and female volunteers, respectively. In the older (≥ 45 to < 65 years) and elderly (≥ 65 years) groups, mirabegron 50 mg demonstrated less increase in pulse rate compared with young volunteers. The largest mean difference from baseline in supine SBP at 6 hours after dosing was observed in young volunteers in the mirabegron 100 mg group (9.0 and 9.1 mm Hg in male and female volunteers, respectively). In the older (≥ 45 to < 65 years) and elderly groups (≥ 65 years) SBP tended to increase to a lesser extent compared with young volunteers and dose-dependency was not present. Changes from baseline in DBP were small and inconsistent for mirabegron 25 mg and 50 mg across all age categories. DBP tended to increase with mirabegron 100 mg in each age and gender category.

The changes in pulse, SBP and DBP in the male and female young volunteers in Studies 178-CL-077 and 178-CL-081 and in the younger and older volunteers in Study 178-CL-072 are consistent with beta 1-AR-mediated activity of mirabegron at supratherapeutic doses.

The results of the clinical pharmacology and pharmacology studies support that increases in heart rate and blood pressure following administration of mirabegron are likely to primarily come from beta 1-AR stimulation in the heart and kidney, with subsequent chronotropic stimulation and renin release. Importantly, this beta 1-AR stimulation was principally seen following administration of supratherapeutic doses (with 8.4- and 6.5-fold increased C_{max} and AUC_{tau} compared with a therapeutic 50 mg dose). In contrast to observations at high doses in clinical pharmacology studies, heart rate and blood pressure changes, whether examined as a population mean change or as a categorical change, were small and comparable to tolterodine following administration of mirabegron 50 mg in the OAB patient population.

Heart rate at any moment in time reflects the dynamic balance between the sympathetic and parasymapathetic divisions of the autonomic nervous system. While there is no change in resting heart rate with adult aging, starting from early adulthood, maximal heart rate declines with age at a rate of approximately 0.7 bpm per year in healthy sedentary, recreationally active and endurance exercise-trained adults [Tanaka et al, 2001]. This decrease is linear (r = -0.90). The rate of decline in heart rate is not different between men and women [Tanaka et al, 2001] and stepwise regression analysis of 514 gender-balanced subjects in the study by Tanaka et al

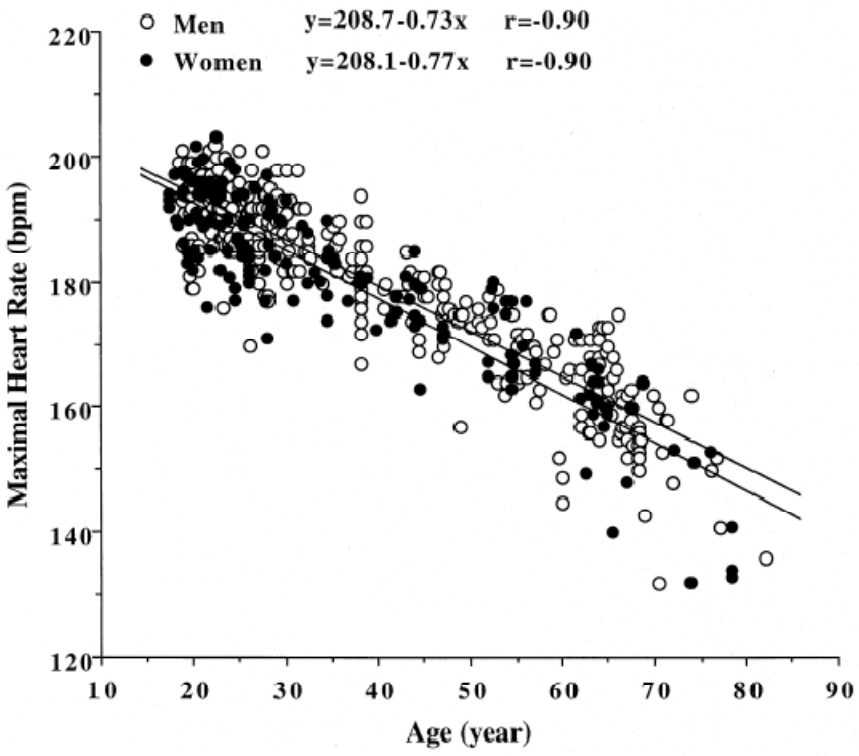
revealed that age alone explained approximately 80% of the individual variance in maximal heart rate.

The OAB studies enrolled a primarily older population, consistent with the disease characteristics, while the phase 1 studies had a largely younger population.

Consistent with across-gender similarity of the beta 1-AR chronotropic effect, pharmacokinetic/pharmacodynamic modeling supports the greater increase in pulse seen in females is substantially accounted for by the approximately 30% to 60% higher mean C_{max} and 40% to 50% higher AUC_{tau} mirabegron blood levels in females compared with males.

The noticeably greater chronotropic effect of mirabegron in young volunteers (median age of approximately 30 years) compared with OAB patients in the phase 2/3 studies (median age of approximately 60 years) is expected based on the heightened sensitivity to adrenergic-mediated increased heart rate in young subjects. This is supported by a marked decline in maximal heart rate with age in healthy adults, as shown in a meta-analysis by Tanaka et al. [Figure 1, Tanaka et al, 2001]. It is noted that the decline at age 60 years and above is even greater than predicted by the regression line [Figure 1].

Figure 1 Relationship Between Maximal Heart Rate (Group Mean Values) and Subject Group Age, Tanaka et al, 2001



bpm: beats per minute.
Source: Tanaka et al, 2001, Figure 1

Additional data support diminished adrenergic-mediated chronotropism with age. Kitzman and Tafet [2009] report that isoproterenol doses increasing heart rate by 25 bpm in healthy young men produce an increase of only 10 bpm in older subjects.

Similarly, Gronich and Abernethy [2009] summarize that "Both beta 1- and beta 2-adrenergic responses decrease with advancing age. The mechanism for this is not well understood; however, a number of postreceptor events have been studied in detail. The decline in beta 1-adrenergic responsiveness results in decreased tachycardic response in response to sympathetic stimulation".

Consistent with this marked, diminished adrenergic responsiveness with age, mirabegron 50 mg in young volunteers (median age of approximately 30 years) caused an adjusted mean difference vs placebo for increase from baseline of 4.0 to 6.3 bpm [Section 2.1; Study 178-CL-077] for pulse rate compared with an adjusted mean difference vs placebo for increase from baseline of approximately 1 bpm in OAB phase 2/3 patients (median age of approximately 60 years). Similarly in a phase 1 study [Study 178-CL-072], the mean increase in pulse rate from baseline to 6 hours postdose was higher in young volunteers treated with mirabegron 50 mg compared with older (≥ 45 to < 65 years) and elderly volunteers (≥ 65 years).

Data from the OAB phase 2/3 patients also suggest a greater effect of mirabegron on pulse rate in younger compared with older patients, although this finding was inconsistent. For the 12-week studies, there were no clear trends observed in adjusted mean difference vs placebo for change from baseline to final visit in pulse rate for patients < 65 years vs ≥ 65 years in any treatment group, while in the long-term study, adjusted mean changes from baseline AM and PM pulse rate were greater in patients < 65 years of age than in patients ≥ 65 years of age. In an additional analysis categorizing patients into < 45 years, ≥ 45 to < 65 years and ≥ 65 years of age, change from baseline and adjusted mean difference vs placebo in change from baseline was generally smaller in older compared with younger patients who received mirabegron, with the greatest change generally seen in the patients < 45 years of age, while in the long-term study, adjusted mean change from baseline for pulse rate was similar in older and younger patients.

Increases in SBP and DBP following the administration of mirabegron in young volunteers, more evident with dose exposures 2- to 7-fold greater than the proposed recommended dose, are consistent with potential beta 1-adrenergic activated renin release. Beta 1-adrenergic mediation of renin release is well described [Osborn et al, 1981]. PRA increases were observed following a single 200 mg dose of mirabegron suggesting that SBP increases at high doses of mirabegron may be due to release of renin.

Unlike heart rate increases, numerous studies support that renin release is greater in males than females, possibly mediated by androgenic/estrogenic hormone levels [Fischer et al, 2002; Kang & Miller, 2002; Reckelhoff, 2001].

Consistent with the increased renin release seen in men, SBP/DBP increases following administration of mirabegron did not show the difference between female and male volunteers that was evident with pulse rate, despite the approximately 30% to 60% higher mean C_{max} and 40% to 50% higher AUC_{tau} mirabegron blood levels in females compared with males.

In Study 178-CL-077, the day 9 adjusted mean difference vs placebo for change from baseline pulse rate was greater in female volunteers than in male volunteers at all time points (predose and 3, 6, 9 and 24 hours) and in all treatment groups, with values in female volunteers 1.5 to 1.7 times higher, consistent with the approximately 30% to 60% higher mean C_{max} and 40% to 50% higher AUC_{tau} mirabegron blood levels in females compared with males [Table 2]. In contrast, the day 9 adjusted mean difference vs placebo for change from baseline in SBP/DBP showed no consistent trend favoring male or female volunteers, with values in female volunteers generally similar to those seen in male volunteers, with the exception of DBP in the mirabegron 50 mg group (where female changes were higher), despite the increased mirabegron exposure [Table 2].

Similarly, although few volunteers in Study 178-CL-077 had changes in pulse rate or SBP/DBP that exceeded clinically significant criteria, greater numbers were generally seen in males

compared with the females for SBP/DBP and greater numbers were generally seen in females compared with males for pulse rate [Table 8].

Table 8 PCS Changes in Pulse Rate, SBP and DBP During Treatment, Study 178-CL-077

Clinically Significant Criterion†, n (%) of Volunteers	Placebo‡	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Moxifloxacin 400 mg
Pulse rate (bpm)					
Females, n	168	41	42	43	42
> 100 bpm and change from baseline > 15 bpm	4 (2.4%)	0	8 (19.0%)	10 (23.3%)	4 (9.5%)
> 100 bpm	4 (2.4%)	0	8 (19.0%)	10 (23.3%)	4 (9.5%)
Males, n	171	43	41	43	43
> 100 bpm and change from baseline > 15 bpm	0	0	2 (4.9%)	4 (9.3%)	0
> 100 bpm	0	0	3 (7.3%)	4 (9.3%)	0
SBP (mm Hg)					
Females, n	168	41	42	43	42
> 140 and change from baseline > 20 mm Hg	1 (0.6%)	3 (7.3%)	0	4 (9.3%)	2 (4.8%)
Males, n	171	43	41	43	43
> 140 and change from baseline > 20 mm Hg	9 (5.3%)	6 (14.0%)	9 (22.0%)	9 (20.9%)	3 (7.0%)
DBP (mm Hg)					
Females, n	168	41	42	43	42
> 90 and Change from baseline > 15 mm Hg	1 (0.6%)	2 (4.9%)	1 (2.4%)	1 (2.3%)	1 (2.4%)
Males, n	171	43	41	43	43
> 90 and Change from baseline > 15 mm Hg	2 (1.2%)	0	3 (7.3%)	0	0

All randomized volunteers who received at least one dose of randomized study drug (Safety Analysis Set [SAF]).
The denominator was the number of volunteers who had at least one nonmissing value during treatment.
PCS: potentially critically significant; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.
† For each volunteer, the worst case among all postbaseline measurements was used, i.e., difference between maximum value and baseline value (the last measurement prior to first dose in each treatment period) was used.
‡ Placebo was pooled across all treatment groups.

This finding is consistent with the reported greater renin levels in males compared with females.

The greater SBP/DBP increases following administration of mirabegron in young volunteers (median age of approximately 30 years) compared with OAB patients in the phase 2/3 studies (median age of approximately 60 years) are expected based on the greater renin release in young subjects. Numerous studies show a decrease in renin activity with age, regardless of volume status [Crane & Harris, 1976; Hall et al, 1989].

Consistent with this renin activity with age, young volunteers (median age of approximately 30 years) receiving mirabegron 50 mg had a mean placebo-adjusted increase from baseline of 2.9 to 4.0 mm Hg for SBP and 0.9 to 3.7 mm Hg for DBP compared with a mean placebo-adjusted increase from baseline of approximately 0.5 to 0.6 mm Hg for SBP and approximately 0.4 mm Hg for DBP in the EU/NA OAB 12-week Phase 3 patients (median age of approximately 60 years).

4 COMPARISON OF PULSE RATE CHANGES WITH MIRABEGRON AND ANTIMUSCARINIC AGENTS

The effects of mirabegron on pulse rate in healthy volunteers were compared with pulse rate changes observed with approved OAB antimuscarinic products. The change from baseline pulse rate following treatment with mirabegron at doses of 50 mg was similar to or less than the change from baseline pulse rate following treatment with antimuscarinics, agents known to increase heart rate [Table 9]. Figure 2 shows the change from baseline in heart rate on days 1 and 3 for fesoterodine 4 and 28 mg from the TQT study.

The change in pulse rate observed in the TQT study for fesoterodine at the supratherapeutic dose (28 mg) was similar to the change observed with mirabegron 200 mg, a supratherapeutic dose with exposure 6.5-times greater than exposure with mirabegron 50 mg. None of the volunteers treated with mirabegron 50 mg met a predefined criterion of increase in pulse rate >100 bpm and > 15 bpm with mirabegron 50 mg whereas the number of volunteers with increases in heart rate > 100 bpm and > 25% with fesoterodine 4 mg, the therapeutic dose, was higher than that observed with placebo-treated volunteers [Table 10].

Table 9 Impact of OAB Treatments on Pulse Rate in Healthy Volunteers in Thorough QT Studies

Drug	Dose (mg)	Increment of Maximum Recommended Dose	Increment of Maximum Recommended Dose Based on Exposure	Mean Increase in Pulse (bpm)
Mirabegron	50	1x	1	4.1
	100	2x	2.6	4.7
	200	4x	6.5	10.3
Fesoterodine	4	0.5x	0.5	3
	28	3.5x	3.5	11
Tolterodine	2 BID	1x	1	2
	4 BID	2x	2	6.3
Trospium (IR)	20 BID	1x	1	9
	100 BID	5x	5†	18
Darifenacin	15	1x	1	3.1
	75	5x	7.8-11.3‡	1.3

IR: immediate release.
† Dose linearity in AUC was observed after single doses of 20, 40 and 60 mg of the IR formulation.
‡ Exposure at 75 mg was 7.8-fold higher compared with 15 mg in CYP2D6 poor metabolizers and 11.3-fold higher in CYP2D6 extensive metabolizers.
Source: Study 178-CL-077; Malhotra, Wood et al, 2010; Malhotra, Glue et al, 2007; Sanctura XL, 2011 ; Clinical Pharmacology and Biopharmaceutics Review Application Number 21-595 (Sanctura, Trospium Chloride), Serra et al, 2005.

Table 10 Changes in Pulse Rate During Treatment with Mirabegron and Fesoterodine in TQT Studies

Clinically Significant Criterion, n (%) of Volunteers	Placebo‡	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Moxifloxacin 400 mg
Study 178-CL-077	**n = 339**	**n = 84**	**n = 83**	**n = 86**	**n = 85**
Pulse rate (bpm)					
> 100 bpm and change from baseline > 15 bpm	4 (1.2%)	0	10 (12.0%)	14 (16.3%)	4 (4.7%)
> 100 bpm	4 (1.2%)	0	11 (13.3%)	14 (16.3%)	4 (4.7%)
	Placebo	**Fesoterodine 4 mg**	**Fesoterodine 28 mg**		**Moxifloxacin 400 mg**
Study SP686	**n = 65**	**n = 64**	**n = 68**		**n = 64**
Heart rate increase >25% and > 100 bpm	11 (16.9%)	25 (39.1%)	52 (76.5%)		15 (23.4%)

Source: Study 178-Cl-077; FDA Medical Review, Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008.

Figure 2 Change from Baseline in Heart Rate on Day 1 and 3 in the Fesoterodine TQT Study SP686

(a) Day 1

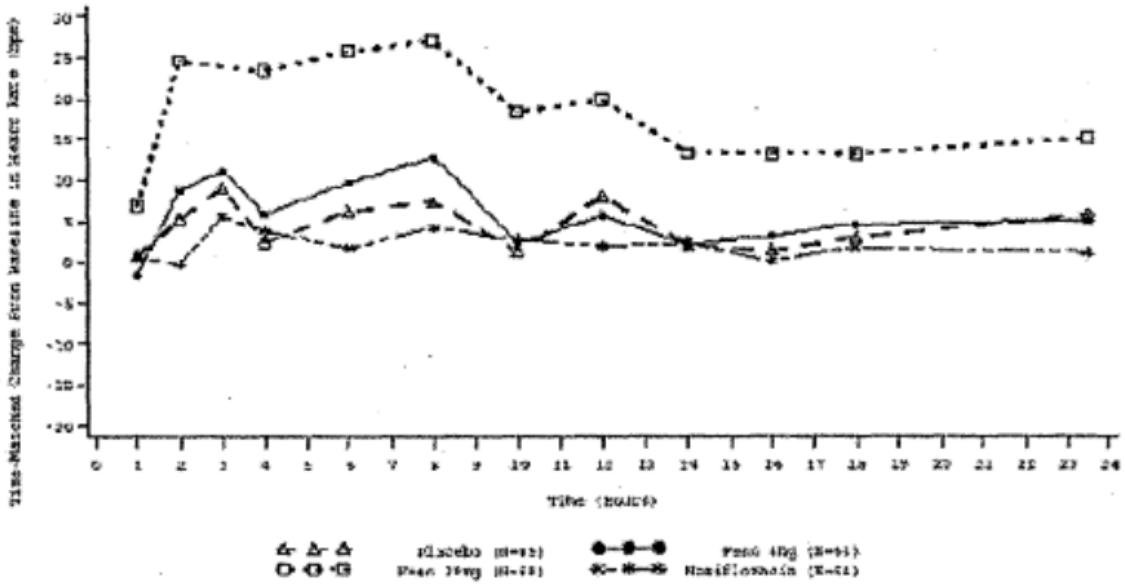
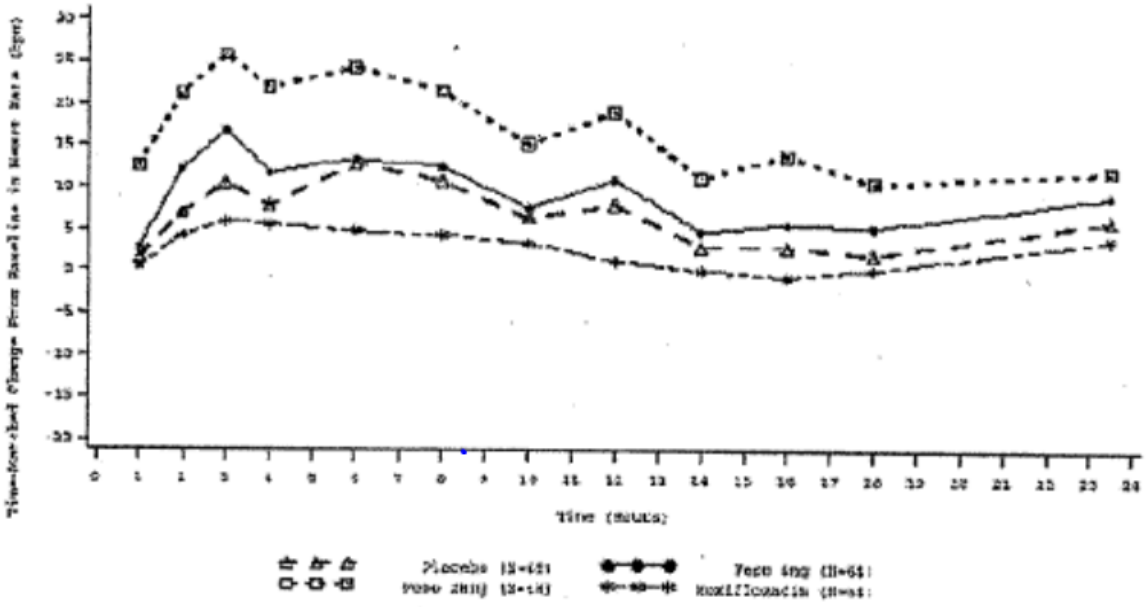


Figure continued on next page.

(b) Day 3



FDA Medical Review, Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008.

5 SUMMARY OF VITAL SIGNS

Female subjects demonstrated a generally higher increase in pulse rate compared with male subjects, consistent with the approximately 40 to 50% increased exposure in females, although this finding was inconsistent across treatment groups and AM/PM measurements in the phase 2/3 studies.

Mirabegron increased pulse rate to a greater extent in young volunteers compared with older OAB patients. Mirabegron also increased pulse rate to a greater extent in younger compared with older OAB patients, although this finding was inconsistent in the phase 2/3 studies.

The highest observed increases in pulse rate occurred in Study 178-CL-077 which could be attributed to the use of young, healthy volunteers as well as the study conditions as evidenced by the lower change in observed in Study 178-CL-081, a study of young, healthy volunteers in an ambulatory setting [Table 5].

Mirabegron increased SBP/DBP to a greater extent in young volunteers compared with older OAB patients and overall data suggest a greater effect of mirabegron on SBP/DBP in younger compared with older OAB patients, although this finding was inconsistent.

Changes in vital signs in young healthy volunteers are larger than observed in OAB population. This is expected in a younger population which has more variability in sympathetic tone than an older, OAB population.

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Appendix 4 Framingham 10-year General Cardiovascular Disease Risk Estimates

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1 INTRODUCTION

At the request of the FDA DRUP and DCRP, a posthoc analysis was performed of the 10-year general cardiovascular disease (CVD) risk estimates using the gender-specific Cox proportional hazard model derived from the Framingham Heart Study [D'Agostino et al, 2008]. The Framingham model is based on the long-term cardiac study of residents of Framingham, Massachusetts.

The CVD risk estimates were derived for the EU/NA OAB 12-week Phase 3 studies (Studies 178-CL-046, 178-CL-047 and 178-CL-074) and the EU/NA Long-term controlled Study 178-CL-049 in the mirabegron development program. These studies included patients from more than 30 countries including the US, Canada, Eastern Europe, Western Europe, South Africa, Australia and New Zealand.

2 METHODOLOGY

The analysis on the 10-year general CVD risk estimates was performed on the safety analysis set from the EU/NA OAB 12-week Phase 3 population (Studies 178-CL-046, 178-CL-047 and 178-CL-074) individually and combined as well as the EU/NA Long-term Controlled Population (Study 178-CL-049).

The risk prediction Cox model described by D'Agostino et al includes the following variables: gender, age, total cholesterol, HDL, systolic blood pressure, treatment of hypertension, smoking status, and diabetes status.

The 10-year general CVD risk estimates were derived using data collected in the phase 3 EU/NA mirabegron studies including gender, age, systolic blood pressure (SBP), treatment of hypertension and diabetes status. The 10-year general CVD risk estimates were derived 3 times for each patient based on using the mean AM/PM SBP value, the mean AM SBP value and the mean PM SBP value. The mean AM SBP and mean PM SBP values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 vial sign diary days within each study [See Section 5.6.1.2 of the Briefing Document]. The mean AM/PM SBP value for SBP was the average of the mean AM and the mean PM SBP value from the patient's vital sign diary.

Total cholesterol, HDL cholesterol and smoking status were not collected in the EU/NA phase 3 mirabegron studies. Therefore, the following information was utilized to assign values for these parameters to each patient.

The mean total cholesterol value and mean HDL cholesterol value by age and gender based on the National Health and Nutrition Examination Surveys (NHANES) [Carroll et al, 2005] were used for each patient. The mean total cholesterol values and mean HDL cholesterol values from NHANES are presented by age and gender in Table 1.

Table 1 Mean Total Cholesterol Value and Mean HDL Cholesterol Value by Age and Gender Based on the National Health and Nutrition Examination Surveys (NHANES)

	Total Cholesterol (mg/dL) Mean (SD)		HDL Cholesterol (mg/dL) Mean (SD)	
Age Group (years)	Male	Female	Male	Female
≥18 to < 30 †	183 (1.9)	183 (1.3)	45.3 (0.47)	53.0 (0.60)
≥30 to < 40	200 (1.5)	194 (1.5)	45.1 (0.52)	54.7 (0.55)
≥40 to < 50	212 (2.9)	203 (1.6)	46.1 (0.59)	55.9 (0.86)
≥50 to < 60	215 (2.2)	216 (1.6)	46.2 (0.65)	58.5 (0.98)
≥60 to < 70	207 (1.7)	223 (1.5)	46.8 (0.82)	58.3 (0.83)
≥70	196 (2.1)	220 (1.3)	46.8 (0.76)	59.0 (0.62)

Footnotes appear on next page.

HDL: high-density lipoprotein; NHANES: National Health and Nutrition Examination Surveys; SD: standard deviation.

† Patients between the ages of 18 and 19 years were assigned the mean total cholesterol value and mean HDL cholesterol value for the age group of ≥ 20 to < 30 years by gender based on NHANES.

Smoking status was based on the age- and gender-specific average percent of current cigarette smokers in 2010 for the United States from the National Health Interview Survey (NHIS) [Center for Disease Control, 2011] as presented in Table 2. The smoking status for each patient was assigned the value of the proportion of the US population who are current cigarette smokers by age and gender based on the NHIS results. For example, a 61-year-old male would be assigned a smoking status value of 0.232.

Table 2 Age- and Gender-Specific Average Percent of Current Cigarette Smokers in 2010 for the United States from the National Health Interview Survey (NHIS)

Year	Age Group (years)	% of Current Cigarette Smoking	
		Male	Female
2010	≥ 18 to < 25	22.8	17.4
	≥ 25 to < 45	24.3	19.8
	≥ 45 to < 65	23.2	19.1
	≥ 65	9.7	9.3

Analyses are presented for Studies 178-CL-046, 178-CL-047, 178-CL-074, the EU/NA OAB 12-week Phase 3 population and the EU/NA Long-term Controlled population. Each of the analyses were performed separately based on the mean SBP values (mean of the AM and PM values, mean AM value, and mean PM value) at baseline and the Final Visit.

The 10-year general CVD risk estimates based on the Cox model were summarized by treatment group at baseline, Final Visit, and the difference between Final Visit and baseline using descriptive statistics. In addition, the number and percent of patients with a ≥5% and ≥10% increase from baseline to Final Visit in the 10-year general CVD risk estimate were summarized by treatment group.

3 RESULTS

3.1 10-year General CVD Risk Estimates

The 10-year general CVD risk estimates are presented based on using the mean SBP value in Table 3 (Mean AM/PM SBP Values), Table 4 (Mean AM SBP Values) and Table 5 (Mean PM SBP Values) and in Figure 1.

3.2 Categorical Changes in 10-Year General CVD Risk Estimates

The number and percent of patients with a ≥5% and ≥10% increase from baseline to Final Visit in the 10-year general CVD risk estimates are presented in Table 6 (Mean AM/PM SBP Values), Table 7 (Mean AM SBP Values), and Table 8 (Mean PM SBP Values).

Table 3 10-year General Cardiovascular Disease Risk Estimates Using Mean AM/PM SBP Values

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-046						
n	478		471	477	948	475
Baseline						
Mean (SD)	13.1 (9.0)		12.7 (9.0)	12.9 (9.4)	12.8 (9.2)	13.1 (9.1)
Median	11.3		10.3	10.0	10.1	10.6
95% 2-sided CI	12.3, 13.9		11.9, 13.5	12.0, 13.7	12.2, 13.4	12.3, 13.9
Final Visit						
Mean (SD)	13.4 (9.1)		13.0 (9.1)	13.3 (9.5)	13.1 (9.3)	13.4 (9.2)
Median	11.8		10.4	10.6	10.5	10.8
95% 2-sided CI	12.6, 14.2		12.2, 13.8	12.5, 14.2	12.6, 13.7	12.5, 14.2
Change from Baseline to Final Visit						
Mean (SD)	0.4 (2.1)		0.3 (2.0)	0.4 (1.8)	0.4 (1.9)	0.3 (2.1)
Median	0.1		0.1	0.2	0.1	0.0
95% 2-sided CI	0.2, 0.5		0.1, 0.5	0.3, 0.6	0.2, 0.5	0.1, 0.5
Study 178-CL-047						
n	431		425	412	837	
Baseline						
Mean (SD)	11.6 (9.0)		11.8 (9.1)	12.5 (9.3)	12.1 (9.2)	
Median	8.8		8.8	9.5	9.2	
95% 2-sided CI	10.7, 12.4		11.0, 21.7	11.6, 13.3	11.5, 12.8	
Final Visit						
Mean (SD)	11.7 (8.9)		12.3 (9.3)	12.8 (9.4)	12.6 (9.4)	
Median	9.3		9.6	9.7	9.6	
95% 2-sided CI	10.9, 12.6		11.4, 13.2	11.9, 13.7	11.9, 13.2	
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.1)		0.5 (2.3)	0.4 (2.2)	0.4 (2.2)	
Median	0.0		0.1	0.1	0.1	
95% 2-sided CI	-0.0, 0.4		0.3, 0.7	0.1, 0.6	0.3, 0.6	

Table continued on next page

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-074						
n	415	409	426		835	
Baseline						
Mean (SD)	13.2 (9.8)	13.9 (9.6)	14.6 (9.7)		14.3 (9.6)	
Median	10.3	11.5	12.3		11.9	
95% 2-sided CI	12.3, 14.2	13.0, 14.8	13.7, 15.5		13.6, 14.9	
Final Visit						
Mean (SD)	13.3 (9.9)	14.0 (9.5)	15.0 (9.7)		14.5 (9.6)	
Median	10.5	11.7	13.1		12.3	
95% 2-sided CI	12.4, 14.3	13.1, 14.9	14.1, 15.9		13.8, 15.1	
Change from Baseline to Final Visit						
Mean (SD)	0.1 (1.9)	0.1 (2.1)	0.4 (2.3)		0.2 (2.2)	
Median	0.0	0.0	0.1		0.0	
95% 2-sided CI	-0.1, 0.3	-0.1, 0.3	0.2, 0.6		0.1, 0.4	
EU/NA OAB 12-week Phase 3 Population						
n	1324	409	1322	889	2620	475
Baseline						
Mean (SD)	12.6 (9.3)	13.9 (9.6)	13.0 (9.3)	12.7 (9.3)	13.0 (9.4)	13.1 (9.1)
Median	9.9	11.5	10.6	9.8	10.5	10.6
95% 2-sided CI	12.1, 13.1	13.0, 14.8	12.5, 13.5	12.1, 13.3	12.7, 13.4	12.3, 13.9
Final Visit						
Mean (SD)	12.8 (9.3)	14.0 (9.5)	13.4 (9.4)	13.1 (9.5)	13.4 (9.4)	13.4 (9.2)
Median	10.4	11.7	10.9	10.1	10.7	10.8
95% 2-sided CI	12.3, 13.3	13.1, 14.9	12.9, 13.9	12.5, 13.7	13.0, 13.8	12.5, 14.2
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.0)	0.1 (2.1)	0.4 (2.2)	0.4 (2.0)	0.3 (2.1)	0.3 (2.1)
Median	0.0	0.0	0.1	0.1	0.1	0.0
95% 2-sided CI	0.1, 0.3	-0.1, 0.3	0.3, 0.5	0.3, 0.5	0.3, 0.4	0.1, 0.5

Table continued on next page

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
EU/NA Long-term Controlled Population (Study 178-CL-049)						
n			788	800	1588	789
Baseline						
Mean (SD)			12.8 (9.0)	12.6 (8.8)	12.7 (8.9)	12.7 (8.9)
Median			10.5	10.1	10.3	10.3
95% 2-sided CI			12.2, 13.4	12.0, 13.2	12.3, 13.1	12.1, 13.3
Final Visit						
Mean (SD)			13.2 (9.0)	13.2 (9.0)	13.2 (9.0)	13.1 (9.0)
Median			11.0	10.6	10.8	10.6
95% 2-sided CI			12.6, 13.8	12.5, 13.8	12.7, 13.6	12.5, 13.8
Change from Baseline to Final Visit						
Mean (SD)			0.4 (2.3)	0.6 (2.3)	0.5 (2.3)	0.4 (2.2)
Median			0.1	0.2	0.2	0.1
95% 2-sided CI			0.2, 0.5	0.4, 0.7	0.4, 0.6	0.2, 0.6

For the mean AM SBP and mean PM SBP, values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days. The mean AM/PM SBP value is the average of the mean AM SBP and mean PM SBP values.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

Only patients with CVD risk estimates at both baseline and final visit were included in the analysis.

Table 4 10-year General Cardiovascular Disease Risk Estimates Using Mean AM SBP Values

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-046						
n	478		471	477	948	475
Baseline						
Mean (SD)	13.3 (9.3)		12.7 (9.1)	13.0 (9.5)	12.8 (9.3)	13.2 (9.3)
Median	11.1		10.4	10.1	10.1	10.8
95% 2-sided CI	12.4, 14.1		11.9, 13.5	12.1, 13.8	12.3, 13.4	12.4, 14.1
Final Visit						
Mean (SD)	13.5 (9.3)		13.0 (9.1)	13.3 (9.6)	13.2 (9.4)	13.5 (9.3)
Median	11.7		10.4	10.8	10.6	11.1
95% 2-sided CI	12.7, 14.4		12.2, 13.9	12.4, 14.2	12.6, 13.8	12.6, 14.3
Change from Baseline to Final Visit						
Mean (SD)	0.3 (2.2)		0.3 (2.3)	0.3 (2.0)	0.3 (2.1)	0.2 (2.3)
Median	0.1		0.1	0.1	0.1	0.0
95% 2-sided CI	0.1, 0.5		0.1, 0.5	0.2, 0.5	0.2, 0.5	0.0, 0.4
Study 178-CL-047						
n	431		425	412	837	
Baseline						
Mean (SD)	11.8 (9.2)		11.9 (9.3)	12.7 (9.4)	12.3 (9.4)	
Median	8.9		9.1	9.8	9.4	
95% 2-sided CI	10.9, 12.6		11.1, 12.8	11.8, 13.6	11.7, 13.0	
Final Visit						
Mean (SD)	12.0 (9.1)		12.4 (9.4)	12.9 (9.5)	12.6 (9.4)	
Median	9.2		9.9	9.7	9.7	
95% 2-sided CI	11.1, 12.8		11.5, 13.3	12.0, 13.8	12.0, 13.3	
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.5)		0.5 (2.5)	0.2 (2.5)	0.3 (2.5)	
Median	0.0		0.0	0.0	0.0	
95% 2-sided CI	-0.0, 0.4		0.2, 0.7	-0.1, 0.4	0.2, 0.5	

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	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-074						
n	415	409	426		835	
Baseline						
Mean (SD)	13.3 (9.9)	13.9 (9.7)	14.8 (9.9)		14.4 (9.8)	
Median	10.2	11.6	12.8		12.0	
95% 2-sided CI	12.3, 14.2	13.0, 14.9	13.9, 15.7		13.7, 15.0	
Final Visit						
Mean (SD)	13.4 (10.0)	14.0 (9.6)	15.1 (9.9)		14.6 (9.7)	
Median	10.7	11.5	13.6		12.2	
95% 2-sided CI	12.4, 14.3	13.1, 15.0	14.2, 16.1		13.9, 15.2	
Change from Baseline to Final Visit						
Mean (SD)	0.1 (2.0)	0.1 (2.3)	0.3 (2.6)		0.2 (2.4)	
Median	0.0	0.0	0.0		0.0	
95% 2-sided CI	-0.1, 0.3	-0.1, 0.3	0.1, 0.6		0.0, 0.4	
EU/NA OAB 12-week Phase 3 Population						
n	1324	409	1322	889	2620	475
Baseline						
Mean (SD)	12.8 (9.5)	13.9 (9.7)	13.1 (9.5)	12.9 (9.5)	13.2 (9.5)	13.2 (9.3)
Median	10.0	11.6	10.7	9.9	10.5	10.8
95% 2-sided CI	12.3, 13.3	13.0, 14.9	12.6, 13.6	12.2, 13.5	12.8, 13.5	12.4, 14.1
Final Visit						
Mean (SD)	13.0 (9.5)	14.0 (9.6)	13.5 (9.5)	13.1 (9.5)	13.5 (9.5)	13.5 (9.3)
Median	10.4	11.5	10.8	10.3	10.8	11.1
95% 2-sided CI	12.5, 13.5	13.1, 15.0	13.0, 14.0	12.5, 13.7	13.1, 13.8	12.6, 14.3
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.3)	0.1 (2.3)	0.4 (2.4)	0.3 (2.3)	0.3 (2.4)	0.2 (2.3)
Median	0.0	0.0	0.0	0.1	0.0	0.0
95% 2-sided CI	0.1, 0.3	-0.1, 0.3	0.2, 0.5	0.1, 0.4	0.2, 0.4	0.0, 0.4

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	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
EU/NA Long-term Controlled Population (Study 178-CL-049)						
n			788	800	1588	789
Baseline						
Mean (SD)			12.9 (9.1)	12.7 (9.0)	12.8 (9.1)	12.8 (9.1)
Median			10.9	10.1	10.5	10.2
95% 2-sided CI			12.3, 13.5	12.0, 13.3	12.3, 13.2	12.2, 13.5
Final Visit						
Mean (SD)			13.3 (9.2)	13.2 (9.1)	13.3 (9.1)	13.2 (9.2)
Median			11.1	10.6	10.8	10.4
95% 2-sided CI			12.7, 14.0	12.6, 13.9	12.8, 13.7	12.5, 13.8
Change from Baseline to Final Visit						
Mean (SD)			0.4 (2.6)	0.6 (2.3)	0.5 (2.5)	0.3 (2.5)
Median			0.1	0.3	0.2	0.1
95% 2-sided CI			0.3, 0.6	0.4, 0.7	0.4, 0.6	0.2, 0.5

For the mean AM SBP and mean PM SBP, values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

Only patients with CVD risk estimates at both baseline and final visit were included in the analysis.

Table 5 10-year General Cardiovascular Disease Risk Estimates Using Mean PM SBP Values

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-046						
n	476		471	476	947	475
Baseline						
Mean (SD)	12.8 (8.8)		12.6 (9.0)	12.8 (9.2)	12.7 (9.1)	12.9 (8.9)
Median	10.5		10.4	10.3	10.3	10.6
95% 2-sided CI	12.0, 13.6		11.8, 13.5	11.9, 13.6	12.1, 13.3	12.1, 13.7
Final Visit						
Mean (SD)	13.3 (8.9)		12.9 (9.0)	13.3 (9.4)	13.1 (9.2)	13.2 (9.1)
Median	11.8		10.4	10.6	10.5	10.9
95% 2-sided CI	12.5, 14.1		12.1, 13.7	12.4, 14.1	12.5, 13.7	12.4, 14.0
Change from Baseline to Final Visit						
Mean (SD)	0.4 (2.4)		0.3 (2.3)	0.5 (2.2)	0.4 (2.3)	0.3 (2.5)
Median	0.1		0.1	0.2	0.1	0.0
95% 2-sided CI	0.2, 0.7		0.1, 0.5	0.3, 0.7	0.3, 0.5	0.1, 0.6
Study 178-CL-047						
n	431		425	412	837	
Baseline						
Mean (SD)	11.3 (8.8)		11.7 (9.0)	12.2 (9.1)	11.9 (9.1)	
Median	8.5		8.7	8.9	8.9	
95% 2-sided CI	10.5, 12.2		10.9, 12.6	11.3, 13.1	11.3, 12.6	
Final Visit						
Mean (SD)	11.5 (8.8)		12.2 (9.2)	12.7 (9.4)	12.5 (9.3)	
Median	8.9		9.6	9.6	9.6	
95% 2-sided CI	10.7, 12.3		11.4, 13.1	11.8, 13.6	11.9, 13.1	
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.3)		0.5 (2.5)	0.6 (2.4)	0.5 (2.5)	
Median	0.0		0.1	0.2	0.1	
95% 2-sided CI	-0.1, 0.4		0.3, 0.8	0.3, 0.8	0.4, 0.7	

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	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-074						
n	414	409	426		835	
Baseline						
Mean (SD)	13.2 (9.8)	13.9 (9.5)	14.4 (9.5)		14.1 (9.5)	
Median	10.1	11.4	11.8		11.6	
95% 2-sided CI	12.3, 14.1	12.9, 14.8	13.5, 15.3		13.5, 14.8	
Final Visit						
Mean (SD)	13.3 (9.8)	13.9 (9.4)	14.8 (9.6)		14.4 (9.5)	
Median	10.2	11.3	12.9		12.0	
95% 2-sided CI	12.4, 14.3	13.0, 14.8	13.9, 15.7		13.7, 15.0	
Change from Baseline to Final Visit						
Mean (SD)	0.1 (2.3)	0.0 (2.4)	0.5 (2.5)		0.2 (2.5)	
Median	0.0	0.0	0.0		0.0	
95% 2-sided CI	-0.1, 0.3	-0.2, 0.3	0.2, 0.7		0.1, 0.4	
EU/NA OAB 12-week Phase 3 Population						
n	1321	409	1322	888	2619	475
Baseline						
Mean (SD)	12.5 (9.1)	13.9 (9.5)	12.9 (9.2)	12.5 (9.2)	12.9 (9.3)	12.9 (8.9)
Median	9.8	11.4	10.3	9.8	10.3	10.6
95% 2-sided CI	12.0, 12.9	12.9, 14.8	12.4, 13.4	11.9, 13.1	12.6, 13.3	12.1, 13.7
Final Visit						
Mean (SD)	12.7 (9.2)	13.9 (9.4)	13.3 (9.3)	13.0 (9.4)	13.3 (9.4)	13.2 (9.1)
Median	10.2	11.3	10.6	10.2	10.6	10.9
95% 2-sided CI	12.2, 13.2	13.0, 14.8	12.8, 13.8	12.4, 13.6	12.9, 13.7	12.4, 14.0
Change from Baseline to Final Visit						
Mean (SD)	0.2 (2.3)	0.0 (2.4)	0.4 (2.4)	0.5 (2.3)	0.4 (2.4)	0.3 (2.5)
Median	0.0	0.0	0.1	0.2	0.1	0.0
95% 2-sided CI	0.1, 0.4	-0.2, 0.3	0.3, 0.6	0.4, 0.7	0.3, 0.5	0.1, 0.6

Table continued on next page

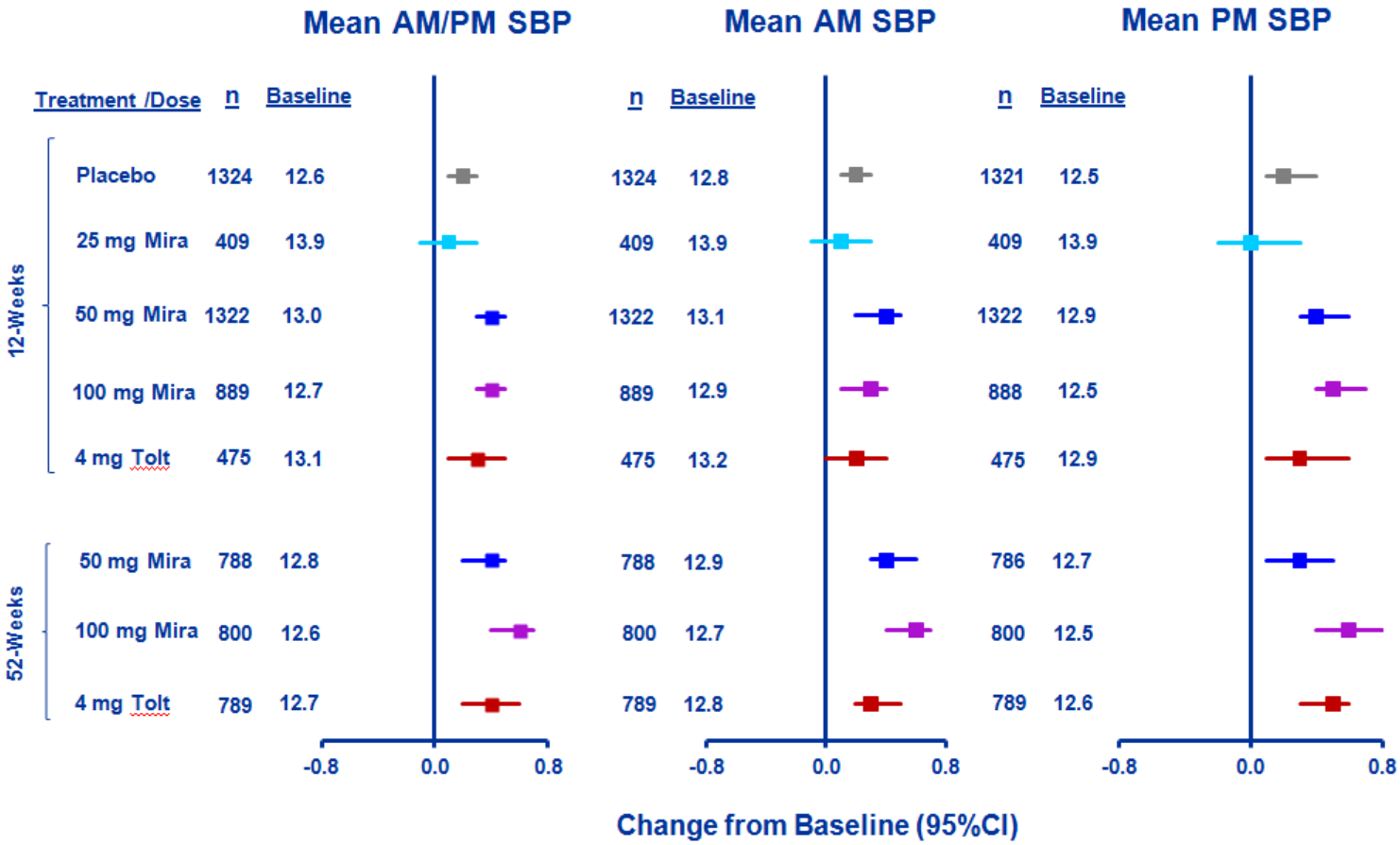
	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
EU/NA Long-term Controlled Population (Study 178-CL-049)						
n			786	800	1586	789
Baseline						
Mean (SD)			12.7 (8.9)	12.5 (8.7)	12.6 (8.8)	12.6 (8.8)
Median			10.5	10.0	10.2	10.3
95% 2-sided CI			12.1, 13.3	11.9, 13.1	12.2, 13.0	12.0, 13.2
Final Visit						
Mean (SD)			13.0 (8.9)	13.1 (8.9)	13.0 (8.9)	13.1 (9.0)
Median			10.8	10.6	10.7	10.4
95% 2-sided CI			12.4, 13.6	12.4, 13.7	12.6, 13.5	12.5, 13.7
Change from Baseline to Final Visit						
Mean (SD)			0.3 (2.5)	0.6 (2.7)	0.4 (2.6)	0.5 (2.5)
Median			0.1	0.2	0.1	0.1
95% 2-sided CI			0.1, 0.5	0.4, 0.8	0.3, 0.6	0.3, 0.6

For the mean AM SBP and mean PM SBP, values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

Only patients with CVD risk estimates at both baseline and final visit were included in the analysis.

Figure 1 10-year General Cardiovascular Disease Risk Estimates Change from Baseline to Final Visit Using Mean SBP Values



12-Weeks is the EU/NA OAB 12-week Phase 3 Population and includes Studies 178-CL-046, 178-CL-047 and 178-CL-074. 52-Weeks is the EU/NA Long-term Controlled Population and includes Study 178-CL-049. Only patients with CVD risk estimates at both baseline and final visit were included in the analysis.

For the mean AM SBP and mean PM SBP, values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days. The mean AM/PM SBP value is the average of the mean AM SBP and mean PM SBP values.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

Table 6 Outliers for Increase from Baseline to Final Visit in 10-year General Cardiovascular Disease Risk Estimates Using Mean AM/PM SBP Values

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-046						
≥5%	15/478 (3.1%)		13/471 (2.8%)	11/477 (2.3%)	24/948 (2.5%)	20/475 (4.2%)
≥10%	1/478 (0.2%)		1/471 (0.2%)	0/477	1/948 (0.1%)	0/475
Study 178-CL-047						
≥5%	9/431 (2.1%)		20/425 (4.7%)	12/412 (2.9%)	32/837 (3.8%)	
≥10%	0/431		1/425 (0.2%)	2/412 (0.5%)	3/837 (0.4%)	
Study 178-CL-074						
≥5%	5/415 (1.2%)	9/409 (2.2%)	18/426 (4.2%)		27/835 (3.2%)	
≥10%	0/415	0/409	2/426 (0.5%)		2/835 (0.2%)	
EU/NA OAB 12-week Phase 3 Population						
≥5%	29/1324 (2.2%)	9/409 (2.2%)	51/1322 (3.9%)	23/889 (2.6%)	83/2620 (3.2%)	20/475 (4.2%)
≥10%	1/1324 (0.1%)	0/409	4/1322 (0.3%)	2/889 (0.2%)	6/2620 (0.2%)	0/475
EU/NA Long-term Controlled Population (Study 178-CL-049)						
≥5%			28/788 (3.6%)	33/800 (4.1%)	61/1588 (3.8%)	32/789 (4.1%)
≥10%			1/788 (0.1%)	4/800 (0.5%)	5/1588 (0.3%)	0/789

For the mean AM SBP and mean PM SBP, values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days. The mean AM/PM SBP value is the average of the mean AM SBP and mean PM SBP values.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

The denominator is the number of patients with CVD risk estimates at both baseline and final visit.

Table 7 Outliers for Increase from Baseline to Final Visit in 10-year General Cardiovascular Disease Risk Estimates Using Mean AM SBP Values

	Placebo	Mirabegron				Tolterodine ER
		25 mg	50 mg	100 mg	Total	4 mg
Study 178-CL-046						
≥5%	18/478 (3.8%)		14/471 (3.0%)	13/477 (2.7%)	27/948 (2.8%)	16/475 (3.4%)
≥10%	1/478 (0.2%)		1/471 (0.2%)	0/477	1/948 (0.1%)	0/475
Study 178-CL-047						
≥5%	14/431 (3.2%)		26/425 (6.1%)	16/412 (3.9%)	42/837 (5.0%)	
≥10%	2/431 (0.5%)		2/425 (0.5%)	2/412 (0.5%)	4/837 (0.5%)	
Study 178-CL-074						
≥5%	6/415 (1.4%)	13/409 (3.2%)	20/426 (4.7%)		33/835 (4.0%)	
≥10%	0/415	0/409	4/426 (0.9%)		4/835 (0.5%)	
EU/NA OAB 12-week Phase 3 Population						
≥5%	38/1324 (2.9%)	13/409 (3.2%)	60/1322 (4.5%)	29/889 (3.3%)	102/2620 (3.9%)	16/475 (3.4%)
≥10%	3/1324 (0.2%)	0/409	7/1322 (0.5%)	2/889 (0.2%)	9/2620 (0.3%)	0/475
EU/NA Long-term Controlled Population (Study 178-CL-049)						
≥5%			34/788 (4.3%)	34/800 (4.3%)	68/1588 (4.3%)	32/789 (4.1%)
≥10%			4/788 (0.5%)	3/800 (0.4%)	7/1588 (0.4%)	6/789 (0.8%)

Mean AM SBP values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

The denominator is the number of patients with CVD risk estimates at both baseline and final visit.

Table 8 Outliers for Increase from Baseline to Final Visit in 10-year General Cardiovascular Disease Risk Estimates Using Mean PM SBP Values

	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
Study 178-CL-046						
≥5%	27/476 (5.7%)		14/471 (3.0%)	21/476 (4.4%)	35/947 (3.7%)	24/475 (5.1%)
≥10%	1/476 (0.2%)		2/471 (0.4%)	3/476 (0.6%)	5/947 (0.5%)	3/475 (0.6%)
Study 178-CL-047						
≥5%	16/431 (3.7%)		22/425 (5.2%)	19/412 (4.6%)	41/837 (4.9%)	
≥10%	0/431		4/425 (0.9%)	3/412 (0.7%)	7/837 (0.8%)	
Study 178-CL-074						
≥5%	7/414 (1.7%)	11/409 (2.7%)	21/426 (4.9%)		32/835 (3.8%)	
≥10%	2/414 (0.5%)	0/409	2/426 (0.5%)		2/835 (0.2%)	
EU/NA OAB 12-week Phase 3 Population						
≥5%	50/1321 (3.8%)	11/409 (2.7%)	57/1322 (4.3%)	40/888 (4.5%)	108/2619 (4.1%)	24/475 (5.1%)
≥10%	3/1321 (0.2%)	0/409	8/1322 (0.6%)	6/888 (0.7%)	14/2619 (0.5%)	3/475 (0.6%)
EU/NA Long-term Controlled Population (Study 178-CL-049)						
≥5%			28/786 (3.6%)	42/800 (5.3%)	70/1586 (4.4%)	41/789 (5.2%)
≥10%			1/786 (0.1%)	11/800 (1.4%)	12/1586 (0.8%)	6/789 (0.8%)

Mean PM SBP values were calculated using the last 2 out of 3 measurements within a day, on the last 3 out of 5 diary days.

Values of CVD Risk Estimates were calculated using the Cox proportional hazards model. For baseline and final visit, risk estimates less than 1.0% or greater than 30.0% were imputed as 1.0% and 30.0%, respectively.

The denominator is the number of patients with CVD risk estimates at both baseline and final visit.

4 SUMMARY

In the EU/NA OAB 12-week Phase 3 Population, the mean change from baseline to final visit in the 10-year general CVD risk estimates across the treatment groups was small; the median was 0 to 0.1% for the mirabegron 50 mg, placebo and tolterodine ER 4 mg groups and the 95% CIs for the mirabegron and tolterodine treatment groups overlapped with the 95% CIs for placebo. The percent of patients with a categorical change in CVD risk estimate of ≥10% was small (0 to 0.7%).

The assessment of CVD risk change associated with pharmacotherapy may be more accurately assessed using data from the 1-year double-blind study 178-CL-049, which included tolterodine ER as an active control, rather than data from the 12-week studies. In the EU/NA Long-term Controlled Population (Study 178-CL-049), median changes from baseline to final visit in CVD risk estimate using mean AM/PM SBP values were the same for mirabegron 50 mg (0.1%) and tolterodine ER 4 mg (0.1%). The percent of patients with increases from baseline to final visit in the 10-year general CVD risk estimate ≥ 5% based on mean AM/PM SBP values was 3.6% for the mirabegron 50 mg group and 4.1% for the tolterodine ER 4 mg group; 1 patient in the mirabegron 50 mg group and 0 patients in the tolterodine ER 4 mg group had a value ≥10%.

Limitations of the application of the 10-year general CVD risk estimates to the mirabegron study population include that the model is based on a US population whereas approximately 50% of the mirabegron study population is from Europe. Additionally, the 10-year CVD risk as described by D'Agonstino et al only includes 1 vital sign measurement, SBP, and does not include pulse or DBP.

Cumulative distribution function plots are currently being prepared and were not available at the time this document was finalized.

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